

## Development of a core outcome set to evaluate physical activity interventions for people living with dementia: study protocol

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### Abstract

**Background:** Evidence on the benefits of physical activity for people with dementia (PwD) remains disparate, mainly due to the selection of heterogeneous outcomes and measurement tools. This delays clear and specific recommendations for research and clinical practice. The development of Core Outcome Sets (COS) can contribute to overcoming this heterogeneity.

**Content:** This is a study protocol for the development of a COS applicable to physical activity interventions, in any setting, for PwD, across stages of the disease progression. This is a mixed methods study divided in four phases: i) literature review to identify outcomes used in previous literature; ii) a qualitative study to explore valued outcomes in the perspective of different stakeholder; iii) a Delphi survey and consensus meeting to reach a minimum set of outcomes and iv) a literature review to link the agreed core outcomes to the most appropriate measurement tool.

**Conclusions:** A COS in this field has the potential to allow fast-tracking recommendations to research and clinical practice. However, dissemination activities are required to encourage researchers to implement the COS.

**Key words:** Core Outcome Set; Dementia; Physical activity; Methodology

## **Background**

It is estimated that currently 47 million people live with dementia worldwide (World Health Organization, 2015), a number that may reach to 76 million by 2030 (Alzheimer Disease International, 2013). Enormous costs are being predicted, informal care being a significant component of these (Wimo et al., 2007). Higher levels of functional dependence are linked to an increased carer burden and consequently an increased risk of institutionalisation (Stephan et al., 2014). Evidence suggests that physical activity interventions may have a positive impact on the levels of independence of people living with dementia (PwD) (Forbes et al., 2015), potentially reducing care needs. Physical activity is also recommended for the general older population as it is known to have a positive impact on levels of mobility, risk of depression and mental wellbeing (National Institute for Health and Care Excellence, 2008). In line with these potential benefits, the National Institute for Health and Care Excellence (2006) guides health professionals to recommend appropriate physical activity for PwD. Yet, caution is needed. Despite the large body of research, systematic reviews report limitations in their results due to the use of heterogeneous outcomes and measurement tools (Forbes et al., 2015; Rao et al., 2014). This heterogeneity hinders the effective synthesis of evidence (Macefield et al., 2014) and delays the development of clear recommendations for research and clinical practice.

The use of Core Outcome Sets (COS) has emerged as a solution for the heterogeneity of reported outcomes in clinical trials (Williamson et al., 2012; Idzerda et al., 2014). COS are an agreed minimum set of outcomes that are recommended to be measured and reported as a minimum standard across clinical trials of a particular health condition or trial population (Williamson et al., 2012). The adherence to COS ensures that clinical trials measure meaningful outcomes for different stakeholders (Clarke and Williamson, 2015); reduces reporting bias; and allows a direct comparison between trials in meta-analysis, which will subsequently lead to clearer recommendations for clinical practice (Williamson et al., 2012; Waters et al., 2014). A COS to evaluate the effectiveness of physical activity interventions for PwD may also inform health professionals delivering these interventions. Health professionals can use this COS to select meaningful outcomes for patients and monitor the effects of their interventions against the results reported in the literature.

### Study aims and overview

No “gold standard” methodology currently exists for COS development. The COS-STAR statement therefore recommends that COS protocols are made publically available to increase the transparency of the COS development and minimise any biases (Kirkham et al., 2016).

The present protocol represents the proposed methodology to develop a COS to evaluate physical activity interventions for PwD.

Specific objectives for each of the four phases that form the development of this COS are to: phase I) comprehensively list the outcomes and measurement tools used in previous literature; phase II) explore what outcomes are meaningful for professionals delivering physical activity, PwD and their friends, relatives or informal carers, adding to the list of outcomes identified in the literature; phase III) reach consensus, across stakeholders, of what outcomes should be prioritised into the COS; and phase IV) link each agreed COS outcome to the most appropriate measurement tool.

## **Methods**

### Registration and Ethical approval

This project has been registered with Core Outcome Measures in Effectiveness Trials (COMET) initiative and its registration is available from:

<http://www.comet-initiative.org/studies/details/708?result=true>.

