**KEYWORDS**

Delirium; long-term care; geriatric, core outcome set; systematic review

**KEY POINTS**

1. In a relatively small number of studies, we identified considerable heterogeneity in outcomes, measures, and measurement parameters used to evaluate efficacy of interventions to prevent or treat delirium in older adults resident in long-term care.

2. At present, there is little evidence on effective interventions to prevent or treat delirium in this patient population warranting further research

3. Development of a Core Outcome Set will help to harmonise trial design and improve ability to synthesize data across studies thereby informing clinical decision-making and policy development.

**ABSTRACT**

**Objectives:** To inform development of a core outcome set we evaluated outcomes, definitions, measures, and measurement time-points in clinical trials of interventions to prevent and/or treat delirium in older adults resident in long-term care.

**Data Sources:** We searched electronic databases, systematic review repositories, and trial registries (1980 to 10December 2021).

**Study Selection and Data Extraction:** We included randomized, quasi-randomized, and non-randomized intervention studies. We extracted data on study characteristics, outcomes, and measurement features. We assessed outcome reporting quality using the MOMENT study scoring system. We categorized outcomes using the Core Outcome Measures in Effectiveness Trials taxonomy.

**Data Synthesis:**  We identified 18 studies recruiting 5,639 participants. All evaluated non-pharmacological interventions; most (16 studies, 89%) addressed delirium prevention. We identified 12 delirium-specific outcomes (mean [SD] 2.4 [1.5] per study), of which delirium incidence (14 studies, 78%) and severity (6 studies, 33%) were most common. We found heterogeneity in description of outcomes and measurement time points. The Confusion Assessment Method (3 versions) was the most common measure used to ascertain delirium incidence (7 of 14 studies, 50%). We identified 25 non-delirium specific outcomes (mean [SD] 4.0 [2.3] per study), with hospital admission the most commonly reported (9 studies, 50%).

**Conclusions:** We identified few studies of interventions for the prevention or treatment of delirium in older adults resident in long-term care. These studies were heterogeneous in the outcomes reported and measures used. These data inform the consensus-building stage of our core outcome set.

**INTRODUCTION**

Long-term care (LTC) refers to the provision of a range of health and social care services to support older adults with needs arising from functional limitations imposed by medical illness, cognitive impairment, or frailty[1]. While these services can be delivered in people’s own homes, in many cases they are provided in institutional settings, such as nursing or residential care homes. These institutions support large resident numbers: 2016 US data indicates 2.63 million people were living in nursing homes or residential care[2]. UK data from 2017 showed 0.46 million people were living in nursing homes or residential care[3].

The LTC population is aged, with 39% of 2016 US nursing home residents aged 85 years or over. These older adults have high rates of long-term medical conditions, with one in three having heart disease or diabetes, and nearly half diagnosed with dementia[2]. These elderly LTC residents, being both physically and cognitively frail, are at high risk of developing delirium. Delirium is a common condition, characterised by alterations in attention, awareness, and cognition, caused by changes in physical health state [4]. One evidence review found the LTC resident delirium prevalence was 14%, rising to 33% in those with advanced dementia[5].

The consequences of delirium in this population are severe. Arinzon *et al.* [6] found that nearly a quarter of LTC residents with a diagnosis of dementia who developed delirium died within one month. Other studies report LTC residents with delirium have higher rates of falls, more rapid functional decline, higher healthcare associated costs, increased mortality and more hospital admissions compared to residents without delirium[7,8]. Effective prevention and treatment of delirium in the LTC setting is therefore an important goal. However, as in other settings in which delirium is common such as critical care, determination of which interventions are effective has been hampered by heterogeneity in trial outcome selection, measurement, and reporting[9].

Core outcome sets (COS) define the outcomes critical for inclusion in all trials for a defined condition and population[10]. They facilitate robust comparisons of effectiveness, through combination of outcome data. COS development follows a well-established methodology. First, outcomes and measures used in published and ongoing studies are identified. This is followed by a consensus building process with input from researchers, clinicians, and members of the public affected by the condition [11,12]. As part of the Del-COrS study[9], we have developed COS for trials of interventions to prevent or treat delirium in critical care[13], acute care[14], and for palliative care[15]. Given the burden of delirium in older adults resident in LTC settings, we sought to develop a COS for older adults resident in LTC, following the process recommended by the Core Outcome Measures in Effectiveness Trials (COMET) Handbook version 1.0[16].

