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## **Cluster randomized trials in nursing homes should better be planned as open-cohort than as closed-cohort**

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## **Abstract**

**Background:** two designs are frequently used in cluster randomized trials in nursing homes: closed cohort and open cohort. The former design includes residents at the beginning of the trial and then follows them. In the latter design, participants are enrolled at the beginning of the trial or while it is ongoing; at dates of assessment, all residents present in the nursing home are assessed. The open-cohort design is much less used than the closed-cohort design, but it offers several advantages such as less exposure to individual attrition.

**Objective:** to assess whether an open-cohort design could have been feasible in trials with a closed-cohort design.

**Study design and setting:** 22 closed-cohort trials in nursing homes.

**Results:** An open-cohort design was considered a relevant alternative for 20 trials. For 16 trials, a resident newly admitted could not opt of the intervention, and for all trials, the resident could benefit from an intervention effect, if it existed. For 2 trials, newly admitted residents could not benefit from the intervention effect, if it existed.

**Conclusion:** the open-cohort design is well adapted for most of the interventions assessed in nursing homes by means of a cluster randomized trial and should be considered more often.

**Key words:** Cluster randomized trial; nursing homes; research design; geriatric

**Running title:** design in nursing home cluster trials

**Word counts:** Abstract: 191; main text: 2633; figure: 1

## **Introduction**

Clinical research in nursing homes (NHs) is becoming more important with the ageing of the population (1). However, clinical research in NHs is still considered very challenging for numerous reasons including the challenge of obtaining consent from residents with cognitive impairment or the high rate of participant attrition (2) (3) (4). Those obstacles are often seen as a limitation to the expansion of high-evidence clinical trials conducted in those settings (5), with most research actually being observational studies.

Because residents are not patients, most interventional studies aim at enhancing resident well-being and preventing health issues rather than curing them (5) (6) (7). Such interventions often have NH-level components such as staff training, guideline implementation or environment adaptations. Hence, the cluster randomized trial (CRT), in which the units of randomization are NHs rather than residents themselves, is a well-adapted design. In such trials, Poupin et al. (8) showed that the two most-used strategies for recruiting residents are the closed- and open-cohort designs. In a closed-cohort CRT (9), all residents are recruited at the very beginning of the trial, and new recruitments are not allowed while the trial is ongoing. In an open-cohort CRT, most of the participants are recruited at the very beginning of the trial, but new residents meeting eligibility criteria and exposed to the intervention are recruited while the trial is ongoing. In the Poupin et al. review (8), the closed-cohort design was the most frequently used design, probably because of its similarity with the individually randomized trial in which participants are recruited, individually followed up and then assessed. In this latter review, a given intervention could have been investigated using a closed- or an open-cohort design. Thus, two CRTs have evaluated the effectiveness of similar interventions aimed at reducing the use of physical restraints in NH residents. Both interventions had a cluster-level component with staff training, which meant that residents could not really opt out of the intervention. Koczy et al. (10) used a closed cohort design: the primary outcome was the complete cessation of restraint use at 3 months among residents recruited at the beginning of the trial. However, the attrition rate was more than 22% in this trial, essentially due to death. The intervention effect was then estimated from the subgroup of participants who completed the trial, with characteristics that were probably not the same as those of non-completers. Kopke et al. (11) used an open-cohort design to assess a similar intervention. The primary outcome was the prevalence of physical restraints use and was assessed by a cross-sectional measurement 6 months after cluster randomization. All the residents present in the NH at the time of data collection were assessed, including newly admitted residents. These distinct situations are illustrated in Figure 1A. The open-cohort design seems attractive because of no individual-level attrition issue.

The aim of our study was to review closed-cohort NH CRTs to evaluate how often an open-cohort design could have been an alternative. We also discuss the pros and cons of opting for an open-cohort design over a closed-cohort one in the context of CRTs in NHs.

## **Method**

### **Articles for data collection**

We used a series of 22 articles reporting results of closed-cohort CRTs (Supplementary file). These reports were the closed-cohort subset of a series of 37 reports of cluster randomized trials used for a previous methodological review (8). These 37 articles were original reports of CRTs conducted in NHs that were published between January 1, 2005 and December 31, 2020 in medical or geriatric journals with high impact factor (*The British Medical Journal Clinical Research Edition, The New England Journal of Medicine, The Lancet, The Journal of American Medical Association, The Annals of Internal Medicine, PLoS Medicine, The Journal of Gerontology, Age and Ageing, Ageing Research Reviews, The Journal of the American Geriatrics Society, The Journal of the American Medical Association*).

### **Data collection process**

The data collection process was introduced by a brief meeting planned and conducted by one of us (PP). All reviewers were present. The objective of the present work and the underlying methodological concepts were developed. After this meeting, reviewers proceeded to the data collection independently. PP extracted data from all articles, and the other reviewers had a subset of articles each. For each article, the reviewers were given a brief description of the objective of the trial in the article, the intervention and the primary outcome. Concerning the intervention, the description also specified how, in the previously conducted methodological review, the intervention was classified according to both Eldridge and Kerry, and Beard et al. classifications (12) (13). Those two classifications are described in Box 1. In addition to this information and using a standardized data collection form, reviewers were asked signaling questions to judge whether an open-cohort design was feasible. These signaling questions were whether a resident newly admitted to a NH allocated to the experimental group could opt out from the intervention and whether the individual could benefit (completely or partially) from the potential effect of the intervention as for residents present in the NH from the beginning of the trial. The following example based on Nijs et al. trial (14) gives an illustration of the issues concerning those two questions. The aim of the Nijs et al. trial was to assess whether changing a mealtime style could improve the quality of life of residents. The intervention was a family-style mealtime for 6 months, with “table dressing, food services and protocol for the staff” instead of

pre-plated service in the control group. A newly admitted NH resident in the intervention arm could not opt out of the intervention because they would have meals with the other residents. After 2 or 3 months in the NH, we may assume that the resident would benefit, at least in part, from the intervention effect (assuming that it has a positive effect on quality of life), even if the resident was not exposed during the 6 months. Reviewers were finally asked to decide whether an open-cohort design could have been used as an alternative to a closed-cohort design. For that, they could suggest required slight modifications of the intervention and/or the outcome assessment, such that an open-cohort design would be well adapted. The modifications that the reviewers could suggest were only those needed to use an open-cohort design. As mentioned previously, reviewers answered independently, and discrepancies were resolved by discussion with PP.