Informed consent will be obtained from all participants of each of the empirical phases of this study. This protocol has received ethical approval from the Ethics Committee of the Faculty of Health Sciences of the University of Southampton, United Kingdom. The design and implementation of this project was informed and supported by the involvement of patient representatives.

### Scope

The present COS will be applicable to any physical activity intervention, as per the World Health Organisation definition: “Any body movement produced by skeletal muscles that requires energy expenditure”, for PwD, at any stage of the condition, in any setting. This excludes interventions for people diagnosed with a mild cognitive impairment or people with a cognitive impairment as a result of any other health conditions but dementia. It is anticipated that the final COS will be subdivided into “mild to moderate” and “severe stages”, as different outcomes might have more or less relevance in different stages of the disease. The final COS will be recommended for use in clinical trials. Additionally, guidance on the assessment of effectiveness of physical activity interventions for PwD in clinical practice will be drawn.

### Stakeholders

The selection of participants for the development of this COS aims to reflect the variety of stakeholders involved in physical activity interventions for PwD. Two stakeholder groups will

be included. A professional group including health and social care professionals, researchers and members of volunteering organisations; and a second group including PwD, their relatives, friends and informal carers.

### Phase I: systematic literature review

One systematic mixed studies literature review will be conducted with the aim of comprehensively listing the outcomes and measurement tools used in previous literature.

#### *Information sources and search strategy*

The search strategy will begin with a key word search on Delphis, a single interface that allows a key word search in providers such as Medline, PsycINFO, Cinahl, Scopus and ScienceDirect. The search strategy below has been developed in collaboration with an experienced librarian in health sciences:

S1. "Physical activity" OR exercis\*

S2. dement\* OR Alzheimer

S3. S1 AND S2

S4. S3 AND source type: academic journals OR reviews OR thesis/dissertations (excluded books, magazines, news, conference materials, electronic resources and reports).

S5. S4 AND studies written in English, Portuguese or Spanish.

S6: studies published from the 1<sup>st</sup> of January 2005.

A subheading search will be performed using the database identified as the most important source of studies (based on the Delphis results) to ensure literature saturation.

#### *Participants*

Studies including PwD at any stage of disease progression will be included.

#### *Types of studies and interventions*

Experimental designs (with or without comparators), qualitative studies and study protocols investigating the impact of any physical activity intervention, will be included. No restrictions will be made regarding intervention setting.

#### *Exclusion criteria*

Studies will be excluded if they are not written in English, Portuguese or Spanish; or relate to physical activity interventions for relatives or carers only. All searches will be limited to studies published from January 2005 onwards. Although this decision is recognised as a limitation, it is anticipated that any important outcomes not captured by this review will emerge during the interviews with different stakeholders (phase II).

### *Data extraction and analysis*

The screening and eligibility of papers generated by the searches will be conducted by one author. A random sample of 10% of the studies will be independently screened by a second author to ensure accurate application of inclusion and exclusion criteria. Standardised data extraction will ensure the identification of all outcomes (positive or negative) and measurement tools reported by the included papers in their methods, results and discussion sections.

A content analysis methodology (Macefield et al., 2014) will be used to synthesise the diversity of the outcomes used in physical activity interventions for PwD. Verbatim outcomes, from qualitative, quantitative and mixed methods studies will be extracted and analysed using the same content analysis approach. Verbatim outcomes will be grouped in outcome domains (outcomes with different taxonomies but the same perceived meaning). The outcome domains will subsequently be organised into broader themes by the research team. An analysis of the outcome domains per stage of disease progression, study paradigm and identified by each stakeholder group, will be performed. With regards to the stakeholder groups, outcomes reported in clinical trials will be considered as outcomes selected by professionals, unless described otherwise in the papers. Outcomes reported by qualitative studies will be linked to the participants in these studies.