As the first step to developing this COS, we conducted a systematic review to summarise the scope and variability of outcomes, definitions, measures, and measurement timing in published and ongoing clinical trials of interventions, including quality improvement projects, designed to prevent and/or treat delirium in LTC residents. These data, in combination with that derived from interviews with family members of LTC-resident delirium survivors, and professionals who provide care to this group, will be used to inform a Delphi consensus-building process identifying outcomes considered by key stakeholders as critically important for inclusion in the COS.

**METHODS**

An experienced medical information specialist developed and tested the search strategy through an iterative process in consultation with the review team. Another senior information specialist peer reviewed the strategy prior to execution using the PRESS checklist [17]. Using the OVID platform, we searched Embase, PsycINFO, and OVID MEDLINE, including Epub Ahead of Print, In-Process & Other Non-Indexed Citations. We also searched the Cochrane Library on Wiley, CINAHL on Ebsco and the Web of Science.

All searches were performed on June 26, 2019, updated on July 28, 2020 and finally updated on 10 Dec 2021. Strategies utilized a combination of controlled vocabulary (e.g., “Delirium”, “Homes for the Aged”, “Aged”) and keywords (e.g., delirious, nursing home, elderly). Vocabulary and syntax were adjusted across databases. When possible, animal-only and opinion pieces were removed from the results.

Grey literature searches for systematic reviews and clinical trials were conducted in the Joanna Briggs Institute EBP Database, PROSPERO, ClinicalTrials.gov and the ICTRP Search Portal on July 9-10, 2019 , updated on July 28, 2020 and 10 Dec 2021.

Specific details regarding the strategies appear in Appendices 1 and 2. This Core Outcome Set is registered on the COMET website (http://www.

comet- initiative. org/ studies/ details/ 796). The systematic review is registered on PROSPERO-ID: CRD42016052704 (https://www. crd. york. ac. uk/ PROSPERO/ display\_record. asp? ID= CRD42016052704).

*Inclusion/Exclusion Criteria*: We included studies of interventions for delirium prevention, treatment, or both, conducted in older adults resident in LTC. These settings were defined as institutions which were the residents’ permanent home. This included nursing homes (where some aspects of care are carried out by, or under the direction of qualified nurses) and residential care homes (where care is provided by staff with no nursing qualification). We included randomized (individual, cluster, and cross-over), quasi-randomized, and non-randomized intervention studies. There were no language restrictions. We excluded studies conducted in post acute care settings, where the institution was not intended as the older adult’s permanent place of residence.

*Study Selection:* One author (NR or GR) screened titles and abstracts applying the inclusion/exclusion criteria above. Any publications where the eligibility for full text review was unclear were discussed with a second author (LR). Full-text review was conducted independently by two authors (NR; GR) with disagreements or uncertainties being discussed with a third author (LR) until consensus was reached.

*Data extraction:* Authors in pairs (NR, GR, SR, RW) independently extracted study characteristics; intervention type; verbatim descriptions of primary and secondary outcomes and rationale for their selection; measurement tools; measurement initiation, discontinuation, frequency and timing; and who measured the outcomes. We used a specifically designed and piloted data extraction form, adapted from that used in previous Del-COrS reviews. Two authors independently assessed quality of describing and reporting outcomes using the six question MOMENT study scoring system (range 0 to 6), with a score of ≥4 representing high quality outcome reporting[18]. Any differences in scoring were resolved by discussion until consensus was achieved.

*Data synthesis*: Two authors (GR, NR) grouped outcome descriptions into outcome domains considered specific to delirium. Non-delirium-specific outcomes were grouped into outcome domains within the COMET taxonomy classifications[19]. Discrepancies were discussed to reach agreement and reviewed by a third author (LR). We calculated the proportion of studies reporting each outcome overall and as the study primary outcome. We calculated the mean and standard deviation (SD) of the number of delirium-specific and total outcomes reported. We described the range of tools used to determine the presence of delirium, and the proportion of studies using each tool.

**RESULTS**

*Study characteristics*

We screened 3863 citations, reviewed 39 full-text publications and identified 26 citations relating to 18 individual studies recruiting 5639 participants. The 26 citations comprised 16 completed trials, 2 publications describing preliminary findings of subsequently published trials, 3 published protocols relating to trials that were subsequently published, one published protocol relating to an ongoing trial, 2 trial registrations with subsequent results published, and one trial registration without published results (Figure 1). Eight studies (44%) were randomized trials, with the remaining being controlled before and after (6 studies; 33%), or non-randomised studies (4 studies; 22%). Four (22%) were single centre studies; 14 (78%) were multi-centre.

