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## Music Interventions for Dementia and Depression in ELderly care (MIDDEL): Protocol and statistical analysis plan for a multinational cluster-randomised trial

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6 **statistical analysis plan for a multinational cluster-randomised trial**  
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#### 35 36 **Autors' contributions:**

37 CG took the initiative for the study; CG, JE, JA, BS, HMOR, SZ and RR developed the concept and  
38 design; FAB, JT, IC, YCL, GK, DM, TW, EC, AR, MR, AV, HOM, MO, JS, and MG helped to  
39 revise the concept and design. CG drafted the manuscript; JE, JA, RR, and MG helped drafting the  
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45 approved the final version of the manuscript.

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## Abstract

*Introduction:* In older adults, dementia and depression are associated with individual distress and high societal costs. Music interventions such as group music therapy (GMT) and recreational choir singing (RCS) have shown promising effects, but their comparative effectiveness across clinical subgroups is unknown. This trial aims to determine effectiveness of GMT, RCS, and their combination for care home residents and to examine heterogeneity of treatment effects across subgroups.

*Methods and analysis:* This large, pragmatic, multinational cluster-randomised controlled trial with a 2x2 factorial design will compare the effects of GMT, RCS, both, or neither, for care home residents aged 65 years or older with dementia and depressive symptoms. We will randomise 100 care home units with  $\geq 1000$  residents in total across 8 countries. Each intervention will be offered for 6 months (3 months 2x/week followed by 3 months 1x/week), with extension allowed if locally available. The primary outcome will be the change in the Montgomery-Åsberg Depression Rating Scale score at 6 months. Secondary outcomes will include depressive symptoms, cognitive functioning, neuropsychiatric symptoms, psychotropic drug use, caregiver burden, quality of life, mortality, and costs over at least 12 months. The study has 90% power to detect main effects and is also powered to determine interaction effects with gender, severity, and socio-economic status.

*Ethics and dissemination:* Ethical approval has been obtained for one country and will be obtained for all countries. Results will be presented at national and international conferences and published in scientific journals.

*Trial registration numbers:* NCT03496675, ACTRN12618000156280

**Keywords:** group music therapy, recreational choir singing, depression, dementia, non-pharmacological interventions, psychosocial interventions, randomised controlled trial

### Strengths and limitations of this study

- As a multinational trial, this study will provide internationally generalisable results concerning the effects of music interventions in older adults with dementia and depression.
- Based on previous small-scale studies, this trial will have adequate power to determine clinical effects as well as to explain variation in treatment effects in relation to patient characteristics.
- A comprehensive set of core outcomes will be measured, including long-term effects in key variables, with assessor blinding where relevant.
- The trial will also enable modelling of trajectories of change and will thereby contribute to an improved understanding of the mechanisms of music interventions.
- Limitations include the potential bias inherent in cluster-randomised studies if recruitment within clusters is incomplete. Due to the nature of the intervention, care providers and participants cannot be blinded, which may bias measures that rely on their reports.

### Glossary of terms

- Site: an organisational or geographical entity containing several units, for example a care home/residential care facility.
- Unit (or care home unit; also 'cluster'): the smallest organisational unit within a site, where residents live together and are cared for together by staff; each unit is randomised.
- Participant: staff or residents within units who have consented to participate.

## INTRODUCTION

Dementia and depression are highly prevalent and comorbid conditions in older adults and are associated with individual distress and high and rising societal costs. Globally, around 50 million people were living with dementia in 2017; this number is predicted to reach 82 million in 2030 and 152 million in 2050.<sup>1</sup> The societal costs of dementia are increasing from a total estimated worldwide amount of US\$ 818 billion in 2015, about 1.1% of global gross domestic product,<sup>1</sup> to US\$ 1 trillion in 2018.<sup>2</sup> Further, the disease's ramifications for families and carers are significant with respect to financial outlay and carer burden.<sup>3</sup> Dementia is highly prevalent among care home residents; more than half of all Australian care home residents in 2016-2017 had dementia.<sup>4</sup>

Depression is the leading cause of disability worldwide.<sup>5</sup> In older adults, it co-occurs and interacts with dementia in complex ways. Depression can cause cognitive impairment and may increase the risk of developing dementia;<sup>6,7</sup> conversely, depression is very common in the early stages of dementia<sup>6</sup> and often exacerbated by admission to a long-term care facility.<sup>8</sup> Psychotropic medication is only a second-line intervention due to limited efficacy and severe adverse effects, including increased mortality from antipsychotics,<sup>9</sup> but is in practice often used to reduce challenging behaviours in later stages of dementia. Non-pharmacological interventions are available and have some supporting evidence, but further research is needed.<sup>10</sup> Among the most promising non-pharmacological approaches to depression and dementia are music interventions, and in the following section we scope out this evidence.

Music interventions for older adults are based on the notion that music elicits emotional responses and helps to retrieve memories,<sup>11</sup> with recent support from research suggesting that brain regions responsible for processing music, particularly known familiar songs, may be spared even in late-stage dementia.<sup>12,13</sup> They are offered in individual,<sup>14,15</sup> group,<sup>16,17</sup> and community settings<sup>18</sup>



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5 and range from targeted clinical interventions offered by trained music therapists to broader  
6 recreational activities, which may be facilitated by choir leaders or nursing staff. However, overlaps  
7 between the levels of targeting and training do exist. The most common group-based music  
8 interventions may be described as group music therapy (GMT) and recreational choir singing  
9 (RCS), where GMT is offered by a music therapist and may use a variety of activities ranging from  
10 singing through instrumental music making to music listening, whereas RCS is often facilitated by a  
11 choir leader and focuses centrally on singing. Both GMT and RCS rely on a combination of  
12 biological, psychological (cognitive and emotional), and social mechanisms (Figure 1, left part):  
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- 23 • Among the *psychological mechanisms*, *emotional processing*, such as using musical  
24 interactions to reflect on biographical or current relationships, may be most important in  
25 GMT, but is also present to some extent in RCS. *Cognitive processing*, for example through  
26 learning and memorising music pieces, is a central mechanism in RCS and less pronounced  
27 in GMT, although this may vary between cases, groups, or therapists.<sup>16 19 20</sup>  
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- 34 • *Social mechanisms* are important in both GMT and RCS. Meeting as a group may be  
35 important in itself. The function of the group in itself may be relatively more important in  
36 RCS, whereas GMT to a greater extent also relies on the one-to-one relationship between  
37 the therapist and each group member. Another important part of the social mechanisms is  
38 developing a shared sense of mastery and achievement through learning and performing  
39 music pieces, which is more central in RCS than in GMT but may again vary from case to  
40 case.<sup>21</sup>  
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- 50 • *Biological mechanisms* include the physical training effects of singing and other music-  
51 related activities, which may include movement. They are important in both GMT and RCS  
52 but may be more central in RCS.<sup>18 22</sup>  
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5 Systematic reviews of the clinical effects of GMT and RCS have reported mixed results,<sup>10 17 19 20 23</sup>  
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8 <sup>24 25 26 27</sup> possibly owing to the heterogeneity of treatment effects across types of participants and  
9  
10 music interventions. One small trial comparing GMT and RCS directly suggested that the  
11  
12 comparative effects of these music interventions may depend on the comorbidity of dementia and  
13  
14 depressive symptoms.<sup>16</sup> Process-outcome relations of music interventions may be described as  
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16 follows (Figure 1, right part):

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19 • *Emotional processing* in a therapist-client relationship may lead to finding meaning and  
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21 regaining orientation, and thereby to reduced *agitation* and related *neuropsychiatric*  
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23 *symptoms*. Such effects have been suggested in some systematic reviews,<sup>17 26</sup> but not in  
24  
25 others.<sup>19</sup> Reduced agitation may in consequence reduce *burden on staff*<sup>15</sup> and consequently  
26  
27 reduce *sick leave*. This may also help to reduce inappropriate use of *medication*,<sup>21</sup> which is a  
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29 concern in care homes.<sup>28</sup>
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32 • *Cognitive processing* through practicing music may promote or maintain *cognitive*  
33  
34 *functioning* in older adults. Such effects have been shown for active music therapy, but not  
35  
36 music listening, for people with dementia.<sup>20</sup>
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39 • *Emotional processing*, but also social, biological, and cognitive mechanisms may be  
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41 associated with improved mood and reduced *depressive symptoms*. Systematic reviews have  
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43 suggested effects of music therapy on depressive symptoms in older adults in general<sup>29</sup> and  
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45 in people with dementia.<sup>19</sup>
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48 • As downstream outcomes of all four mechanisms and of the intermediate outcomes above,  
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50 one may expect improved *quality of life*, and possibly reduced *mortality*, although these  
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52 effects may be small<sup>30 31</sup> and indirect.<sup>9</sup> Music interventions may also reduce costs by  
53  
54 reducing time spent on treating and alleviating neuropsychiatric symptoms and reducing  
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56 absence by staff.

## Hypotheses

Through these different pathways of GMT and RCS, one may hypothesise differential effects for different outcomes, and therefore for different subgroups of care home residents. Specifically:

- GMT may be more effective than no GMT, and RCS may be more effective than no RCS, with respect to reducing depression symptoms and other outcomes shown in Figure 1.
- GMT and RCS may differ in the pattern of effects across outcome domains, which may be explained by their different mechanisms. For example, GMT may be more effective than RCS for reducing aggression and agitation and may therefore be more beneficial for people with late-stage dementia who often present with these neuropsychiatric symptoms.<sup>32 33</sup> RCS may be more effective than GMT with respect to cognitive functioning. Effects on depression symptoms may be achieved through different pathways (Figure 1), and the strength of those effects may therefore depend on severity or comorbidity.<sup>16</sup>
- When offered together, synergistic effects of GMT and RCS may occur through activation of different pathways.
- Cost-effectiveness may differ accordingly across interventions and subgroups. As RCS is likely to be associated with lower intervention costs, it may have better cost-effectiveness ratio in areas where clinical effects are similar; however, this will depend also on each intervention's effects on use of other treatments and services.