## **Results**

Results of the data extraction are available in the supplementary file. For 16 of the 22 closed-cohort CRTs, the reviewers concluded that a resident newly admitted could not opt out of the intervention. Furthermore, for 20 trials, they concluded that newly admitted residents could benefit from an intervention effect (if it existed), although for 15 of these, the reviewers considered that a minimal time of exposure (to be specified) would have been necessary. In the end, for 20 of the 22 CRTs, the reviewers considered that an open-cohort design was a relevant alternative to the closed-cohort design. A modification of the intervention was suggested for 3 of the 20 CRTs consisting in making the interventions to be more permanent. In these trials, intervention periods were followed by observational periods, and the reviewers suggested expanding the intervention period over the complete trial period.

Concerning the primary outcomes, the reviewers considered that 2 of the 20 CRTs needed a modification. For the first trial, a count-data outcome seemed more relevant than the original outcome, which was the proportion of residents who fell. For the second CRT, the proportion of potentially inappropriate medications at month 12 was suggested instead of the original primary outcome, which was the proportion of potentially inappropriate medications present at baseline and resolved at month 12.

For 2 CRTs, the open-cohort design was not considered relevant. These CRTs assessed interventions that applied to the individual resident and were designed as progressive but intensive rehabilitation programs in a limited period rather than regular and continuous maintenance programs. The interventions were physical exercises with progressive intensity and an expected cumulative effect. The reviewers considered that such interventions prevented newly admitted residents to be involved in the trials because they could not join an ongoing

rehabilitation program whose potential benefit was considered possible only if the program was fully achieved.

## **Discussion**

In our series of 22 articles reporting NH closed-cohort CRTs, we found that i) for 20 of the trials, an open-cohort design was considered a relevant alternative design, conditional on slight modifications, and ii) for the last 2 CRTs for which an open-cohort design was judged inappropriate, assessed interventions were progressive rehabilitation programs.

To our knowledge, this is the first study to assess the relevance of opting for an open-cohort rather than a closed-cohort design in CRTs. However, it has some limitations. The main one is that the series of articles was a subset of articles used in a review that was not a systematic review: a limited time period was considered and articles were published in a selection of 11 general or geriatric journals only. Another limitation is that our sample of CRTs was small.

Murray (15) distinguished two types of designs in CRTs: the “nested-cohort design” and the “nested cross-sectional design”. In a nested-cohort design, participants are individually identified within clusters and followed up until being assessed. In a nested cross-sectional design, there is no individual follow-up (but still cluster follow-up): participants are assessed once, using a cross-sectional survey. Sometimes, there may be several surveys, and the design then is a “repeated cross-sectional design”. The closed-cohort design corresponds to Murray’s nested-cohort design. The open-cohort design actually shares important similarities with Murray’s nested cross-sectional design. Indeed, in most open-cohort CRTs (but not all, see later) participants are assessed with a cross-sectional survey, whether they were already present in the cluster when it was randomized or not. The choice between the two designs depends on the question of interest, which refers to the concept of estimand (16) (17). As stated by Turner et al (18), *“the cross-sectional design is preferred when the question is about change in a population”*. As observed in our series, interventions assessed by CRTs in NHs, such as staff training or environment adaptation, are mostly directed at the entire population of the NH. Therefore, clinical research in NH seems more similar to public health research, at a population level, than to clinical research at an individual level.

Besides being a feasible option in many NH CRTs, the open-cohort design offers several advantages. The first is that there is only one unit of interest, in accordance with the theory of the experimental design (19). Indeed, a well-known particularity of CRTs is that the randomization units, the units on which the assessed interventions apply, the measurement units and the units of analysis may differ (19). In an open-cohort design, the NH unit is the only one to be considered because of an estimation of a cluster-average treatment effect based on a

cluster-level primary outcome (which may be collected by cross-sectional measurements summarized in cluster statistics such as means or proportions), with a cluster-level analysis allowing for cluster-level inference (20). For example, Fossey et al. (21) used an open-cohort design to assess a professional-cluster intervention delivered to staff and focusing on the non-pharmacological management of agitation of residents with dementia. The primary outcome was the proportion of residents receiving neuroleptic treatment at 12 months. All the residents present in the NH 12 months after the randomization were assessed (because they were considered to have been exposed to the change in professional practices) and NH proportions were estimated. A cluster-level analysis was performed with a weighted  $t$  test. As a consequence, NHs were at the same time the randomization units, the units for which the intervention applied, the assessed units, the units of analysis, and then the inference units.

A further advantage of the open-cohort design is that assessed participants are representative of the NH population, whatever the time the measurement is planned. Conversely, using a closed-cohort design, which is exposed to individual attrition, leads to a cohort of participants whose representativeness decreases over time. This is especially true in NH settings where attrition is substantial and mainly due to death (22), thus raising concerns regarding the comparability of completers and non-completers. Moreover, cluster-level interventions such as staff training are expected to affect both residents present when the intervention is implemented as well as those who join the NH later on, notably because they most often cannot opt out of the intervention. Therefore, taking into account these latter residents makes sense and doing so allows for assessing whether an NH-level change has been observed, due to the intervention assessed.