Thirteen (72%) studies evaluated an intervention for delirium prevention, 2 (11%) a delirium treatment intervention, with the remaining studies (3; 17%) evaluating an intervention to both prevent or treat delirium. All studies reported non-pharmacological interventions. Nine (50%) were single component interventions; 9 (50%) were multicomponent interventions. Table 1 shows study characteristics.

*Delirium specific outcome domains*

Nine (50%) studies evaluated the effect of the intervention on a delirium-specific outcome as primary objective. Five (28%) studies reported a delirium-specific outcome as a secondary outcome; in the remaining 4 (22%) studies we were unable to determine which outcome was primary due to a lack of clarity in described methods. We identified 12 delirium-specific outcomes. The mean (SD) number of delirium-specific outcomes reported per study was 2.4 (1.5). The most common outcome in studies of interventions for delirium prevention was delirium incidence (14/16; 87%) (Table 2).

Of the 14 studies reporting delirium incidence, 7 (50%) used the Confusion Assessment Method (CAM) alone including standard[20], short[21], and nursing home[22] versions. Three studies used the CAM in conjunction with the Delirium Index[23]. Other tools included a combination of the Mini Mental State Examination[24] and the Neelon and Champagne Confusion Scale (NEECHAM; 2 studies)[25]; DSM-V (2 studies)[4]; and the Delirium Observation Screening Scale (2 studies)[26]. Other measures used in single studies included the Neuropsychiatric Inventory Questionnaire (NPI-Q)[27]; the Recognizing Acute Delirium As part of your Routine tool (RADAR)[28]; the Nursing Delirium Screening Scale (Nu-DESC)[29]; the Cohen Mansfield Agitation Inventory[30]; and the Delirium-O-Meter[31]. The measures used and information relating to their timing and frequency are set out in Appendix 3.

We found multiple descriptions of delirium-specific outcomes and measurement time-points. Rationale for the selection of delirium-specific outcomes were provided infrequently, as were rationales for selection of measures. Delirium assessment frequency was daily in 3 studies (17%), weekly in 6 studies (33%), and less frequently than weekly in 4 studies (22%). In three studies (17%), no face-to-face assessment took place, and the presence of delirium was determined only by a retrospective review of clinical records. In 2 studies (11%) the information provided did not allow us to determine assessment frequency. In those studies that included a delirium-specific outcome as its primary outcome, delirium assessments were conducted daily, or on alternate days, in all but one study. In studies where a delirium-specific outcome was secondary, assessment frequency was far more infrequent with three studies conducted only a case note reviews at baseline and conclusion of study. Reporting on aspects of outcome ascertainment, i.e., time of day assessments were conducted, training of staff collecting measures, and rationale for the assessment schedule was limited.

*Other outcome domains*

We identified 25 non-delirium-specific outcomes within 13 of the COMET taxonomy classifications, of which delivery of care (4, 16%) (including medication appropriateness and polypharmacy) was the most common. Hospital resource use, mental health outcomes, and emotional wellbeing were also common categories (3 outcomes each). Studies reported a mean (SD) 4.0 (2.3) non-delirium-specific outcomes, with hospital admission (9, 50%), mobility and falls (8, 44%), activities of daily living, and mortality (both 6, 33%) being most common. The most reported non-delirium-specific outcome in treatment studies was activities of daily living (3/5; 60%) (Table 3).

*MOMENT criteria*

Of the 18 studies, 11 (61%) scored an aggregate of 4 or more against the six MOMENT criteria, indicating high-quality outcome reporting (Table 4). Four (22%) studies satisfied only one of the MOMENT criteria including both studies evaluating delirium treatment interventions.

DISCUSSION

In this systematic review conducted to inform a COS for trials of interventions for prevention and/or treatment of delirium of older adults resident in LTC, we identified 12 delirium-specific outcomes and 25 non-delirium-specific outcomes relating to 13 of the 38 COMET taxonomy classifications. The CAM, in original, short, or nursing home versions, was the most common method to ascertain delirium occurrence. As with our previous Del-COrS systematic reviews[14,15,50] we found substantial heterogeneity in selected measures, measurement time points, and measurement frequency.