## METHODS AND ANALYSIS

### Design

This large, multinational cluster-randomised controlled trial will be conducted in care homes in Australia, Denmark, Germany, Italy, Netherlands, Norway, Poland, and the UK. The list of study

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5 sites is provided in the trial registration record. We will use a 2x2 factorial design to examine the  
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7 effects of GMT, RCS, both, or neither, for elderly care home residents with dementia and  
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9 depressive symptoms (Figure 2). This design enables investigating the effects of two music  
10  
11 interventions as well as potential synergy effects between them. These may occur between  
12  
13 intervention providers on the cluster level (GMT and RCS providers learning from each other) and  
14  
15 through residents on the individual or cluster level (participants gaining in different ways from the  
16  
17 combination). We will randomise 100 or more care home units (clusters) in eight countries for a  
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19 total of 1000 or more participants.  
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23 Block randomisation (block size 4 clusters) will be used to ensure that each site will have a  
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25 balanced distribution between the interventions. The computer-generated randomisation list will be  
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27 created and kept concealed at the central study office. Only after the eligibility of a care home unit  
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29 is confirmed and eligible participants (residents and staff) within that unit have formally consented  
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31 and completed baseline assessment, will site investigators be informed of the randomisation result  
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33 for that unit. Where possible, a number of care home units will be randomised at the same time,  
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35 which will further ensure allocation concealment.  
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39 Blinding will be difficult to achieve. Intervention providers and study participants cannot be blinded  
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41 to the intervention they receive or provide. However, participants may be unaware of the specific  
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43 differences between GMT and RCS. Plain language summaries and consent forms will use neutral  
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45 wording to maintain equipoise and to avoid expectancy effects. Blinding of assessors will be  
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47 attempted by using assessors external to the care homes, but this may be incomplete because they  
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49 will have to rely on information from proxy informants (care staff who know the participant well)  
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51 due to the inability of most residents to report on themselves. Assessors will remind informants not  
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53 to reveal the unit's allocation to them. At the time of the last assessment, success of blinding will be  
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55 verified by asking assessors whether they inadvertently discovered the unit's allocation.  
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5 GMT and RCS may entail “ripple effects” beyond the individual participants by leading to changes  
6 of the local milieu/culture at the care home unit. These will be assessed by measuring objective and  
7 perceived burden on care staff. The cluster design is ideally suited for that situation because it  
8 facilitates application in a naturalistic setting and avoids some of the problems of individually  
9 randomised trials (such as treatment contamination); it also minimises the additional workload for  
10 care staff. Trial procedures will be tested in the Australian cohort before applying them in the other  
11 countries. The trial will be conducted and reported in accordance with relevant legal frameworks  
12 and research guidelines.<sup>34 35 36 37</sup>

### 23 **Participants**

24 Eligibility is defined on two levels, care home units and individual participants. Participating care  
25 home units will be those that are expected to have at least 10 eligible and consenting residents. Care  
26 home units that are currently providing music-based interventions as part of their usual care  
27 programme will be excluded. Eligible participants will meet all of the following inclusion criteria:

- 34 • aged 65 years or older, resident (full-time, 24h/day) at a participating care home;
- 35 • dementia as indicated by a Clinical Dementia Rating score of 0.5 to 2 and a Mini-Mental  
36 State Examination (MMSE) score of 26 or less;
- 37 • at least mild depressive symptoms, as indicated by a Montgomery-Åsberg Depression  
38 Rating Scale (MADRS) score of at least 8;
- 39 • a clinical diagnosis of dementia according to ICD-10 research criteria;
- 40 • have given written informed consent (may be assent by proxy for those unable to provide  
41 consent themselves).

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55 Clinical diagnosis will be ascertained by a clinician or researcher, based on the ICD-10 dementia  
56 criteria of memory decline; decline in other cognitive abilities; impairment in activities of daily  
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5 living; preserved awareness of the environment; decline in emotional control or motivation or  
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7 change in social behaviour; and more than 6-month duration of memory decline and other cognitive  
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9 symptoms.<sup>38</sup> People with a known diagnosis of schizophrenia or Parkinson's disease or those who  
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11 are known to be severely hearing-impaired, in short-term care, or unable to tolerate sitting in a chair  
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13 for at least part of the sessions, will be excluded. People may however have other clinical diagnoses  
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15 such as pre-morbid substance use disorders or anxiety disorders. The list of exclusion criteria is  
16  
17 intentionally short to ensure generalisability.<sup>37</sup>  
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## 20 21 **Interventions**

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23 *General aspects.* Units in all intervention arms will continue with standard care as locally available.  
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25 In the units allocated to music interventions, GMT, RCS, or both will be provided twice weekly for  
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27 the first three months, followed by weekly sessions for the next three months. Continuation of GMT  
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29 and RCS is allowed after that period, depending on local availability. GMT and RCS sessions will  
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31 be 45 minutes each. In line with usual practice, GMT may be divided into smaller groups (e.g.  
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33 around 5 participants, but this may differ across local contexts), whereas RCS may be conducted in  
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35 larger groups (e.g. with all residents of the unit in one group). GMT and RCS providers will receive  
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37 training and implement intervention guidelines developed in the initial phase of the study. Regular  
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39 exchange and peer supervision for GMT and RCS providers will be organized in conjunction with  
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41 guidelines and training. This will include monthly online or in-person meetings between researchers  
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43 and intervention providers to ensure intervention quality and fidelity, to discuss potential threats  
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45 that might undermine study quality, and to refine the guidelines accordingly. Intervention providers  
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47 will also attend weekly staff meetings at intervention sites where possible, to maximise local  
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49 knowledge transfer and benefit. Data on the resources related to the interventions will be measured  
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51 (number of sessions attended by each participant, duration of each session, non-contact time spent  
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53 by the intervention provider to prepare or follow up a session, recorded by the provider). The  
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55 components of standard care provided will also be recorded (see Outcomes).  
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5 *GMT*. The core principle of GMT is affect regulation through active, reciprocal music making with  
6 the use of singing and musical instruments. This facilitates the relationship between the music  
7 therapist and the person living with dementia, and between participants in the group. The approach  
8 takes into account the level of dementia severity and symptoms that can vary from resident to  
9 resident and from session to session. A core intention of GMT is to meet the psychosocial needs of  
10 each individual resident, which in turn is thought to reduce depressive symptoms and anxiety and to  
11 stimulate overall social and emotional wellbeing.<sup>39 40 41</sup> GMT aims to work in the “here and now”  
12 by responding to participants’ immediate emotional expressions, containing them, and incorporating  
13 them into meaningful musical expressions for therapeutic gain.<sup>21</sup> GMT is provided by a trained  
14 music therapist, who is registered with the appropriate professional association or registration body  
15 in his or her country and should also be skilled as a musician. To facilitate individual relationship-  
16 building, the music therapist will offer each resident an initial 20-minute assessment with the aim of  
17 determining their musical preferences and starting to build individual rapport. The music therapist  
18 will also use other sources to determine the participants’ musical biography, cultural background,  
19 history, personal strengths, resources, and disabilities, and any other information that could be  
20 useful to bring into GMT sessions.  
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40 *RCS*. The core principle of RCS is to sing familiar songs and to provide a familiar musical  
41 environment for participants. Choral singing involves a combination of cognitive, physical, and  
42 psychosocial engagement components.<sup>42</sup> Drawing on the psychosocial aspects of a choir setting,  
43 RCS in this trial aims to foster connectedness in a group either with other older adults residing in  
44 the care homes or family caregivers; emotional wellbeing; and enjoyment of music-making in a  
45 group. Where participants have engaged in music activities in their past, this may also enable the  
46 continuation, as far as possible, of the familiar social experience of music-making in everyday life.  
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5 experiences shared by groups of individuals. Sections of RCS sessions may vary in their focus; for  
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7 example, sessions may focus on developing familiarity with well-known songs; learning and  
8  
9 developing new material as a group; singing rounds to encourage listening to each other; or offering  
10  
11 space for solo singing.<sup>43</sup> The materials can be familiar songs from a range of repertoires, including  
12  
13 but not restricted to festive songs (e.g. birthday songs, Christmas carols), folk songs, traditional,  
14  
15 classical, or popular songs. The selection of songs can vary from country to country, within and  
16  
17 between choir leaders, and may also depend on seasonal and other circumstantial factors. RCS may  
18  
19 be specifically useful in the context of mild to moderately severe dementia, as vocal singing  
20  
21 expressivity is often spared in the presence of cognitive decline. RCS is provided by a skilled  
22  
23 musician with choir leading skills.  
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25