As previously mentioned, outcome assessment in open-cohort designs is not limited to cross-sectional measurements of residents present at a given time point. Count data is also an option, notably for rate of falls. In such a situation, all participants contribute to the data collection, whether they were present from the beginning of the trial or joined the NH while the trial was ongoing and whether they completed the trial or not. Indeed, for count data, each resident contributes both to the number of events (e.g., number of falls) and the total time of follow-up. Such an approach applies equally to open-cohort and closed-cohort designs. Nevertheless, open-cohort designs offer increased statistical power and better representativeness, as previously discussed. That situation is illustrated in Figure 1B.

Nevertheless, the open-cohort design may have some constraints. The first is that the use of the design supposes that there is independence between the intervention assessed and death, the main cause of attrition. Indeed, an intervention that would increase mortality would imply an imbalanced turnover between arms, with a possibly higher rate of more robust newly admitted

residents in the intervention arm, which therefore may be associated with a biased intervention effect estimate. Among the trials we reviewed, we did not identify an intervention that seems to have an evident impact on mortality, but it is a crucial question at the time of the choice of design. A second constraint is that using an open-cohort design supposes that a newly admitted NH resident should benefit, at least in part, from the intervention effect, if it exists, as for residents present from the beginning of the study. Then, the open-cohort design is not relevant for trials with individual interventions such as an individually tailored rehabilitation program in which partial exposure makes no sense. Furthermore, using an open-cohort design often supposes that newly admitted participants have to be exposed during a minimal period of exposure. Indeed, there is a risk of weakening the potential intervention effect estimate by including participants who are not fully or sufficiently exposed to the intervention (15). A solution could be to discard the residents too recently admitted. Finally, a potential drawback is the risk of potential bias due to recruitment occurring after cluster randomization, when there is no longer allocation concealment (12) (23). However, this risk is probably limited because residents live permanently in their NH. Such circumstances favor the inclusion of all or nearly all residents, which thus limits recruitment bias.

### **Conclusion**

The open-cohort design is a well-adapted design for most of the interventions of interest that could be assessed in NHs by means of a CRT. However, it is currently underused. Such an approach could be considered more often by researchers when they plan CRTs in NHs. This corresponds to a paradigm change, inviting researchers to consider investigation in NHs at a population level rather than an individual level. While reproducing the classical scheme of an individually randomized trial in which residents would be included and then followed up until being assessed, the approach invites focusing on NHs, including them, following them up, and assessing them by considering a sample of residents present at the time of evaluation. The latter design is well adapted when the objective is to assess change over time of NH indices (24).

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### **Box 1. Eldridge and Kerry (12) and Beard et al. (13) classifications of interventions in cluster randomized trials**

In a cluster randomized trial (CRT), interventions may apply at the cluster and/or the individual level. Eldridge and Kerry (12) classified CRT interventions as i) individual-cluster interventions, ii) external-cluster interventions, iii) professional-cluster interventions and iv) cluster-cluster interventions.

The common feature of an individual- or external-cluster intervention is that participants can opt-out of the intervention:

- in the Hewitt et al. trial (25), residents were proposed an individual physical training to prevent falls; such an intervention applies at the individual level, and residents have the opportunity not to be exposed to it if they live in a nursing home allocated to the intervention group.
- in a CRT with an external-cluster intervention, the intervention is provided by a professional who is external to the NH as in the Patterson et al. trial (26), in which external pharmacists visited NHs monthly to review the residents' prescriptions and reduce the number of inappropriate medications. In such a situation, residents may refuse to have their medical record reviewed by these external pharmacists.

The common feature of a professional-cluster or a cluster-cluster intervention is that participants cannot opt out of the intervention, which applies at the cluster level:

- A professional-cluster intervention is targeted to the staff working in the cluster, as in the COME-ON study (27), in which staff were trained to reduce the number of inappropriate medications given to residents. Because staff are trained, their behavior is expected to change, regardless of the residents they care for.
- In a CRT with a cluster-cluster intervention, the intervention is expected to modify the environment of the cluster, as in the Nijs et al. trial (14), in which the intervention consists of implementing family-style mealtimes rather than an individual pre-plated service.

CRTs often assess multifaceted interventions. Then, each component of the intervention can be classified according to the four categories described above.

The Beard et al. classification aims to specify whether the effect of an intervention is expected to be immediate or immediate but progressive, whether it needs a delay before being effective, and whether it has the potential remaining effect after it has been stopped (13) (28). Four categories can be considered:

- Interventions with an immediate onset and a continuous effect for which there is no time lag before observing the potential full effect of the intervention. This was the case in the

Kannus et al. trial (29), with the objective to assess the effectiveness of hip protectors on reducing hip fractures.

- Interventions with an immediate onset but a delay in implementation: the response to the intervention needs a delay or the potential full effect of the intervention is observed only after a set-up or a training period, as in the Ballard et al. trial (30), in which staff were trained in person-centered care during the first 5 months of an 8-month intervention.
- Interventions with an immediate onset but a non-continuous effect. The intervention then has a potential on-off effect, with no more effect when stopped. An example is the Husebo et al. trial (31), with the objective to assess the effectiveness of a pain management protocol based on the use of daily treatment of pain medications that have an immediate but limited time effect on agitation of residents with dementia.
- Repeated and discrete interventions whose potential full effect is obtained after being repeated, as in the Toots et al. trial (32), which assessed the effectiveness of a physical training program in improving gait.