### *Risk of bias*

The methodological quality of included papers will be assessed using the Mixed Methods Assessment tool – version 2011 (Pluye et al., 2009), a tool designed for the purpose of complex reviews, including studies from different paradigms. The quality of the included studies will be used purely to inform the readers of the quality of research in this field. It will not be used as an exclusion criterion and will not influence data analysis.

### Phase II: qualitative Interviews

This qualitative study will aim to complement the results from the literature review in the previous phase and allow a deeper understanding of what outcomes are valued to each stakeholder group. Phases I and II will be conducted in a sequence because the findings from the qualitative study will complement the results from literature review. However, it is possible that a temporal overlap may occur between data analysis for the literature review and data collection for this qualitative study.

### *Participants*

The “professional” stakeholder group includes any health and social care professional or member of a volunteering organisation who has been involved in the design, implementation

or support of physical activity for PwD, in any setting. To be included, “professionals” have to live or work in the United Kingdom and have sufficient English language skills.

PwD, at any stage of the disease progression, who have been involved in any type of physical activity since diagnosis, will be eligible regardless of age or accommodation setting. Capacity to consent to take part in research is required. Sufficient verbal communication skills in English language are also required to undertake the interview. Relatives, friends or informal carers of PwD, who have been in contact with the patient during their involvement in physical activity, and have sufficient English skills, will be interviewed either independently or in a joint interview with the patient.

Factors such as age, gender, accommodation setting, levels of physical activity and stage of disease progression will be used for purposive sampling (Coyne, 1997). Both stakeholder groups will be recruited from charities, community centres, privately run care and nursing homes, support and professional groups. The sample size will follow the principles of data saturation (Guest, 2006), to a maximum of 30 participants (8 to 10 professionals, 4 to 10 PwD and 4 to 10 relatives).

#### *Interview format*

A Semi-structured interview format will be followed. The interviews will be conducted through the use of open-ended questions which will not be influenced by the results of the literature review. PwD will be conducted face to face, to allow for ongoing capacity assessment throughout the interview. Telephone interviews will be a possibility for other participants. Topic guides will address the valued outcomes of physical activity for all stakeholders. It is anticipated that the concept of “outcome” may be unfamiliar for many participants. Thus, this terminology will be replaced by “effects” or “results” of physical activity, for purposes of clarity during the interviews. In addition to outcomes, participants will be asked about barriers and facilitators for the application of a COS for this population, in research and clinical practice. These data will inform final recommendations for the applicability and dissemination of the COS.

PwD will be encouraged to have a relative or friend with them at all times, for their own comfort. The interview will be conducted in a familiar venue (i.e., their home) to reduce possibilities of distress caused by being in an unfamiliar location. The researcher conducting the interview will have experience in communicating with PwD.

#### *Interview analysis*

All interview data will be audio-recorded, transcribed verbatim. NVivo software (NVivo10 software, QSR International, Burlington, Massachusetts, United States) will be used to aid data management. A framework methodology will be followed (Ritchie and Spencer, 1994),

coding the interview data against a framework of outcomes generated by the literature review in Phase I. This methodology also enables novel outcomes, emergent from the interviews, to be added to the initial framework.

At the end of Phase II, a comprehensive list of potential outcomes will be generated and used in the Delphi survey, described in Phase III.

### Phase III: Delphi and consensus meeting– what to measure

The OMERACT (Outcome Measures in Rheumatology) initiative recommends that the number of outcomes in a COS is limited to a maximum of nine, in order to promote its applicability (Boers et al., 2014). A Delphi survey will be used as a method to reach consensus regarding what outcomes should be prioritised for inclusion in the COS. A Delphi technique utilises several rounds where participants receive feedback from previous rounds and have opportunity to review their choices. The main advantages of this method are the anonymous participation of experts, minimising possible role pressures from fellow participants; and expenses and logistical challenges of face-to-face meetings (Boers et al., 2014; Prinsen et al., 2014; Sinha et al., 2012), making it a commonly used consensus method in the development of COS. A two round modified Delphi survey, including both stakeholder groups is planned for the development of this COS. Modifications to the Delphi survey, detailed below, were made to enable the participation of PwD in this phase of the study. Each item in the Delphi survey will consist of one outcome identified in the literature review and qualitative interviews (Phases I and II) and reviewed by patient representatives, to guarantee content clarity of the items.