26  
27 *Training and assessment of treatment fidelity.* A challenge in designing manuals for complex  
28  
29 interventions such as GMT and RCS is to standardize the quality of interventions to avoid  
30  
31 unwarranted variation between therapists and countries while preserving the possibility for  
32  
33 meaningful tailoring to local contexts and individuals.<sup>44</sup> This will be addressed by focusing on  
34  
35 general principles rather than fixed behaviours. One of the strengths of these interventions is that  
36  
37 they can be applied in a way that is tailored to fit the current situation/status of the group and its  
38  
39 individual members, and the therapist is able to adapt the therapy. A tentative comparison showing  
40  
41 different and similar principles of GMT and RCS is shown in Table 1. Interventionists will be  
42  
43 trained at all sites, both through local in-person meetings with all intervention providers at each site  
44  
45 and through remote online training across sites. The purpose of this training is to supplement rather  
46  
47 than replace the existing training and expertise of intervention providers. For assessment of  
48  
49 adherence and competence, providers of GMT and RCS will be video-recorded in 3-4 randomly  
50  
51 selected sessions per unit. We will record and analyse the entire session. To avoid performance bias  
52  
53 due to the awareness of being videotaped in a selected session, we will use sham video monitoring  
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55 in other sessions where possible. Videos will be uploaded and stored on a secure central server and  
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5 will be available only to those who check treatment fidelity. Two independent researchers will  
6  
7 assess the different components used by intervention providers and the degree of person-  
8  
9 centeredness (i.e. tailoring of the intervention to the current situation/needs of the group and its  
10  
11 members). This process-related data will help us to understand the mechanisms or effective  
12  
13 ingredients of each intervention.  
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16  
17 *Further development.* While the description above provides general guidance and will form the  
18  
19 basis for fidelity assessment in this study, no consensus guidelines exist for GMT and RCS.  
20  
21 Descriptions in the literature vary in many aspects such as: theoretical frame; session structure;  
22  
23 specific therapeutic goals; types of musical instruments and materials; inclusion of music listening  
24  
25 in addition to active music-making; structured versus improvisational techniques in active music-  
26  
27 making; and adaptation/tailoring to reach each person individually. Therefore, flexible manuals,  
28  
29 including sets of detailed principles and techniques for GMT and RCS, will be developed and  
30  
31 agreed upon by scientific and clinical experts from different countries using a modified Delphi  
32  
33 consensus procedure.  
34  
35

### 36 37 **Outcomes**

38  
39 The study uses a broad array of resident-, staff-, and unit-level outcomes measured at 3 months, 6  
40  
41 months (primary), and 12 months after randomisation (Figure 3). A long-term extension with later  
42  
43 follow-ups is planned but will be beyond the present project. As described above, blinding of  
44  
45 assessors will be attempted but may be incomplete; most residents will be unable to self-rate their  
46  
47 status so that assessors will have to rely on staff who know the resident well as proxy informants.  
48  
49 Where possible, core outcomes ([www.comet-initiative.org](http://www.comet-initiative.org)) for psychosocial intervention research  
50  
51 in dementia care were selected.<sup>45</sup>  
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54  
55 The primary endpoint will be change in the total score of the Montgomery-Åsberg Depression  
56  
57 Rating Scale (MADRS). The MADRS is a 10-item scale where each item is rated from 0 (no  
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5 abnormality to 6 (severe).<sup>46</sup> In the total sum score ranging from 0 to 60, higher scores indicate  
6  
7 higher severity of depressive symptoms. Assessment is based on an interview with the resident  
8  
9 where possible, but where definite answers cannot be elicited from them, all relevant clues as well  
10  
11 as information from other sources should be used as a basis for the rating, in line with usual clinical  
12  
13 practice.<sup>47</sup> The total time of administration is approximately 20 minutes. The MADRS has been  
14  
15 used successfully in previous studies of music interventions<sup>16 48</sup> and has shown higher sensitivity to  
16  
17 change in this population than other scales evaluating depression severity, such as the Cornell Scale  
18  
19 for Depression in Dementia (CSDD).<sup>49</sup>  
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22  
23 Secondary outcomes will include the following:  
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- 26 • Dementia severity including cognitive and functional performance – Clinical Dementia Rating  
27 (CDR), a standard assessment of dementia severity.<sup>50</sup> The CDR is used widely in clinical  
28 settings. Its score is derived from a semi-structured interview with the person living with  
29 dementia and an appropriate caregiver/relative. It rates impairment in each of 6 cognitive  
30 categories (memory, orientation, judgment and problem solving, community affairs, home and  
31 hobbies, and personal care). Its score is useful for characterising and tracking a person's level of  
32 impairment or dementia: 0 = normal; 0.5 = very mild or questionable dementia; 1 = mild  
33 dementia; 2 = moderate dementia; 3 = severe dementia.  
34  
35
- 36 • Neuropsychiatric symptoms – Neuropsychiatric Inventory (NPI), “a *de facto* standard for  
37 measuring neuropsychiatric symptoms in clinical trials”.<sup>45</sup> Developed to assess behaviour in  
38 people living with dementia, the NPI has substantial evidence of validity and reliability and has  
39 been translated into more than 40 languages.<sup>51 52</sup> The NPI uses a screening approach to  
40 minimise administration time, examining and scoring only the domains with positive responses  
41 to screening questions. In this study, the NPI – Questionnaire (NPI-Q)<sup>53</sup> will be used; another  
42 version specific for nursing homes (NPI-NH) was considered but rejected because it is not  
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5 available across all languages. The NPI-Q includes 12 domains where if a symptom is present,  
6 both its severity (from 1= mild to 3=severe) and the associated distress on caregivers (from  
7 0=Not distressing at all to 5=Extreme or very severe) are assessed by the professional carer who  
8 is most familiar with the resident's behaviour. Item scores across the 12 domains are summed,  
9 leading to a total severity score from 0 to 36, where higher values represent higher severity. The  
10 additional total distress score can range from 0 to 60, also with higher values representing  
11 higher distress.<sup>53</sup>

- 21 • Generic quality of life – EuroQol (EQ-5D-5L), a generic health utility measure.<sup>45</sup> The  
22 standardized, non-disease-specific instrument for evaluating health-related quality of life was  
23 developed by the international EuroQol group and is used to derive quality-adjusted life-years  
24 (QALYs). It is based on a descriptive system that defines health in the five dimensions mobility,  
25 self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five  
26 response categories from “no problems” to “extreme problems”, which are combined using  
27 preference weights to form an overall quality of life score ranging from lower than 0 (worse  
28 than death) to 1 (best possible). An additional visual analogue scale indicates today's health on a  
29 scale from 0 (“The worst health you can imagine”) to 100 (“The best health you can imagine”).  
30 As most residents will be unable to self-rate the EQ-5D-5L, the rating will rely on the judgment  
31 of the carer as a proxy. Careful selection of assessment mode (self/proxy/both) and choice of  
32 appropriate proxies is important to ensure the measure's validity in studies of people with  
33 dementia.<sup>54</sup>
- 34 • Disease-specific quality of life – Quality of Life in Alzheimer's Dementia (QOL-AD).<sup>45 55</sup> This  
35 13-item scale with a self-rating and proxy version has demonstrated sensitivity to psychosocial  
36 intervention, correlates with health-utility measures, is widely translated and used  
37 internationally and can be used by people with very low MMSE scores. Items such as “Physical  
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5 health”, “Memory”, or “Ability to do things for fun” are scored on a scale from 1 (poor) to 4  
6  
7 (excellent), resulting in a total score ranging from 13 (worst) to 52 (best).  
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- 10 • All-cause mortality (time to death), as recorded in official electronic registries.
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13 • Any increase in psychotropic drug use: Data on type (ATC Codes N065, N06) of psychotropic  
14 medication used and any increase or decrease over time will be collected from care staff using  
15 the 'medication profile' section of a tailored version of the Client Socio-Demographic and  
16 Service Receipt Inventory (CSSRI).<sup>56</sup> Available electronic health registry data will be used  
17 where possible. Psychotropic medications are sometimes used inappropriately to manage  
18 behavioural symptoms of dementia.<sup>57 58 59</sup> An earlier study suggested that music therapy may  
19 help prevent increase in medication.<sup>14</sup>  
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21  
22 • Costs: Total and component costs of the interventions will be assessed from a societal  
23 perspective, including the cost of the intervention as well as statutory health and social care  
24 services used, using a tailored version of the Client Socio-Demographic and Service Receipt  
25 Inventory (CSSRI).<sup>56</sup>  
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28 • Any adverse events (safety): No adverse effects of music interventions are known from earlier  
29 trials. Intervention providers are trained to work closely with and adapt their interventions to the  
30 needs of participants in order to avoid adverse reactions. Because little knowledge exists about  
31 what the potential adverse events could be, all types of adverse events and serious adverse  
32 events (e.g. unexpected worsening of symptoms), whether related or unrelated to the  
33 interventions, will be reported.  
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51 Staff-level outcomes will be as follows:  
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54 • Subjective perceived burden of care staff: Professional Care Team Burden Scale.<sup>60</sup> The 10-item  
55 scale provides a valid and reliable means of obtaining ratings of burden from formal care teams  
56 working in care homes in order to evaluate different interventions targeted at the reduction of  
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5 burden in care teams. Items are scored on a 5-point scale from 0 (strongly disagree) to 4  
6  
7 (strongly agree), yielding a total sum score from 0 to 40, with higher scores indicating higher  
8  
9 burden.  
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- 12 • Days on sick leave of care staff, as recorded monthly by the employer.
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### 15 **Sample size and test power**

16  
17 There is no consensus on the minimal clinically important difference (MCID)<sup>61</sup> on the MADRS.  
18  
19 Generally, effect sizes in the small- to medium range (i.e. between  $d = 0.20$  and  $0.50$ ) may be  
20  
21 considered relevant.<sup>62</sup> Effect sizes in that range were also found in a previous trial on GMT and  
22  
23 RCS ( $d = 0.33$  at 6 weeks and  $0.49$  at 12 weeks).<sup>16</sup> Studies of other depression scales have used  
24  
25 anchor-based approaches to determine clinically important percent reductions;<sup>63</sup> we will not use  
26  
27 such approaches for the primary analyses, but will include an additional responder analysis.<sup>61</sup>  
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31 The trial has the multiple aim of identifying main effects of GMT versus no GMT and RCS versus  
32  
33 no RCS, interaction effects of GMT and RCS, and predictive effects of clinical characteristics  
34  
35 including severity of dementia; severity of depression; gender; and socio-economic differences.  
36  
37 (Although individual socio-economic differences tend to become more equal amongst residents in a  
38  
39 given care home, they may still exist at the cluster level, as different homes may have different  
40  
41 standards; we will use the average cost of living in each care home unit as a cluster-based proxy  
42  
43 measure for socio-economic status.) Power for interaction effects and subgroup analyses is difficult  
44  
45 to determine because of the unknown distributions and effect sizes of the different variables.  
46  
47 Therefore, the power calculation for the primary outcome was based on the main comparisons of  
48  
49 GMT versus no GMT and RCS versus no RCS. This approach maximises power by fully exploiting  
50  
51 the factorial design. A general two-sided significance level of 5% will be used, leading with  
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53 Bonferroni adjustment to a marginal two-sided level of 2.5%. The power calculation was adjusted  
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55 for cluster effects using the intraclass correlation coefficient (ICC, between 0.01 and 0.10, Figure  
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5 4), assuming average cluster size 10. It was further assumed that attrition, which may occur due to  
6 death, moving to another care home, or withdrawal from the study, will be no higher than 20%  
7  
8 overall. With 100 clusters and 1000 participants randomised, 90% power is reached for effect sizes  
9  
10 between 0.25 and 0.35 (Figure 4). Any further increase beyond this sample size will serve  
11  
12 heterogeneity of treatment effects analyses.  
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### 16 **Statistical analyses**