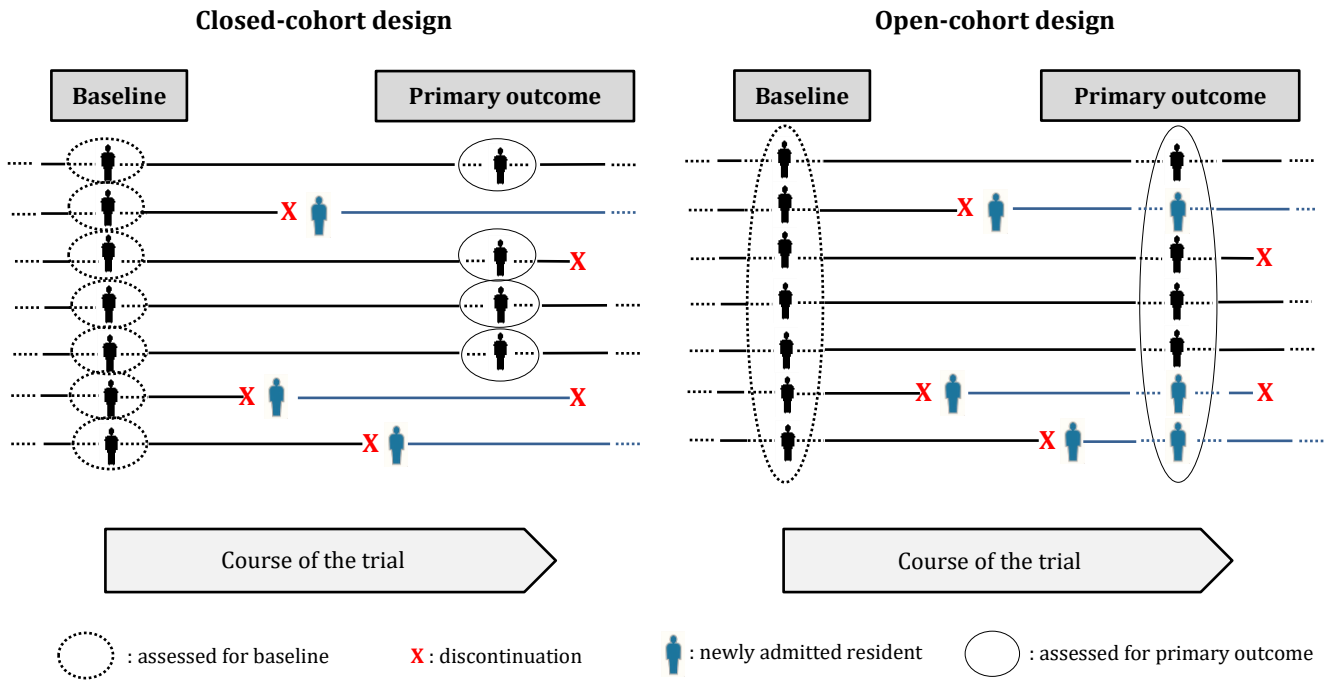
## REFERENCES

1. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *The Lancet*. avr 2017;389(10076):1323-35.
2. Lam HR, Chow S, Taylor K, Chow R, Lam H, Bonin K, et al. Challenges of conducting research in long-term care facilities: a systematic review. *BMC Geriatr*. déc 2018;18(1):242.
3. Simmons S, Resnick B, Schnelle J, Ouslander JG. Clinical trials in nursing homes: challenges and practical solutions. In: Cherubini A, Bernabei R, Ferrucci L, Marchionni N, Studenski S, Vellas B, éditeurs. *Clinical trials in older adults* [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2016 [cité 31 mai 2023]. p. 231-53. Disponible sur: <https://onlinelibrary.wiley.com/doi/10.1002/9781118323434.ch13>
4. Gustavson AM, Drake C, Lakin A, Daddato AE, Falvey JR, Capell W, et al. Conducting Clinical Research in Post-acute and Long-term Nursing Home Care Settings: Regulatory Challenges. *Journal of the American Medical Directors Association*. juill 2019;20(7):798-803.
5. Rolland Y, de Souto Barreto P. Research Can Improve Care in the Nursing Home. *Journal of the American Medical Directors Association*. avr 2013;14(4):233-5.
6. Medical Crises in Older People Study Group, Gordon AL, Logan PA, Jones RG, Forrester-Paton C, Mamo JP, et al. A systematic mapping review of Randomized Controlled Trials (RCTs) in care homes. *BMC Geriatr*. déc 2012;12(1):31.
7. Pham T, Bugeja L, Holmes A, Ibrahim JE. Systematic Review of Randomized Controlled Trials in Australian Nursing Homes from 2000 to 2018. *J Am Geriatr Soc*. avr 2021;69(4):1086-93.
8. Poupin P, Ansoborlo M, Caille A, Dibao-Dina C, Fougère B, Giraudeau B. Management of death-related noncompleters in cluster randomized trials carried out in nursing homes: a methodological review. *Journal of Clinical Epidemiology*. nov 2022;151:132-42.
9. Copas AJ, Lewis JJ, Thompson JA, Davey C, Baio G, Hargreaves JR. Designing a stepped wedge trial: three main designs, carry-over effects and randomisation approaches. *Trials*. déc 2015;16(1):352.
10. Koczy P, Becker C, Rapp K, Klie T, Beische D, Büchele G, et al. Effectiveness of a Multifactorial Intervention to Reduce Physical Restraints in Nursing Home Residents: REDUCING PHYSICAL RESTRAINTS IN NURSING HOME RESIDENTS. *Journal of the American Geriatrics Society*. févr 2011;59(2):333-9.
11. Köpke S, Mühlhauser I, Gerlach A, Haut A, Haastert B, Möhler R, et al. Effect of a Guideline-Based Multicomponent Intervention on Use of Physical Restraints in Nursing Homes: A Randomized Controlled Trial. *JAMA* [Internet]. 23 mai 2012 [cité 11 déc 2022];307(20). Disponible sur: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.4517>
12. Eldridge S, Kerry S. *A Practical Guide to Cluster Randomised Trials in Health Services Research*. John Wiley&Sons. 2012.
13. Beard E, Lewis JJ, Copas A, Davey C, Osrin D, Baio G, et al. Stepped wedge randomised controlled trials: systematic review of studies published between 2010 and 2014. *Trials*. déc 2015;16(1):353.