We found considerable overlap between the delirium-specific outcomes in this review and those we reported for the other three patient populations included in the Del-COrS project, with incidence, duration, severity being common to all. We found three process type outcomes that were unique to studies in older adults resident in LTC: nurse knowledge of delirium, nurse confidence in managing delirium, and nurse ability to recognise delirium. Delirium incidence was the most commonly reported outcome in studies of delirium prevention which is in line with our previous reviews in critical and acute care[14,50], but not in our palliative care review[15] in which delirium severity was the most commonly reported. Given concern over harms associated with antipsychotics in dementia, and the overlap between dementia, and risk of delirium, an unexpected finding in this review was how infrequently use of antipsychotics featured as an outcome (one study).

We found delirium was most often screened for using variants of the CAM, yet we identified ten other measures used in the 18 trials, with four studies not using a validated delirium measure. This indicates an urgent need for consensus on the most appropriate delirium screening measure for use in trials recruiting LTC residents. Frequency of assessment was also highly variable with only three studies reporting daily outcome measurement. Given that fluctuating mental state is a core clinical feature of delirium, assessments must be done frequently to detect its presence reliably. Where delirium measurement is infrequent, there is a high risk it’s presence will remain unrecognised.

Quality of measurement of delirium outcomes specifically introduced a high risk of detection bias in these studies. The heterogeneity of measure selection and administration frequency across a limited number of trials is striking and supports the needs for a COS for delirium prevention and treatment trials in this setting. This may reflect specific challenges to data collection in LTC, with participants in trials often spread across sites which may be remote from the research teams conducting the study, and where the level of training and resource constraints may make frequent administration of ‘gold standard’ measures by LTC staff members impracticable.

A further issue in the assessment of delirium is the challenge of ascertaining delirium in the presence of dementia [52]. Dementia and delirium are both more common in older populations [53,54]. People with dementia frequently present with behavioural and psychological symptoms of dementia (BPSD), defined as symptoms and signs of disturbed mood, behaviour, perception or thought content. Since BPSD can mimic delirium, differentiating between the two is challenging [52]. A systematic review found that the Confusion Assessment Method (CAM) had an overall sensitivity and specificity of 94% and 89% respectively [55]. However, it found studies in populations with higher rates of dementia reported lower rates of sensitivity (≤ 70%) and specificity (63%)[55].

Furthermore, people with dementia are four times more likely to develop delirium [52,56] and patients with delirium have 12 times greater odds of developing dementia [57]. People with delirium and dementia present significantly more behavioural symptoms of dementia than people with dementia alone [58]. The complex inter-relationship and challenges in distinguishing between the two conditions have been previously reported [52, 58]. This poses a particular challenge for delirium COS development in the LTC setting, as even the ‘gold standard’ assessment measures have significantly lower performance, and highlights a need for new or adapted measures that have better power to discriminate between these two conditions.

A striking difference detected during the conduct of systematic reviews of intervention studies to prevent or treat delirium as part of the Del-COrS project is the difference in amount of research carried out in the four study populations. Both the critical and acute care setting reviews[14,50] identified large numbers of studies (195 and 183 respectively). There were only 18 studies identified by this review, and 13 by the palliative care review[15]. Delirium is common in older adults resident in LTC, has negative consequences in terms of patient outcomes such as hospital admission, rapid deterioration in health, and death [6,7] and in outcomes related to use of health and social care (e.g., resource use, including primary care consultations and acute hospital bed occupancy). Reasons for this difference in the number of trials being carried out are likely complex but may include challenges to research conduct in LTC settings such as high staff turnover [59], lack of familiarity with research data collection methods, and complex governance arrangements (including a requirement to get approvals from each participating LTC institution, which may not be familiar with processes needed to set up and to efficiently manage research)[60]. This contrasts with trials conducted in critical and acute care, which are more frequently conducted in academic centres with a strong research culture and study support resources in place. This review therefore highlights an important gap in research activity i.e., the need to find effective interventions to prevent and treat delirium in the large number of older adults living in LTC care institutions and at high risk of developing delirium. Development of this delirium in LTC COS, which this review informs, is a key step to addressing this gap.

*Strengths and Limitations*

This review used rigorous methods to identify relevant studies, extract data, and categorize outcomes. We used a range of search terms to reflect the evolution of delirium definition over the past four decades. We included data from publications relating to studies at more than one time point on their lifecycle, e.g., protocol papers and published findings, to get a comprehensive account of the outcome measures used. We set out to include studies in any language but found none in languages other than English. A limitation related to the small number of studies identified means there may be outcomes important to patients, family members and clinicians that have not been included. We will be conducting interviews with these key stakeholders to address this limitation.