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19 The statistical analyses will use multivariate longitudinal statistical models, which make optimal  
20 use of the data by using data from all time points at once and can account for the effects of  
21 clustering within care home units and sites. We will use a modified intention-to-treat (ITT)  
22 approach using all available data from all participants as randomised, regardless of the intervention  
23 actually received. Sensitivity analyses using multiple imputation for missing data will enable a full  
24 ITT analysis. Additional per-protocol analysis will address the effects of treatments as actually  
25 received and will complement the ITT analyses. All tests in the study will be two-sided. The general  
26 significance level is set to 0.05. Since there are two comparisons in the primary analysis (GMT vs.  
27 no GMT, RCS vs. no RCS), we will use a marginal Bonferroni level of 0.025. Continuous variables  
28 will be screened for normality. All computations will be done using R.<sup>64</sup>  
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41 Sociodemographic and clinical baseline properties for the groups will be characterized by  
42 descriptive methods (mean (SD), median [range], n (%)) and presented in a table. A similar table  
43 will compare those who dropped out versus those who completed the primary outcome.  
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48 The primary outcome, change of MADRS score from baseline to 6 months, will be assessed by a  
49 linear mixed-effects model (LME).<sup>65</sup> We will fit the unadjusted model for each treatment (RCS vs.  
50 no RCS) as well as the multivariate model containing both treatments as predictors both unadjusted  
51 and adjusted for the interaction between the treatments.  
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57 Secondary analyses of MADRS scores will include the following:  
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- The development of MADRS in the treatment groups over the entire study period will be assessed by a LME including time, treatment type and the interaction of time and treatment type as fixed effects, and participant nested within cluster as random effects. We will use both linear and simple contrasts in the time domain because it is not known whether there is a linear association in time. This will be illustrated by a figure showing the predicted mean of MADRS for each treatment type at each time point with confidence intervals.
- The synergy of the two treatments will be assessed by the LME containing both treatments as well as their interaction as predictors. The interaction in the model will estimate the synergy effect.
- The predictive effect of several covariates (severity of dementia; severity of depression; gender; and socio-economic differences) will be assessed as odds ratios using LMEs for each covariate containing time, treatment type and their interaction as well as the covariate and the interaction between the covariate and the treatment type as predictors. The interaction in the model will estimate the predictive effect.

Secondary endpoints will be analysed as for the primary analysis, using LMEs for continuous outcomes (both resident-level and staff-level). Special considerations apply for the following variables:

- Binary outcomes, including response rates (the proportion of residents improved by at least 50% from their baseline MADRS score), prevalence of medication use, and adverse events, will be assessed as odds ratios using generalised linear mixed models (GLMMs) with a logit link function. The predictive effect of several covariates (severity of dementia; severity of depression; gender; and socio-economic differences) will be assessed by GLMMs for each covariate containing time, treatment type and their interaction as well as the covariate and

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5 the interaction between the covariate and the treatment type as predictors. The interaction in  
6 the model will estimate the predictive effect.  
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10 • Count data (days of sick leave) and cost data are more likely to follow a Poisson distribution  
11 than a normal distribution and will be analysed using the respective GLMMs.  
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  - 13  
14 • Time-to-event data include mortality (time to death of any cause) and will be assessed by  
15 Kaplan-Meier and log-rank- or Breslow tests for differences between the treatment types  
16 and the hazard ratios at 12 months.  
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  - 18  
19 • Loss to follow-up in all other outcomes can be influenced by mortality. Thus, if the survival  
20 analysis shows differences between the groups, it will be meaningful to use a joint  
21 modelling approach which combines the longitudinal models and the survival analysis.<sup>66</sup>  
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28 In addition to analysing effects of interventions as randomised, we will conduct mediator analyses  
29 to examine relations between elements of the therapy approach (mechanisms), direct and  
30 downstream outcomes, as depicted in Figure 1, using structural equation modelling (SEM).  
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### 33 **Cost-effectiveness analysis**

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38 Total and component costs of the interventions and the cost-effectiveness of alternative  
39 interventions will be assessed from a societal perspective. This perspective will cover three  
40 categories of costs: the cost of the intervention, statutory health and social care (and voluntary  
41 sector) service costs, and costs of unpaid carer support. The cost per session for each of the  
42 interventions will be derived employing established approaches used in a compendium of costs and  
43 in published studies.<sup>67 68 69</sup> Information on the time inputs by GMT and RCS providers (for running  
44 sessions and for other activities) will be obtained and valued using information on the midpoint of  
45 the salary scale and employer's national insurance as well as superannuation contributions. The sum  
46 of the staffing contributions and allocations for overheads for each session will then be summed, to  
47 derive a cost per session. To this cost per session, the average number of sessions delivered as part  
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5 of the intervention will be multiplied to derive a cost per intervention. As there is no clear  
6 agreement on how the costs of group interventions should be allocated, we will calculate the cost  
7 per session of each of the interventions on the basis of the participants allocated to each of the  
8 groups, regardless of whether or not the participant attended, because participants who miss a  
9 session are not replaced.

10 Data on statutory services used will be collected using a tailored version of the Client Socio-  
11 Demographic and Service Receipt Inventory (CSSRI),<sup>56</sup> which contains data on the use of health  
12 and other formal care resources and unpaid care. To service and support data we will attach unit  
13 costs reflecting the long-run marginal opportunity costs drawn from available public sources. Costs  
14 per unit of measurement for each service type will be taken from country-specific sources. We will  
15 adjust country-specific costs to Euros using purchasing power parity methods. Costs and outcomes  
16 will be compared for the comparators using extended dominance approaches. In this approach, the  
17 four treatment combinations (GMT, RCS, GMT and RCS, no GMT or RCS) will be ranked by cost,  
18 and if one is dominated (more expensive and less effective than another), it will be excluded from  
19 further analysis, until two therapeutic groups are left on which to explore which of the two groups is  
20 most cost-effective. The cost-effectiveness of one arm over another will be compared by calculating  
21 incremental cost-effectiveness ratios (ICERs) defined as difference in mean costs (Euros spent)  
22 divided by difference in mean effects (QALYs using the EQ-5D-5L; points improved on MADRS  
23 and QOL-AD). Cost-effectiveness acceptability curves will be plotted for each cost-outcome  
24 combination to show the likelihood of one treatment being seen as cost-effective relative to another  
25 for a range of values placed on incremental outcome improvements. Using the net benefit approach,  
26 monetary values of incremental effects and incremental costs will be combined, and net benefit  
27 (NB) derived as:  $NB = \lambda * (effect_b - effect_a) - (cost_b - cost_a)$ , where  $\lambda$  is the willingness-to-pay for a  
28 unit improvement in effectiveness, and subscript 'a' and 'b' denote two candidate treatment arms.  
29 This approach allows costs and outcomes to be considered on the same monetary scale, taking

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5 account of sampling uncertainty and adjusting for baseline covariates and clustering. The cost-  
6 effectiveness threshold which represents a society's willingness to pay for an additional unit of  
7 outcome is used to determine if an intervention is cost-effective. However, this is problematic in  
8 multinational trials as there is no agreed cross-national threshold, and in some countries there is no  
9 established threshold at all. Other studies have used a threshold of Euros 50,000 per QALY, and we  
10 will consider this in the discussion of the results.  
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18 Sensitivity analyses will be conducted to assess the robustness of the results to changes in key  
19 parameters. One of the possible concerns is likely to be the sample size. If the sample size in some  
20 participating countries is too small, their cost-effectiveness estimates are likely to be unreliable. We  
21 shall therefore consider the added value of pooling the information on costs and outcomes in  
22 sensitivity analyses.  
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### 30 **Patient and public involvement**

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32 The development of the research question and study design was informed by the priorities,  
33 experience and preferences of residents and carers. Co-authors in Australia, Denmark, and the UK  
34 have been actively involved in user and advocacy organisations in their countries for a long time  
35 and have discussed interventions, outcomes and the need for research with them. Relatives and  
36 caregivers spoke to the importance of music interventions as a help for carers and people with  
37 dementia, and to the need for high-quality evidence on their effects. Relatives and caregivers are  
38 important for giving persons with dementia a voice when they cannot speak for themselves.  
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48 Co-authors in Australia had significant involvement with residents, as well as with care staff and  
49 care home managers, in discussing and piloting aspects of the study design. While the interventions  
50 were generally perceived as pleasurable rather than burdening, some of the outcome measures were  
51 felt to be burdening and too demanding due to their length or complexity. As a consequence, the  
52 longer Cornell Scale for Depression in Dementia was replaced with the shorter MADRS, and a  
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5 more extensive quality of life scale was removed. Recruitment strategies were discussed and  
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7 adapted in dialogue with care home staff.  
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10 User representatives will continue to be actively involved throughout the conduct of the trial (see  
11  
12 next section). Results will be disseminated to residents, relatives, and care staff via care homes.  
13