14. Nijs KAND, de Graaf C, Kok FJ, van Staveren WA. Effect of family style mealtimes on quality of life, physical performance, and body weight of nursing home residents: cluster randomised controlled trial. *BMJ*. 20 mai 2006;332(7551):1180-4.
15. Murray DM. Design and Analysis of Group-Randomized Trials. Oxford University Press; 1998.
16. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Step 2b dated 30 August 2017. [https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e9-r1-addendum-estimands-sensitivityanalysis-clinical-trials-guideline-statistical\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e9-r1-addendum-estimands-sensitivityanalysis-clinical-trials-guideline-statistical_en.pdf).
17. Cro S, Kahan BC, Rehal S, Chis Ster A, Carpenter JR, White IR, et al. Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands. *BMJ*. 23 août 2022;e070146.
18. Turner EL, Li F, Gallis JA, Prague M, Murray DM. Review of Recent Methodological Developments in Group-Randomized Trials: Part 1—Design. *Am J Public Health*. juin 2017;107(6):907-15.
19. Donner A, Klar N. Design and Analysis of Cluster Randomization Trials in Health Research. John Wiley & Sons; 2000.
20. Kahan BC, Li F, Copas AJ, Harhay MO. Estimands in cluster-randomized trials: choosing analyses that answer the right question. *International Journal of Epidemiology*. 14 juill 2022;dyac131.
21. Fossey J, Ballard C, Juszcak E, James I, Alder N, Jacoby R, et al. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. *BMJ*. 1 avr 2006;332(7544):756-61.
22. Vossius C, Selbæk G, Šaltytė Benth J, Bergh S. Mortality in nursing home residents: A longitudinal study over three years. Bayer A, éditeur. *PLoS ONE*. 18 sept 2018;13(9):e0203480.
23. Caille A, Kerry S, Tavernier E, Leyrat C, Eldridge S, Giraudeau B. Timeline cluster: a graphical tool to identify risk of bias in cluster randomised trials. *BMJ*. 16 août 2016;i4291.
24. Ukoumunne OC, Thompson SG. Analysis of cluster randomized trials with repeated cross-sectional binary measurements. *Statist Med*. 15 févr 2001;20(3):417-33.
25. Hewitt J, Goodall S, Clemson L, Henwood T, Refshauge K. Progressive Resistance and Balance Training for Falls Prevention in Long-Term Residential Aged Care: A Cluster Randomized Trial of the Sunbeam Program. *Journal of the American Medical Directors Association*. avr 2018;19(4):361-9.
26. Patterson SM, Hughes CM, Crealey G, Cardwell C, Lapane KL. An Evaluation of an Adapted U.S. Model of Pharmaceutical Care to Improve Psychoactive Prescribing for Nursing Home Residents in Northern Ireland (Fleetwood Northern Ireland Study): PHARMACEUTICAL CARE AND PSYCHOACTIVE PRESCRIBING. *Journal of the American Geriatrics Society*. janv 2010;58(1):44-53.

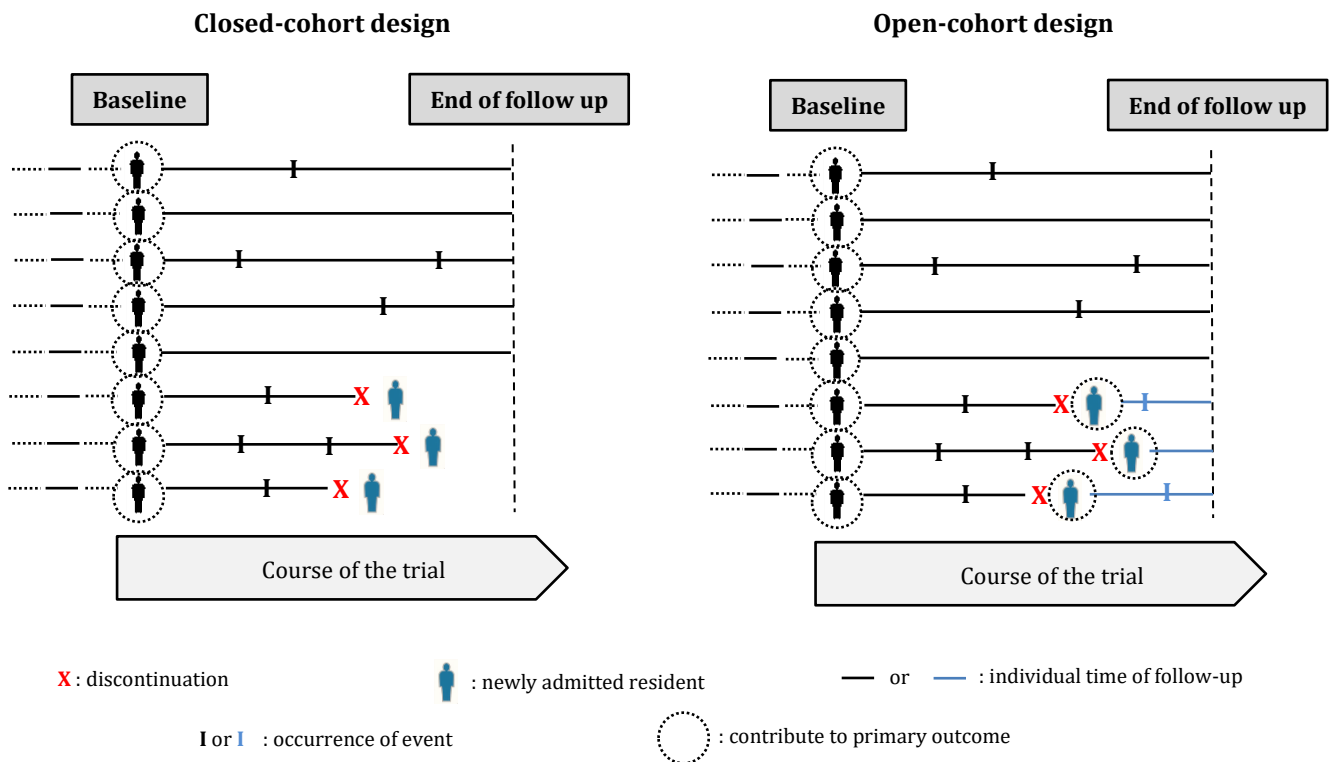
27. Strauven G, Anrys P, Vandael E, Henrard S, De Lepeleire J, Spinewine A, et al. Cluster-Controlled Trial of an Intervention to Improve Prescribing in Nursing Homes Study. *Journal of the American Medical Directors Association*. nov 2019;20(11):1404-11.
28. Davey C, Hargreaves J, Thompson JA, Copas AJ, Beard E, Lewis JJ, et al. Analysis and reporting of stepped wedge randomised controlled trials: synthesis and critical appraisal of published studies, 2010 to 2014. *Trials*. déc 2015;16(1):358.
29. Kannus P, Parkkari J, Niemi S, Pasanen M, Palvanen M, Järvinen M, et al. Prevention of Hip Fracture in Elderly People with Use of a Hip Protector. *N Engl J Med*. 23 nov 2000;343(21):1506-13.
30. Ballard C, Corbett A, Orrell M, Williams G, Moniz-Cook E, Romeo R, et al. Impact of person-centred care training and person-centred activities on quality of life, agitation, and antipsychotic use in people with dementia living in nursing homes: A cluster-randomised controlled trial. *Miller BL, éditeur. PLoS Med*. 6 févr 2018;15(2):e1002500.
31. Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ*. 15 juill 2011;343(jul15 1):d4065-d4065.
32. Toots A, Littbrand H, Holmberg H, Nordström P, Lundin-Olsson L, Gustafson Y, et al. Walking Aids Moderate Exercise Effects on Gait Speed in People With Dementia: A Randomized Controlled Trial. *Journal of the American Medical Directors Association*. mars 2017;18(3):227-33.