CONCLUSION

As in our previous systematic reviews in other patient populations at high risk of delirium[14,15,50], we identified substantial heterogeneity in outcome selection, measures and measurement parameters reported in trials of interventions to prevent or treat delirium conducted in older adults resident in LTC. Delirium incidence was the most frequent outcome measured most frequently with the CAM, although numerous other measures were used in a relatively small number of trials. This heterogeneity supports the need for a COS to inform delirium research for older adults resident in LTC. Unless a COS is developed, this heterogeneity will continue to hamper efforts to find effective interventions to prevent and treat delirium, making comparison of interventions difficult, and interfering with effective clinical decision making. Moreover, this review has established there is currently limited evidence to inform clinicians making decisions as to the most effective interventions to manage patients at risk of, or experiencing, delirium in LTC settings. Once our COS is developed there is an urgent need to apply it in interventional research in this clinically vital area.

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Text

Description automatically generated with low confidence**Figure 1: PRISMA 2009 Flow Diagram**

Full-text articles excluded (n = 27)

Studies included in qualitative synthesis   
(n = 18)

Articles included in qualitative synthesis  
(n = 26)

Full-text articles assessed for eligibility  
(n = 53)

Records excluded  
(n = 4285)

Records screened  
(n = 4338)

Records after duplicates removed  
(n = 3933+405)

Additional records identified through other sources  
(n = 405)

## Identification

## Eligibility

## Included

## Screening

Records identified through database searching  
(n =5527)

**Table 1: Study Characteristics**

|  |  |
| --- | --- |
| N = 17 studies | n (%) |
| Study design |  |
| Cluster RCT | 8 (47) |
| Before and after intervention study | 5 (30) |
| Non-randomized controlled trial | 4 (24) |
| Study region |  |
| North America | 8 (47) |
| Europe | 8 (47) |
| South America | 1 (6) |
| Decade of publication |  |
| 2000-2009 | 3 (18) |
| 2010-2019 | 12 (71) |
| 2020-present | 2 (12) |
| Delirium study objective |  |
| Primary | 8 (47) |
| Secondary | 5 (30) |
| Unclear | 4 (24) |
| Study intervention aim |  |
| Prevention | 12 (71) |
| Treatment | 2 (12) |
| Both | 3 (18) |
| Study intervention |  |
| Single component non-pharmacological | 8 (47) |
| Multicomponent non-pharmacological | 9 (53) |

Table 2: Delirium Outcomes

|  |  |
| --- | --- |
| **Outcome** | **Number of studies (%)** |
| Delirium incidence | 14 (78) |
| Delirium severity | 6 (33) |
| Cognitive functioning | 4 (22) |
| Delirium duration | 3 (17) |
| Delirium prevalence | 3 (17) |
| Nurse knowledge of delirium | 3 (17) |
| Agitation | 2 (12) |
| Delirium motoric subtype | 1 (6) |
| Use of antipsychotic medication | 1 (6) |
| Number of delirium episodes | 1 (6) |
| Nurse confidence in managing delirium | 1 (6) |
| Nurse ability to recognise delirium | 1 (6) |

Table 3: Non-delirium outcomes reported by more than one study

|  |  |
| --- | --- |
| **Outcome** | **Number of studies (%)** |
| Admission to hospital | 9 (50) |
| Mobility and falls | 8 (44) |
| Performance of activities of daily living | 6 (33) |
| Mortality | 6 (33) |
| Quality of life | 4 (22) |
| Infections | 3 (17) |
| Health and social care resource use | 3 (17) |
| Hydration | 3 (17) |
| Polypharmacy | 3 (17) |
| Medication appropriateness | 3 (17) |
| Number of contacts with primary care | 2 (11) |
| Malnutrition | 2 (11) |
| Depressive symptoms | 2 (11) |
| Quality of interprofessional communication | 2 (11) |
| Acceptability/satisfaction with intervention | 2 (11) |

Table 4: MOMENT criteria

|  |  |  |
| --- | --- | --- |
|  | Criteria (N=18) | Number (%) |
| 1 | Is the primary outcome clearly stated? | 14 (78) |
| 2 | Is the primary outcome clearly defined so that another researcher would be able to reproduce the measurement? | 15 (83) |
| 3 | Are the secondary outcomes clearly stated? | 11 (61) |
| 4 | Are the secondary outcomes clearly defined? | 9 (50) |
| 5 | Do the authors explain the use of the outcomes they have selected? | 12 (67) |
| 6 | Are methods used to enhance the quality of outcome measurement (eg repeated measurements, training) used if appropriate? | 9 (50) |