14 Results will also be disseminated to national user and advocacy organisations.  
15

### 16 17 **Monitoring and oversight** 18

19  
20 One representative of each recruiting institution will be a member in the *Trial Steering Committee*  
21  
22 (*TSC*). They will be supplemented by other members who are independent of the investigators, their  
23  
24 organisations, funders and sponsors. The TSC will include service users or their relatives and  
25  
26 representatives of stakeholder organisations such as Alzheimer Europe and Dementia Australia. The  
27  
28 TSC will have regular meetings to closely supervise all aspects of the study, including any protocol  
29  
30 amendments, progress of recruitment, and publication plan.  
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33 *Data quality monitoring* will require a risk-based monitoring approach including remote monitoring  
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35 activities performed centrally and on-site monitoring as needed. The monitoring will be performed  
36  
37 according to the monitoring manual to be developed at the beginning of the project. Recruitment  
38  
39 and retention rates will be monitored closely to mitigate the risk of slow recruitment. The number of  
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41 participating care home units in total and in relation to care home units screened; the number of  
42  
43 participating care home residents in total and in relation to residents screened of potential  
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45 participants; and the retention of participants in the study over the trial period will be closely  
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47 monitored.  
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51 A *Data and Safety Monitoring Committee (DSMC)*, consisting of three people with strong  
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53 methodological and clinical expertise who are not otherwise affiliated with the project or its  
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55 institutions, will be appointed early in the international trial. The DSMC will receive regular  
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57 updates on recruitment, uptake of interventions, any unforeseen events, adverse events, and  
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5 immediate information on serious adverse events from the trial statistician. It will have unblinded  
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7 access to study data. Meetings with the DSMC will be on a biannual basis and will consist of an  
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9 open and a closed part. In the open part, the general progress of the trial will be discussed; in the  
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11 closed part, the DSMC will discuss any safety signals with the trial statistician. If issues arise, the  
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13 DSMC will recommend to the TSC on appropriate action.  
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17 All aspects of the study, from intervention fidelity through recruitment, outcome assessment,  
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19 database and data quality management, to data and safety monitoring, will be pilot-tested in one  
20  
21 country (Australia) before being rolled out internationally. The data of the pilot cohort will be  
22  
23 included in the main trial; no statistical adjustments are made because the decision depends only on  
24  
25 feasibility, not on an interim efficacy analysis. Patient-related documents such as the consent form  
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27 will be tested because they may influence how the study is perceived by potential participants,  
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29 relatives and staff.  
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33 To ensure data quality, a trial database will be set up and maintained using a safe server hosted by  
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35 Uni Research (UHEADS) and OpenClinica software. UHEADS is a system for safely storing health  
36  
37 research data developed by Uni Research AS, that accommodates the safe upload, storage and  
38  
39 retrieval of any sensitive research data. OpenClinica is a web-based system for electronic data  
40  
41 capture and clinical data management for multicenter clinical trials, which conforms to relevant  
42  
43 international standards for health research. Uni Research AS runs an open source version of  
44  
45 OpenClinica.  
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## 50 **ETHICS AND DISSEMINATION**

### 51 **Ethical aspects**

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56 Ethical approval has been obtained from the Medicine and Dentistry Human Ethics Sub-Committee  
57  
58 at the University of Melbourne, Australia (approval date: January 12, 2018) and will be obtained  
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5 from the relevant local institutional human research ethics committee at each international site.

6  
7 Local clinical investigators will work on adaptation of study- and patient-related documentation to  
8  
9 meet national ethical requirements.  
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### 11 **Risk management**

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14 Although this is a project with ambitious hypotheses and goals, the known risks to its  
15  
16 implementation and completion are manageable. The main risks are: slow recruitment; low fidelity  
17  
18 of interventions; and low reliability of outcome measurements. To mitigate the first risk, we will  
19  
20 rely on clinical investigators with a track record of successful recruitment as well as relevant  
21  
22 experience and expertise. Slow recruitment at some sites can be compensated by other sites.  
23  
24 Regarding fidelity of interventions, we will develop clear guidance, selection, and ongoing  
25  
26 monitoring of fidelity, as described above. To prevent low reliability of outcomes, we have chosen a  
27  
28 range of outcome measures. Most have been used extensively and will be familiar in most  
29  
30 countries, taking account of recommended core outcome sets. We will rely on highly qualified staff.  
31  
32 We will also conduct tests of inter-rater reliability early in the process to identify and correct any  
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34 potential problems.  
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### 39 **Publication plan**

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41 The report on the main, pre-planned analyses of the primary endpoint and up until the 12-month  
42  
43 follow-up will be submitted to a leading medical journal. The report on the long-term extension will  
44  
45 also be submitted to a leading medical journal.  
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49 Further publications may focus on the following additional aspects and results:

- 50  
51 • Recruitment and retention strategies and recommendations in international, cluster-  
52  
53 randomised multicentre trials of complex interventions in non-medical settings.
- 54  
55 • Development of an MCID for the MADRS based on an existing anchor question.
- 56  
57 • Inter-relations between outcomes and predictive value of early outcomes for later outcomes
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- A comprehensive, integrated systematic review of effects of music interventions addressing heterogeneity of treatment effects systematically, using meta-regression and/or individual participant data meta-analysis methods.
- Clinical descriptions and qualitative research of therapy processes, for example comparing successful with less successful clinical strategies, interactions between clinical characteristics and effective strategies, or qualitative influences on care home staff, their perception of GMT and RCS and how “ripple effects” may influence the overall atmosphere in the home.
- An analysis of barriers and facilitators for implementation, using a combination of qualitative interviews and surveys with questionnaires of known barriers and facilitators.
- Mixed-methods research combining qualitative and quantitative analyses to gain further insights on process-outcome relations and heterogeneity of treatment effects.
- A consensus guideline to indicate the elements of GMT and RCS.
- Translations of key instruments into different languages.

*Data deposition and curation:* The data and meta-data will be stored in a public repository, such as that of the Norwegian Centre for Research Data (NSD).

### **Relevance and benefit to society**

Music interventions are widely used in care homes for both therapeutic and recreational purposes. Although smaller trials have shown promising results, systematic reviews and one head-to-head trial have suggested heterogeneity of treatment effects. This large multinational trial will provide reliable and broadly generalisable knowledge about the effectiveness, mechanisms and heterogeneity of effects of music interventions. It is designed to overcome limitations of previous studies in this field, including small sample sizes, limited numbers of institutions and therapists, and lack of standard care control. By including longer intervention and follow-up periods, it will also

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5 fill knowledge gaps about potential long-term benefits and preconditions for achieving such  
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7 sustained benefits. The results will drive changes in aged care policy and practice and will  
8  
9 contribute to our understanding of the relation between music and health more generally.  
10

### 11 12 **Implications for practice**

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15 In terms of implementation, GMT and RCS differ with respect to scalability. GMT requires  
16  
17 extensive, specialised music therapy training and is typically provided in small groups to facilitate  
18  
19 interaction in a flexible approach. The number of qualified music therapists varies from country to  
20  
21 country, but fluctuates around 1 in 100 000 (about 6000 in Europe, <http://emtc-eu.com>; 5000 in the  
22  
23 USA, [www.cbmt.org](http://www.cbmt.org); 500 in Australia, [www.austmta.org.au](http://www.austmta.org.au)). In the UK, a 2017 survey found that,  
24  
25 of 900 qualified music therapists, fewer than 200 are working with older people; most work with  
26  
27 children and adolescents. Thus, there are insufficient numbers of trained music therapists to  
28  
29 accommodate the needs of all older people who might benefit . However, not all older adults with  
30  
31 dementia and depressive symptoms may need the clinical expertise of trained music therapists. RCS  
32  
33 is more easily scalable as it can be provided by trained musicians and also in larger groups. With  
34  
35 about 1 million choirs and 37 million choir singers in Europe ([www.singingeurope.org](http://www.singingeurope.org)), choral  
36  
37 singing is one of the most popular arts activities. It is therefore a promising approach to meeting the  
38  
39 needs of many older people, subject to the findings of the present study.  
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43  
44 As complex interventions, both GMT and RCS are applied in a range of care homes with different  
45  
46 methods and probably different effects. To ensure best practice, approaches for improvement and  
47  
48 standardisation are embedded into the interventions under investigation. Internationally applicable  
49  
50 guidelines with an international consensus will be defined, applied further developed during the trial  
51  
52 through process evaluation to improve both interventions.  
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54  
55 Based on previous studies, one may expect this pragmatic trial to confirm clinically relevant effects  
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57 of both GMT and RCS, but with strong heterogeneity of these effects depending on clinical  
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5 characteristics. The highly person-centred approach of GMT may be most beneficial to those with  
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7 neuropsychiatric symptoms, which are typical at late-stage dementia. In contrast, social engagement  
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9 is more emphasised in RCS and may help those at earlier stages. The combination of both GMT and  
10  
11 RCS may be best for another subset of residents who need both the social cohesion of a group and  
12  
13 the opportunity to cope with disease, conflicts and untreated trauma in GMT. This knowledge will  
14  
15 increase the impact of music interventions in care homes with a new best practice model on the  
16  
17 expected largest effect of GMT or RCS, and will inform and provide improved education of future  
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19 music therapists and choir leaders working with older adults in care homes and related contexts,  
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21 such as day care centres for people still living at home.  
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### 24 25 **Implications for future research**