## A. Cluster randomized trials with a binary or a continuous primary outcome



In the closed-cohort, only the residents present both at baseline and at time of assessment contribute to the primary outcome measurement. In the open-cohort design, all residents present in the nursing home at time of assessment contribute for primary outcome.

## B. Cluster randomized trials with a count-data primary outcome



The count-data primary outcome is the number of events relative to the cumulative individual time of follow-up figured with the blue lines. In the closed-cohort design, only residents present at baseline contribute to the outcome; in the open-cohort design all the residents, even those who are admitted in the nursing home while the trial is going on, contribute to the outcome.

Author and reference	Objective	Intervention			Primary outcome	A resident newly admitted		Could an open-cohort design be a relevant alternative? (with modifications if necessary)
		Description	Eldridge and Kerry classification	Timing of delivery		Can opt out of the intervention?	Can benefit from intervention effect?	
Nijs [W1]	To assess whether changing mealtime style can improve quality of life	Family-style mealtimes during a 6-month period	Cluster-cluster intervention	Repeated and discrete intervention with cumulative effect	Quality of life of NH residents at month 6	No	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included
Kerse [W2]	To increase mobility and reduce disability and risk of fall	Individualized program (delivered by external nurses and by trained NH staff) with progressive repetitions of activities of daily living	Individual-cluster, external-cluster and professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Mobility, function, quality of life measured at 3 times (baseline, month 6 and month 12) and falls over a 12-month period	Not totally (staff training component)	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included - Residents newly admitted start individual program at admission
Meyer [W3]	To assess whether a tool developed to detect risk of falls can decrease the number of observed falls	NH staff was trained in the use of a fall risk assessment tool to prevent falls and fall injuries	Professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Proportion of participants with at least one fall during the 12-month study period	No	Yes, if exposed during a minimal period	Yes - Residents too recently admitted (to be specified) must not be included - With a count-data as primary outcome
Huizing [W4]	To reduce the use of physical restraints in NH	An educational program delivered to staff over a 2-month period with the weekly intervention of an external nurse specialist	Professional-cluster and external-cluster intervention	Repeated and discrete intervention with cumulative effect	Use of physical restraint and type of physical restraint at baseline and at months 1, 4 and 8	No	Yes	Yes - No change concerning the intervention

<b>Patterson</b> [W5]	To reduce inappropriate psychotropic medications	Monthly visits of external specially trained pharmacists	External-cluster and professional-cluster intervention	Repeated and discrete intervention with cumulative effect	Proportion of residents with $\geq 1$ inappropriate psychoactive medicines at month 12	Not totally (general practitioner collaboration and training)	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included
<b>Koczy</b> [W6]	To reduce the use of physical restraints	A 6-hour training for someone responsible in each NH (asked to introduce the intervention in their facility). Technical aids were also provided	Individual-cluster and professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Complete cessation of physical restraint use on 3 consecutive days 3 months after implementation of the intervention	No	Yes	Yes - No change concerning the intervention
<b>Husebo</b> [W7]	To reduce agitation in NH residents with dementia	A stepwise protocol to optimize individual pain management of NH residents with dementia	Individual-cluster and professional-cluster intervention	Intervention with immediate-onset and non-continuous effect	Agitation measured at baseline and at 3 times: weeks 2, 4, and 8 (end of the intervention) and week 12	No	Yes	Yes - No change concerning the intervention
<b>Resnick</b> [W8]	To prevent the functional decline of NH residents	Intervention with environmental assessment and improvement; education of staff, residents and family	Individual-cluster, external-cluster and professional-cluster intervention	Repeated and discrete intervention with cumulative effect	Psychosocial domains, function, gait and balance and actigraphy, measured at months 4 and 12	Not totally (environment improvement and staff training components)	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included - Residents newly admitted start an individual program at admission
<b>Rapp</b> [W9]	To reduce agitation and psychotropic prescriptions	Training about management of behavioral symptoms, optimization of pharmacological interventions and individual sessions by occupational therapists	Individual-cluster and professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Level of agitation measured at baseline and at month 10	No	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included