### *Participants and sampling*

Participants from both professional and lay stakeholder groups will be invited to participate in the Delphi survey. Equivalent inclusion/exclusion criteria and recruitment strategies will be used. PwD will require face-to-face contact; but all other participants can be recruited from any part of the globe. The first page of the Delphi survey will list the inclusion criteria and all participants will be asked to confirm these criteria before completing the survey.

The optimum number of participants in a Delphi survey is yet to be established, however previous studies have reported sample ranging from 46 (Sinha et al., 2012) to 218 (Devane et al., 2007). MacLennan et al. (2015) suggested a sample size of up to 150 participants. Therefore, we aim to recruit between 80 (40 for each stakeholder group) and 150 participants. Participants from the qualitative interviews will also be invited for the Delphi study. Additionally, a snowball sampling strategy will be implemented for the online surveys, where participants will be asked to invite peers who may wish to participate (Kottner et al., 2016).

### *Methodological adaptation to enable the participation of People with Dementia*

A card-sorting alternative, in a face to face interaction, will be offered to PwD, aiming to reduce the cognitive demand of the task. Participants will be shown a set of cards, each with a simple description of the outcome and pictorial representation. The participant will be asked to choose the cards that represent their valued outcomes of physical activity. Card sorting strategies are used with PwD as a form of assessment, for instance through the use of the Nelson's Modified card sorting test (Chao et al., 2013). This indicates that using cards to facilitate the selection of information, according to an established criteria, might be appropriate for this population. PwD and their carers, from local support groups will be asked to contribute to the development of the survey and pilot its first version before the beginning of the Delphi survey. Participants other than PwD will receive an on-line or paper survey, via post, according to their preference.

### *Round 1*

Based on what is already known regarding the heterogeneity of the literature on this topic, it is expected that the round 1 survey will consist of over 100 outcomes (survey items). This is a large amount of information, potentially too challenging for PwD, even when using the card sorting strategy described above. Therefore, in this first round, PwD will not be included, and the stakeholder group 1 will be represented only by their relatives, friends or informal carers. All participants of round 1 will be asked to choose responding to the survey designed for mild to moderate or severe stages of dementia (or both) according to their own experience or choice. To each of the surveys (mild to moderate and severe stages) each participant will be asked to choose (without rating) up to nine outcomes from the list.

### *Data analysis and definition of consensus*

Descriptive statistics will be used to describe participants' characteristics and ascertain consensus as follows. At the end of the first round, outcomes will be excluded if: selected by 15% of the participants or less (Waters et al., 2014), and had not been identified by a person living with dementia in the interview stage. All other outcomes will be taken through round 2. At the end of round 2, any outcomes selected by 70% or more of the participants in both stakeholder groups or by 80% in one stakeholder group will be included in the COS (Waters et al., 2014;Boers et al., 2014;Potter et al., 2015). It is anticipated that the Delphi survey will be divided into "mild to moderate" and "severe" stages and in that case, this definition of consensus will apply individually to each of these stages of the condition.



## *Round 2*

All participants of round 1 will be asked to review their answers based on the feedback from round 1. The feedback will consist of the percentage of all participants; and percentage of participants from each stakeholder group, who selected each of the outcomes.

PwD will be included in this round, when the number of outcomes remaining on the survey are likely to be substantially lower. PwD will complete a face-to-face survey, using a card sorting approach as previously described, regarding their own stage of the disease only (mild to moderate or severe). The interaction between the researcher and the participant will be audio recorded.

At the end of this round, all outcomes that remained in the Delphi (selected by 16% or more of the participants) will be taken to a consensus meeting for validation and discussion of possible disagreements.