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28 As a strongly interdisciplinary project building on contributions from medicine, social sciences, and  
29  
30 humanities, this trial will contribute to strengthening the collaborations between these fields, which  
31  
32 is likely to stimulate new cross-disciplinary investigations. The knowledge constructed from this  
33  
34 trial will inform GMT and RCS service providers of the contextual factors and conditions that  
35  
36 support effectiveness. The recommendations derived from our project will inform intervention  
37  
38 delivery across countries, leading to increased safety, effectiveness and cost-effectiveness, and  
39  
40 improved quality of life for care home residents. The study is unique in that it examines the  
41  
42 interaction of depressive symptoms, cognitive impairment, and dementia in an international sample  
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44 of participants. A critical feature of MIDDEL is its attention to interventions as applied within  
45  
46 different health systems. Results will be valid internationally and will contribute to establishing a  
47  
48 model for future research within different health systems.  
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52 In conclusion, MIDDEL will provide essential knowledge that will inform treatment guidelines  
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54 aimed at improving the lives of the rapidly rising number of people living with dementia across  
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56 countries. Building on previous small-scale randomised controlled trials, this large pragmatic  
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5 effectiveness trial will enhance the use of health technology assessment methodology in the area of  
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7 non-pharmacological (psychosocial) interventions in this area. By improving existing interventions  
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9 and providing evidence-based guidance on their application or discontinuation, it is anticipated to  
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11 have a significant positive impact on people living with dementia, their caregivers, and the health  
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13 system. Furthermore, it will also open several new lines of research and development of  
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15 personalised psychosocial interventions in an area of high and rising public health relevance.  
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## Tables

**Table 1. Differences and similarities of group music therapy and recreational choir singing**

	<b>Group music therapy</b>	<b>Recreational choir singing</b>
<b>Core principles</b>	Meet psychosocial needs Affect regulation and attunement Empathic relationship	Cognitive activation Sing familiar songs, learn new songs Focus on melody, lyrics, and rhythm
<b>Core intentions</b>	Facilitate and improve communication Reduce behavioural and psychological symptoms through regulation of emotions	Positive experience of self and others Stimulate expression, semantic autobiographic memory, and positive affect
<b>Shared principles and intentions</b>	Use and support remaining faculty of musical reminiscence Tailor to individuals Support social experience, stimulate social and emotional wellbeing	
<b>Proscribed</b>	Push participants to achieve goals	Instrumental improvisation
<b>Dementia inclusion criteria</b>	All levels of dementia, but may be divided to form homogeneous groups	All levels of dementia, but primarily mild to moderately severe dementia; mixed groups possible (inclusiveness)
<b>Group size</b>	Approx. 5	Approx. 10
<b>Qualification of intervention provider</b>	Music therapy degree; skilled musician; member of professional music therapy association or registration body	Skilled musician, choir leading skills and relevant further training

## Figure captions

### Figure 1. Mechanisms and outcomes of GMT and RCS

*Note.* GMT – group music therapy; RCS – recreational choir singing.

### Figure 2. Flow of participants through the study: Illustration of the study design

*Note.* CDR – Clinical Dementia Rating; MADRS – Montgomery-Åsberg Depression Rating Scale; GMT – group music therapy; MMSE – Mini-Mental State Examination; MT – music therapy; RCS – recreational choir singing.

### Figure 3. Schedule of enrolment, interventions, and assessments

*Note.* CDR – Clinical Dementia Rating; CSSRI – Client Socio-Demographic and Service Receipt Inventory; d – day; ICD – International Classification of Diseases and Related Health Problems; m – month; MADRS – Montgomery-Åsberg Depression Rating Scale; MMSE – Mini-Mental State Examination; NPI – Neuropsychiatric Inventory; PCTB – Professional Care Team Burden Scale; QOL-AD – Quality of Life-Alzheimer Disease.

### Figure 4. Test power as a function of effect size and ICC.

*Note.* The intraclass correlation coefficient (ICC) describes the relative similarity of participants within units and is typically as low as 0.05 or 0.01;<sup>70</sup> we have added the pessimistic scenario of ICC = 0.10 for completeness only.

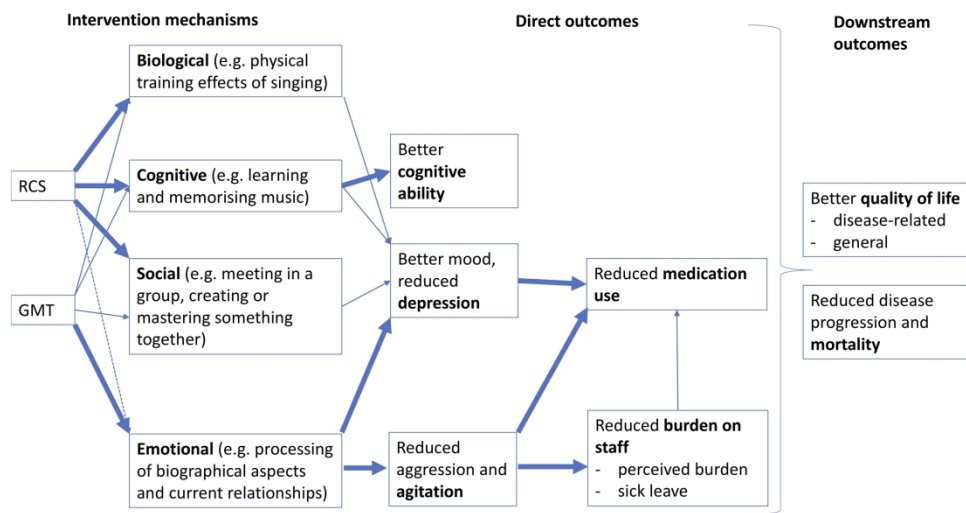


Figure 1. Mechanisms and outcomes of GMT and RCS  
 Note. GMT – group music therapy; RCS – recreational choir singing.

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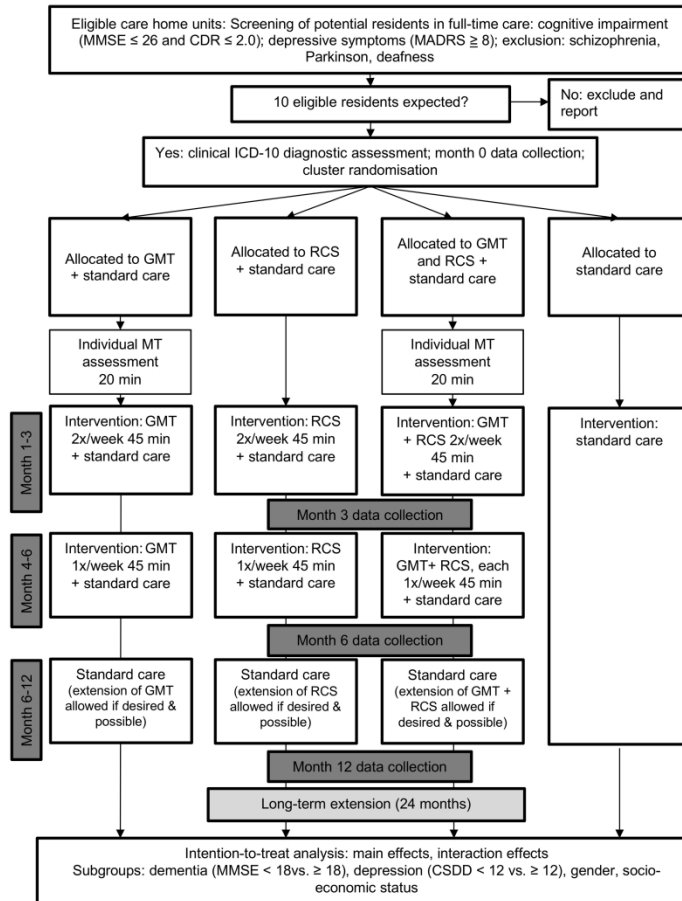


Figure 2. Flow of participants through the study: Illustration of the study design  
 Note. CDR – Clinical Dementia Rating; MADRS – Montgomery-Åsberg Depression Rating Scale; GMT – group music therapy; MMSE – Mini-Mental State Examination; MT – music therapy; RCS – recreational choir singing.

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TIMEPOINT	STUDY PERIOD							Close-out
	Enrol-ment	Alloca-tion	Post-allocation					
	-1d	0	1d	3m	6m	12m	...	
<b>ENROLMENT:</b>								
Unit, residents: Eligibility screen	X							
Residents, staff: informed consent (or assent)	X							
Unit: allocation		X						
<b>INTERVENTIONS:</b>								
Group music therapy			←————→					
Recreational choir singing			←————→					
Standard care			←————→					
<b>ASSESSMENTS:</b>								
Unit baseline: Geographical area Size and costs (CSSRI part 3)	X							
Residents baseline: sociodemographic information (CSSRI part 1); MMSE; dementia diagnosis (ICD-10 code)	X							
Staff baseline: Age, sex	X							
Unit outcomes: Sick leave days			---	---	---	---	---	-----
Residents outcomes: MADRS; CDR; NPI; EQ-5D; QOL-AD; medication and service use (CSSRI part 2)	X			X	X	X	(X)	
Residents outcomes: Adverse events; death			←————→					
Staff outcomes: PCTB; sick leave days	X			X	X	X	(X)	X

Figure 3. Schedule of enrolment, interventions, and assessments

Note. CDR – Clinical Dementia Rating; CSSRI – Client Socio-Demographic and Service Receipt Inventory; d – day; ICD – International Classification of Diseases and Related Health Problems; m – month; MADRS – Montgomery-Åsberg Depression Rating Scale; MMSE – Mini-Mental State Examination; NPI – Neuropsychiatric Inventory; PCTB – Professional Care Team Burden Scale; QOL-AD – Quality of Life-Alzheimer Disease.