<b>Low</b> [W10]	To reduce agitation and increase positive behaviors, positive affects, engagement, and contentment	9 to 12 weekly humor sessions by professional elder-clowns and one staff member trained as a "Laughter Boss"	External-cluster and professional-cluster intervention	Repeated and discrete intervention with cumulative effect	Duration of agitation, episodes of positive behavior, engagement and affects at baseline, at weeks 13 and 26 (end of a 13-week follow-up period)	Not totally (staff member training)	Yes, if exposed during a minimal period	Yes - Intervention should be changed in such a way that humor sessions take place regularly over the complete trial period rather than only over a limited period of time followed by a follow-up period - Residents too recently admitted (to be specified) must not be included
<b>Joranson</b> [W11]	To reduce symptoms of agitation and depression of residents with dementia	Use of a robot (PARO) during group sessions twice a week over 12 weeks and staff training	Individual-cluster and professional-cluster intervention	Repeated and discrete intervention with cumulative effect	Agitation and depression from baseline to month 6	Yes	Yes, if exposed during a minimal period	Yes - Intervention should be changed in such a way that PARO group sessions take place regularly over the complete trial period rather than only over a limited period of time followed by a follow-up period - Residents too recently admitted (to be specified) must not be included
<b>Pieper</b> [W12]	To reduce agitation in residents with advanced dementia	Staff training in the use of a multidisciplinary stepwise protocol design to reduce agitation of NH residents with dementia	Professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Agitation measured 3 and 6 months after the implementation of the intervention	No	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included
<b>Ersek</b> [W13]	To improve pain management	NH staff training to enhance pain management on the basis of the use of an algorithm.	Professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	NH resident pain intensity at 3 times: baseline, end of the intervention and end of a 6-month follow-up	No	Yes	Yes - No change concerning the intervention
<b>Toots</b> [W14]	To improve gait	A 4-months high-intensity functional exercise program with progressive adjustment of load. Participants were individually supervised	Individual-cluster and external-cluster intervention	Repeated and discrete intervention with cumulative effect	4-m usual gait speed measured at baseline, at 4 months (end of the intervention) and at 7 months	Yes	No. Intervention is a physical exercise program with an increasing intensity between 2 group sessions. A newly admitted resident cannot join the group.	No

<b>Chen</b> [W15]	To reduce depression and behavioral problems of wheelchair-bound residents with dementia	A 15-month physical exercise program with progressive training	Individual-cluster intervention	Repeated and discrete intervention with cumulative effect	Depression and behavioral problems measured at baseline and every 3 months	Yes	No. Intervention is a physical exercise program with an increasing intensity between 2 group sessions. A newly admitted resident cannot join the group.	No
<b>Liu</b> [W16]	To improve pain management of residents with dementia	NH staff education and training program in the use of an observational pain management tool	Professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	A score of pain-related behaviors measured at weeks 8 and 16	No	Yes	Yes - No change concerning the intervention
<b>Moyle</b> [W17]	To improve mood and reduce agitation of residents with dementia	Individual sessions with a robot (PARO) 3 times per week over 10 weeks	Individual-cluster intervention	Repeated and discrete intervention with cumulative effect	Changes in level of engagement, mood states and agitation over the 10 weeks of the intervention measured at baseline and at weeks 1, 5 and 10.	Yes	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included
<b>Hewitt</b> [W18]	To prevent falls	A 25-week individually progressive resistance training and balance exercise period followed by a 6-month maintenance period	Individual-cluster intervention	Repeated and discrete intervention with cumulative effect	Rate of falls over the 12-month trial	Yes	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents newly admitted start an individual program at admission - Residents too recently admitted (to be specified) must not be included - No change concerning the outcome
<b>Ballard</b> [W19]	To improve quality of life of NH residents with dementia	A 9-month intervention with staff training in person centered care, tailored person-centered activities and with promotion of antipsychotic review	Professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Quality of life 9 months after the implementation of the intervention	No	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included

<b>Husebo</b> [W20]	To improve quality of life	Training about communication on advance care planning, systematic pain management, medication review and organization of activities	Professional-cluster intervention	Intervention with immediate-onset and with some delay in installation	Change in quality of life from baseline to month 4	No	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included
<b>Strauven</b> [W21]	To reduce the number of inappropriate medications	Repeated interdisciplinary case conferences about inappropriate medications, training program and local interdisciplinary meetings	Professional-cluster intervention	Repeated and discrete intervention with cumulative effect	Proportion of potentially inappropriate medications (PIM) present at baseline and resolved at month 12 and/or no new PIM at month 12	No	Yes, if exposed during a minimal period	Yes - No change concerning the intervention - Residents too recently admitted (to be specified) must not be included - proportion of PIM at month 12 as primary outcome
<b>Slugget</b> [W22]	To reduce medication administration complexity	An external and experienced clinical pharmacist applied a 5-step tool at the individual resident level to reduce medication complexity	External-cluster intervention	Intervention with immediate onset and continuous effect	Total number of charted medication administration times per day for regular medications measured at month 4	Yes	Yes, if exposed during a minimal period	Yes - With more regular interventions of a pharmacist and an assessment at time of admission of a resident newly admitted - Residents too recently admitted must not be included