### *Consensus meeting – final decision on what to measure*

A final consensus meeting aims to present and validate the agreed outcomes from the Delphi survey (as per definition of consensus), resolve any disagreements and to seek consensus for the outcomes in which an agreement has not yet been achieved (MacLennan et al., 2015). Results from the Delphi survey will be presented and discussed by a group consisting of at least one representative of each stakeholder group. An open group discussion methodology will be followed. Consensus will be defined as 90% of agreement to include one more outcome to the COS. If consensus cannot be achieved, a smaller COS, including only the fully agreed outcomes will be defined (Williamson et al., 2012). A separate meeting per stakeholder group may be arranged according to the preference of PwD and their carers, relatives or friends. This option will also be used if a marked disparity in opinions per stakeholder group, would have been noted in the Delphi results (Waters et al., 2014).

### Phase IV: literature review – how to measure

This final literature review aims to link each of the outcomes agreed at the end of the previous phase to the most appropriate measurement tool. Practical guidance on how to select measurement tools for outcomes in a COS has recently been published a result of a collaboration between COMET and the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) initiatives (Prinsen et al., 2016). This guidance suggests 4 steps which will be followed as described below.

### *Conceptual considerations*

A clear definition of the concepts behind each of the outcomes will be decided upon by the research team.

### *Finding existing measurement tools*

The selection of the measurement tools will consider the stage of disease progression (mild to moderate and severe stages separately) and the intervention settings. The process of finding existing measurement tools would have started in phase I (literature review). Additional literature searches will be undertaken to update the literature review on phase I, and to identify the psychometric properties of each of the measurement tools identified. The search strategy will follow the guidance of Prinsen et al. (2016) and the advice from a librarian.

### *Quality assessment of the instrument tools*

This step will follow the criteria indicated by COSMIN (internal consistency, reliability, measurement error, content validity, structural validity, hypothesis testing, cross cultural validity, criterion validity, responsiveness and interpretability) (Mokkink et al., 2010) to assess the quality of the evidence available on the measurement properties of measurement tools linked to each of the outcomes, according to our set population group and intervention setting.

### *Generic recommendations*

Only tools with high quality evidence for good content validity, good internal consistency and that are considered feasible (on the grounds of application time, availability and costs) will be recommended in the final COS. To encourage consistency in clinical trials, each outcome should be linked to one measurement tool only. If multiple tools fit quality and feasibility criteria, an expert panel will be arranged with the stakeholder groups to reach a consensus on which measurement tool will be recommended in the final COS (Coulter et al., 2016).

Measurement tools and their characteristics identified in the literature will be shown to the panel members. Lay terms and examples will be used to explain psychometric properties to non-scientific members of the panel. Patients, friend and relatives stakeholder group may be represented by friends or relatives only. However, if PwD are recruited to take part in this stage, quiet environments and shorter sessions will be arranged to accommodate their needs and facilitate their participation. Advice from patient representatives will also be sought in the planning of this expert panel. Each panel member would then rate each measurement tool individually. The results of the voting will be revealed and followed by a group discussion, which would then lead to another round of voting, until a consensus of 70% of more votes in favour of a particular measurement tool can be reached.

## **Conclusion**

Adherence to COS applicable to all physical activity interventions for PwD in any setting and able to cover all stages of the disease progression will increase the consistency of clinical trials in this field; allow a direct comparison between interventions and consequently lead to more clear guidance for research and clinical practice.

Of the methodology presented above, the Delphi study is the phase requiring particular attention, and careful adaptations to enable PwD to take part. A card sorting strategy and the absence of a ranking system, typically used in Delphi surveys, is suggested. These adaptations will be trialled by carers before implementation. The possible expert panel at the end of phase IV, to vote on one of multiple possible tools to measure one outcome, is also an adaptation of the previously described methods, with the view to include PwD. The use of consensus and prioritisation methods involving PwD and other cognitive impairments requires further methodological research.

Despite the scope for important benefits of the use of a COS in this field, these will be dependent on the adherence of the trialists to the outcomes and measurement tools set by the COS. Therefore dissemination work should not be overlooked once the final COS is achieved and published.

## **Conflicts of interest**

The authors have no conflicts of interest to declare.

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