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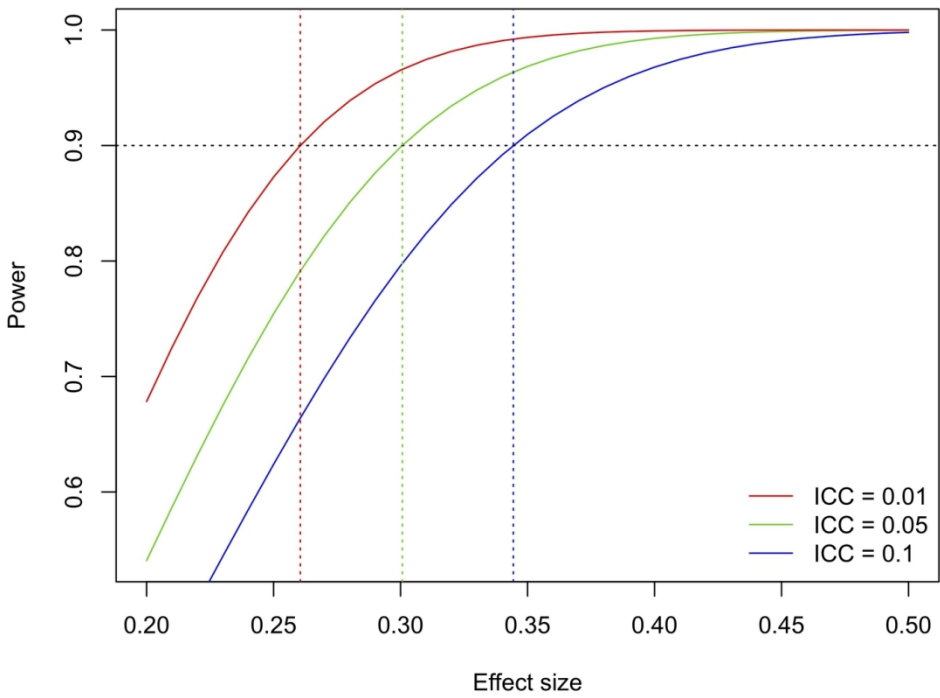


Figure 4. Test power as a function of effect size and ICC.  
Note. The intraclass correlation coefficient (ICC) describes the relative similarity of participants within units and is typically as low as 0.05 or 0.01;70 we have added the pessimistic scenario of ICC = 0.10 for completeness only.

125x88mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____3
	2b	All items from the World Health Organization Trial Registration Data Set	_____3
Protocol version	3	Date and version identifier	_____NA (original)
Funding	4	Sources and types of financial, material, and other support	_____2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1-2
	5b	Name and contact information for the trial sponsor	_____2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____NA/2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____24

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**Introduction**

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____5-7
	6b	Explanation for choice of comparators	_____NA
Objectives	7	Specific objectives or hypotheses	_____8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8-10

**Methods: Participants, interventions, and outcomes**

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____11-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____14-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____Fig. 3

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3	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____18
4				
5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____24-26
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## 8 **Methods: Assignment of interventions (for controlled trials)**

### 9 Allocation:

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12	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____9
13				
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17	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9
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23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA
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## 31 **Methods: Data collection, management, and analysis**

32				
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____14-18
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____24-25
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____19-23
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____20
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____24-25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA/24
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____17, 24-25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____24
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____25-26
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____24-25



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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____10
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____24-25
9				
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____2
12				
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____NA
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____11
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____24, 26-27
21				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____27
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____NA
32				
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
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# BMJ Open

## Music Interventions for Dementia and Depression in ELderly care (MIDDEL): Protocol and statistical analysis plan for a multinational cluster-randomised trial

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Manuscript ID	bmjopen-2018-023436.R1
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<b>Primary Subject Heading</b>:	Geriatric medicine
Secondary Subject Heading:	Mental health, Neurology, Patient-centred medicine, Rehabilitation medicine

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Keywords:	Dementia < NEUROLOGY, Depression & mood disorders < PSYCHIATRY, Care homes, Music therapy, Music interventions, Old age psychiatry < PSYCHIATRY

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Manuscripts

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6 **Music Interventions for Dementia and Depression in ELderly care (MIDDEL): Protocol and**  
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8 **statistical analysis plan for a multinational cluster-randomised trial**  
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40 carers was received from Sarah Yeates and various other people at Caladenia Dementia Care Day  
41 Centre; Bupa; and BlueCross.  
42  
43

#### 44 **Autors' contributions:**

45  
46 CG took the initiative for the study; CG, JE, JA, BS, HMOR, SZ and RR developed the concept and  
47 design; FAB, JT, IC, YCL, GK, DM, TW, EC, AR, MR, AV, HOM, MO, JS, and MG helped to revise  
48 the concept and design. CG drafted the manuscript; JE, JA, RR, and MG helped drafting the  
49 manuscript. BS, JDW, FAB, JT, IC, YCL, SLJ, HMOR, GK, DM, TW, EC, AR, MR, AV, SZ, HOM,  
50 MO, JS, CK revised the manuscript for important intellectual content. CG, FAB, JT, IC, HMOR, and  
51 SZ obtained funding. BS, FAB, JT, IC, YCL, SLJ, HMOR, GK, DM, TW, EC, AR, MR, AV, SZ,  
52 HOM, and MG were involved in setting up the study conduct in each site. JDW, FAB, JT, IC, YCL,  
53 CK, and MG provided administrative, technical, or material support. All authors approved the final  
54 version of the manuscript.  
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## Abstract

*Introduction:* In older adults, dementia and depression are associated with individual distress and high societal costs. Music interventions such as group music therapy (GMT) and recreational choir singing (RCS) have shown promising effects, but their comparative effectiveness across clinical subgroups is unknown. This trial aims to determine effectiveness of GMT, RCS, and their combination for care home residents and to examine heterogeneity of treatment effects across subgroups.

*Methods and analysis:* This large, pragmatic, multinational cluster-randomised controlled trial with a 2x2 factorial design will compare the effects of GMT, RCS, both, or neither, for care home residents aged 65 years or older with dementia and depressive symptoms. We will randomise 100 care home units with  $\geq 1000$  residents in total across 8 countries. Each intervention will be offered for 6 months (3 months 2x/week followed by 3 months 1x/week), with extension allowed if locally available. The primary outcome will be the change in the Montgomery-Åsberg Depression Rating Scale score at 6 months. Secondary outcomes will include depressive symptoms, cognitive functioning, neuropsychiatric symptoms, psychotropic drug use, caregiver burden, quality of life, mortality, and costs over at least 12 months. The study has 90% power to detect main effects and is also powered to determine interaction effects with gender, severity, and socio-economic status.

*Ethics and dissemination:* Ethical approval has been obtained for one country and will be obtained for all countries. Results will be presented at national and international conferences and published in scientific journals.

*Trial registration numbers:* NCT03496675, ACTRN12618000156280

**Keywords:** group music therapy, recreational choir singing, depression, dementia, non-pharmacological interventions, psychosocial interventions, randomised controlled trial

## Strengths and limitations of this study

- As a multinational trial, this study will provide internationally generalisable results concerning the effects of music interventions in older adults with dementia and depression.
- Based on previous small-scale studies, this trial will have adequate power to determine clinical effects as well as to explain variation in treatment effects in relation to patient characteristics.
- A comprehensive set of core outcomes will be measured, including long-term effects in key variables, with assessor blinding where relevant.
- The trial will also enable modelling of trajectories of change and will thereby contribute to an improved understanding of the mechanisms of music interventions.
- Limitations include the potential bias inherent in cluster-randomised studies if recruitment within clusters is incomplete. Due to the nature of the intervention, care providers and participants cannot be blinded, which may bias measures that rely on their reports.

## Glossary of terms

- Site: an organisational or geographical entity containing several units, for example a care home/residential care facility.
- Unit (or care home unit; also ‘cluster’): the smallest organisational unit within a site, where residents live together and are cared for together by staff; each unit is randomised.
- Participant: staff or residents within units who have consented to participate.

## INTRODUCTION

Dementia and depression are highly prevalent and comorbid conditions in older adults and are associated with individual distress and high and rising societal costs. Globally, around 50 million people were living with dementia in 2017; this number is predicted to reach 82 million in 2030 and 152 million in 2050.<sup>1</sup> The societal costs of dementia are increasing from a total estimated worldwide amount of US\$ 818 billion in 2015, about 1.1% of global gross domestic product,<sup>1</sup> to US\$ 1 trillion in 2018.<sup>2</sup> Further, the disease's ramifications for families and carers are significant with respect to financial outlay and carer burden.<sup>3</sup> Dementia is highly prevalent among care home residents; more than half of all Australian care home residents in 2016-2017 had dementia.<sup>4</sup>

Depression is the leading cause of disability worldwide.<sup>5</sup> In older adults, it co-occurs and interacts with dementia in complex ways. Depression can cause cognitive impairment and may increase the risk of developing dementia;<sup>6 7</sup> conversely, depression is very common in the early stages of dementia<sup>6</sup> and often exacerbated by admission to a long-term care facility.<sup>8</sup> Psychotropic medication is only a second-line intervention due to limited efficacy and severe adverse effects, including increased mortality from antipsychotics,<sup>9</sup> but is in practice often used to reduce challenging behaviours in later stages of dementia. Non-pharmacological interventions are available and have some supporting evidence, but further research is needed.<sup>10</sup> Among the most promising non-pharmacological approaches to depression and dementia are music interventions, and in the following section we scope out this evidence.