NH, nursing home

- W1. Nijs KAND, de Graaf C, Kok FJ, van Staveren WA. Effect of family style mealtimes on quality of life, physical performance, and body weight of nursing home residents: cluster randomised controlled trial. *BMJ*. 20 mai 2006;332(7551):1180-4.
- W2. Kerse N, Peri K, Robinson E, Wilkinson T, Radow M v., Kiata L, et al. Does a functional activity programme improve function, quality of life, and falls for residents in long term care? Cluster randomised controlled trial. *BMJ*. 9 oct 2008;337(oct09 3):a1445-a1445.
- W3. Meyer G, Kopke S, Haastert B, Muhlhauser I. Comparison of a fall risk assessment tool with nurses' judgement alone: a cluster-randomised controlled trial. *Age and Ageing*. 1 juill 2009;38(4):417-23.
- W4. Huizing AR, Hamers JPH, Gulpers MJM, Berger MPF. A Cluster-Randomized Trial of an Educational Intervention to Reduce the Use of Physical Restraints with Psychogeriatric Nursing Home Residents: EFFECTS OF INTERVENTION ON PHYSICAL RESTRAINT USE. *Journal of the American Geriatrics Society*. juill 2009;57(7):1139-48.
- W5. Patterson SM, Hughes CM, Crealey G, Cardwell C, Lapane KL. An Evaluation of an Adapted U.S. Model of Pharmaceutical Care to Improve Psychoactive Prescribing for Nursing Home Residents in Northern Ireland (Fleetwood Northern Ireland Study): PHARMACEUTICAL CARE AND PSYCHOACTIVE PRESCRIBING. *Journal of the American Geriatrics Society*. janv 2010;58(1):44-53.
- W6. Koczy P, Becker C, Rapp K, Klie T, Beische D, Büchele G, et al. Effectiveness of a Multifactorial Intervention to Reduce Physical Restraints in Nursing Home Residents: REDUCING PHYSICAL RESTRAINTS IN NURSING HOME RESIDENTS. *Journal of the American Geriatrics Society*. févr 2011;59(2):333-9.
- W7. Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ*. 15 juill 2011;343(jul15 1):d4065-d4065.
- W8. Resnick B, Galik E, Gruber-Baldini A, Zimmerman S. Testing the Effect of Function-Focused Care in Assisted Living. *J Am Geriatr Soc*. déc 2011;59(12):2233-40.
- W9. Rapp MA, Mell T, Majic T, Treusch Y, Nordheim J, Niemann-Mirmehdi M, et al. Agitation in Nursing Home Residents With Dementia (VIDEANT Trial): Effects of a Cluster-Randomized, Controlled, Guideline Implementation Trial. *Journal of the American Medical Directors Association*. sept 2013;14(9):690-5.
- W10. Low LF, Goodenough B, Fletcher J, Xu K, Casey AN, Chenoweth L, et al. The Effects of Humor Therapy on Nursing Home Residents Measured Using Observational Methods: The SMILE Cluster Randomized Trial. *Journal of the American Medical Directors Association*. août 2014;15(8):564-9.
- W11. Jøranson N, Pedersen I, Rokstad AMM, Ihlebæk C. Effects on Symptoms of Agitation and Depression in Persons With Dementia Participating in Robot-Assisted Activity: A Cluster-Randomized Controlled Trial. *Journal of the American Medical Directors Association*. oct 2015;16(10):867-73.
- W12. Pieper MJC, Francke AL, van der Steen JT, Scherder EJA, Twisk JWR, Kovach CR, et al. Effects of a Stepwise Multidisciplinary Intervention for Challenging Behavior in Advanced Dementia: A Cluster Randomized Controlled Trial. *J Am Geriatr Soc*. févr 2016;64(2):261-9.

- W13. Ersek M, Neradilek MB, Herr K, Jablonski A, Polissar N, Du Pen A. Pain Management Algorithms for Implementing Best Practices in Nursing Homes: Results of a Randomized Controlled Trial. *Journal of the American Medical Directors Association*. avr 2016;17(4):348-56.
- W14. Toots A, Littbrand H, Holmberg H, Nordström P, Lundin-Olsson L, Gustafson Y, et al. Walking Aids Moderate Exercise Effects on Gait Speed in People With Dementia: A Randomized Controlled Trial. *Journal of the American Medical Directors Association*. mars 2017;18(3):227-33.
- W15. Chen KM, Kuo CC, Chang YH, Huang HT, Cheng YY. Resistance Band Exercises Reduce Depression and Behavioral Problems of Wheelchair-Bound Older Adults with Dementia: A Cluster-Randomized Controlled Trial. *J Am Geriatr Soc*. févr 2017;65(2):356-63.
- W16. Liu JYW, Lai CKY. Implementation of Observational Pain Management Protocol for Residents With Dementia: A Cluster-RCT. *J Am Geriatr Soc*. mars 2017;65(3):e56-63.
- W17. Moyle W, Jones CJ, Murfield JE, Thalib L, Beattie ERA, Shum DKH, et al. Use of a Robotic Seal as a Therapeutic Tool to Improve Dementia Symptoms: A Cluster-Randomized Controlled Trial. *Journal of the American Medical Directors Association*. sept 2017;18(9):766-73.
- W18. Hewitt J, Goodall S, Clemson L, Henwood T, Refshauge K. Progressive Resistance and Balance Training for Falls Prevention in Long-Term Residential Aged Care: A Cluster Randomized Trial of the Sunbeam Program. *Journal of the American Medical Directors Association*. avr 2018;19(4):361-9.
- W19. Ballard C, Corbett A, Orrell M, Williams G, Moniz-Cook E, Romeo R, et al. Impact of person-centred care training and person-centred activities on quality of life, agitation, and antipsychotic use in people with dementia living in nursing homes: A cluster-randomised controlled trial. Miller BL, éditeur. *PLoS Med*. 6 févr 2018;15(2):e1002500.
- W20. Husebø BS, Ballard C, Aarsland D, Selbaek G, Slettebo DD, Gulla C, et al. The Effect of a Multicomponent Intervention on Quality of Life in Residents of Nursing Homes: A Randomized Controlled Trial (COSMOS). *Journal of the American Medical Directors Association*. mars 2019;20(3):330-9.
- W21. Strauven G, Anrys P, Vandael E, Henrard S, De Lepeleire J, Spinewine A, et al. Cluster-Controlled Trial of an Intervention to Improve Prescribing in Nursing Homes Study. *Journal of the American Medical Directors Association*. nov 2019;20(11):1404-11.
- W22. Sluggett JK, Chen EYH, Ilomäki J, Corlis M, Van Emden J, Hogan M, et al. Reducing the Burden of Complex Medication Regimens: Simplification of Medications Prescribed to Long-term care Residents (SIMPLER) Cluster Randomized Controlled Trial. *Journal of the American Medical Directors Association*. août 2020;21(8):1114-1120.e4.