Music interventions for older adults are based on the notion that music elicits emotional responses and helps to retrieve memories,<sup>11</sup> with recent support from research suggesting that brain regions responsible for processing music, particularly known familiar songs, may be spared even in late-stage dementia.<sup>12 13</sup> They are offered in individual,<sup>14 15</sup> group,<sup>16 17</sup> and community settings<sup>18</sup>



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6 and range from targeted clinical interventions offered by trained music therapists to broader  
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8 recreational activities, which may be facilitated by choir leaders or nursing staff. However, overlaps  
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10 between the levels of targeting and training do exist. The most common group-based music  
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12 interventions may be described as group music therapy (GMT) and recreational choir singing (RCS),  
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14 where GMT is offered by a music therapist and may use a variety of activities ranging from singing  
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16 through instrumental music making to music listening, whereas RCS is often facilitated by a choir  
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18 leader and focuses centrally on singing. Putative mechanisms of GMT and RCS can be described as a  
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20 combination of biological, psychological (cognitive and emotional), and social mechanisms (Figure 1,  
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22 left part), however with strong overlaps:  
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- 26  
27 • Among the *psychological mechanisms*, *emotional processing*, such as using musical  
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29 interactions to regulate affects and to reflect on biographical or current relationships, may be  
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31 most important in GMT, but is also present to some extent in RCS. *Cognitive processing*, for  
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33 example through learning and memorising music pieces, is a central mechanism in RCS and  
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35 less pronounced in GMT, although this may vary between cases, groups, or therapists.<sup>16 19 20</sup>  
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- 39 • *Social mechanisms* are important in both GMT and RCS. Meeting as a group may be important  
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41 in itself. The function of the group in itself may be relatively more important in RCS, whereas  
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43 GMT to a greater extent also relies on the one-to-one relationship between the therapist and  
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45 each group member. Another important part of the social mechanisms is developing a shared  
46  
47 sense of mastery and achievement through learning and performing music pieces, which is more  
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49 central in RCS than in GMT but may again vary from case to case.<sup>21</sup>  
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- 53 • *Biological mechanisms* include the physical training effects of singing and other music-related  
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55 activities, which may include movement. They are important in both GMT and RCS but may be  
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57 more central in RCS.<sup>18 22</sup>  
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6 Systematic reviews of the clinical effects of GMT and RCS have reported mixed results,<sup>10 17 19 20 23 24 25</sup>  
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8 <sup>26 27</sup> possibly owing to the heterogeneity of treatment effects across types of participants and music  
9  
10 interventions. One small trial comparing GMT and RCS directly suggested that the comparative effects  
11  
12 of these music interventions may depend on the comorbidity of dementia and depressive symptoms.<sup>16</sup>  
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14

15 Process-outcome relations of music interventions may be described as follows (Figure 1, right part):  
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17

- 18 • *Emotional processing* in a therapist-client relationship may lead to finding meaning and  
19  
20 regaining orientation, and thereby to reduced *agitation* and related *neuropsychiatric symptoms*.  
21  
22 Such effects have been suggested in some systematic reviews,<sup>17 26</sup> but not in others.<sup>19</sup> Reduced  
23  
24 agitation may in consequence reduce *burden on staff*<sup>5</sup> and consequently reduce *sick leave*. This  
25  
26 may also help to reduce inappropriate use of *medication*,<sup>14</sup> which is a concern in care homes.<sup>28</sup>  
27  
28
- 29 • *Cognitive processing* through practicing music may promote or maintain *cognitive functioning*  
30  
31 in older adults. Such effects have been shown for active music therapy, but not music listening,  
32  
33 for people with dementia.<sup>20</sup>  
34  
35
- 36 • *Emotional processing*, but also social, biological, and cognitive mechanisms may be associated  
37  
38 with improved mood and reduced *depressive symptoms*. Systematic reviews have suggested  
39  
40 effects of music therapy on depressive symptoms in older adults in general<sup>29</sup> and in people with  
41  
42 dementia.<sup>19</sup>  
43  
44
- 45 • As downstream outcomes of all four mechanisms and of the intermediate outcomes above, one  
46  
47 may expect improved *quality of life*, and possibly reduced *mortality*, although these effects may  
48  
49 be small<sup>30 31</sup> and indirect.<sup>9</sup> Music interventions may also reduce costs by reducing time spent on  
50  
51 treating and alleviating neuropsychiatric symptoms and reducing absence by staff.  
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## 57 Hypotheses

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6 Through these different pathways of GMT and RCS, one may hypothesise differential effects for  
7  
8 different outcomes, and therefore for different subgroups of care home residents. Specifically:  
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- 10  
11 • GMT may be more effective than no GMT, and RCS may be more effective than no RCS, with  
12 respect to reducing depression symptoms and other outcomes shown in Figure 1.  
13
- 14  
15 • GMT and RCS may differ in the pattern of effects across outcome domains, which may be  
16 explained by their different mechanisms. For example, GMT may be more effective than RCS  
17 for reducing aggression and agitation and may therefore be more beneficial for people with late-  
18 stage dementia who often present with these neuropsychiatric symptoms.<sup>32 33</sup> RCS may be more  
19 effective than GMT with respect to cognitive functioning. Effects on depression symptoms may  
20 be achieved through different pathways (Figure 1), and the strength of those effects may  
21 therefore depend on severity or comorbidity.<sup>16</sup>  
22
- 23  
24 • When offered together, synergistic effects of GMT and RCS may occur through activation of  
25 different pathways.  
26
- 27  
28 • Cost-effectiveness may differ accordingly across interventions and subgroups. As RCS is likely  
29 to be associated with lower intervention costs, it may have better cost-effectiveness ratio in  
30 areas where clinical effects are similar; however, this will depend also on each intervention's  
31 effects on use of other treatments and services.  
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## 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 **METHODS AND ANALYSIS**

### 52 53 **Design**

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6 This large, multinational cluster-randomised controlled trial will be conducted in care homes in  
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8 Australia, Denmark, Germany, Italy, Netherlands, Norway, Poland, and the UK. The list of study sites  
9  
10 is provided in the trial registration record. MIDDEL uses a 2x2 factorial design to examine the effects  
11  
12 of GMT, RCS, both, or neither, for elderly care home residents with dementia and depressive  
13  
14 symptoms (Figure 2). This design enables investigating the effects of two music interventions as well  
15  
16 as potential synergy effects between them. These may occur between intervention providers on the  
17  
18 cluster level (GMT and RCS providers learning from each other) and through residents on the  
19  
20 individual or cluster level (participants gaining in different ways from the combination). We will  
21  
22 randomise 100 or more care home units (clusters) in eight countries for a total of 1000 or more  
23  
24 participants. Recruitment started in July 2018, and primary completion is anticipated for April 2020.

25  
26  
27 Block randomisation (block size 4 clusters) will be used to ensure that each site will have a balanced  
28  
29 distribution between the interventions. The computer-generated randomisation list will be created and  
30  
31 kept concealed at the central study office. Only after the eligibility of a care home unit is confirmed and  
32  
33 eligible participants (residents and staff) within that unit have formally consented and completed  
34  
35 baseline assessment, will site investigators be informed of the randomisation result for that unit. Where  
36  
37 possible, a number of care home units will be randomised at the same time, which will further ensure  
38  
39 allocation concealment.  
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45  
46 Blinding will be difficult to achieve. Intervention providers and study participants cannot be blinded to  
47  
48 the intervention they receive or provide. However, participants may be unaware of the specific  
49  
50 differences between GMT and RCS. Plain language summaries and consent forms will use neutral  
51  
52 wording to maintain equipoise and to avoid expectancy effects. Blinding of assessors (those evaluating  
53  
54 outcomes) will be attempted by using assessors external to the care homes, but this may be incomplete  
55  
56 because they will have to rely on information from proxy informants (care staff who know the  
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6 participant well) due to the inability of most residents to report on themselves. Assessors will remind  
7  
8 informants not to reveal the unit's allocation to them. At the time of the last assessment, success of  
9  
10 blinding will be verified by asking assessors whether they inadvertently discovered the unit's  
11  
12 allocation.  
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15  
16 GMT and RCS may entail “ripple effects” beyond the individual participants by leading to changes of  
17  
18 the local milieu/culture at the care home unit.<sup>15 34</sup> These will be assessed by measuring objective and  
19  
20 perceived burden on care staff. The cluster design is ideally suited for that situation because it  
21  
22 facilitates application in a naturalistic setting and avoids some of the problems of individually  
23  
24 randomised trials (such as treatment contamination); it also minimises the additional workload for care  
25  
26 staff. Trial procedures will be tested in the Australian cohort before applying them in the other  
27  
28 countries. The trial will be conducted and reported in accordance with relevant legal frameworks and  
29  
30 research guidelines.<sup>35 36 37 38</sup>  
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33

### 34 **Participants**

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36  
37 Eligibility is defined on two levels, care home units and individual participants. Participating care home  
38  
39 units will be those that are expected to have at least 10 eligible and consenting residents. Care home  
40  
41 units that are currently providing music-based interventions as part of their usual care programme will  
42  
43 be excluded. Eligible participants will meet all of the following inclusion criteria:  
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46

- 47 • aged 65 years or older, resident (full-time, 24h/day) at a participating care home;
- 48
- 49
- 50 • dementia as indicated by a Clinical Dementia Rating score of 0.5 to 2 and a Mini-Mental State  
51  
52 Examination (MMSE) score of 26 or less;
- 53
- 54
- 55 • at least mild depressive symptoms, as indicated by a Montgomery-Åsberg Depression Rating  
56  
57 Scale (MADRS) score of at least 8;
- 58
- 59

- a clinical diagnosis of dementia according to ICD-10 research criteria;
- have given written informed consent (may be assent by proxy for those unable to provide consent themselves).

Clinical diagnosis will be ascertained by a clinician or researcher, based on the ICD-10 dementia criteria of memory decline; decline in other cognitive abilities; impairment in activities of daily living; preserved awareness of the environment; decline in emotional control or motivation or change in social behaviour; and more than 6-month duration of memory decline and other cognitive symptoms.<sup>39</sup> People with a known diagnosis of schizophrenia or Parkinson's disease or those who are known to be severely hearing-impaired, in short-term care, or unable to tolerate sitting in a chair for at least part of the sessions, will be excluded. People may however have other clinical diagnoses such as pre-morbid substance use disorders or anxiety disorders. The list of exclusion criteria is intentionally short to ensure generalisability.<sup>38</sup> Residents will always be provided information about the study, and their ability for consent will be assessed directly, before turning to proxies (next of kin/legal representative/carer) for written informed assent. In case of doubt, consent/assent will be provided by both resident and proxy. Residents unable to provide written consent will still be asked if they agree to the interventions and assessments when these begin.<sup>40</sup>

## **Interventions**

Units in all intervention arms will continue with standard care as locally available. In the units allocated to music interventions, GMT, RCS, or both will be provided twice weekly for the first three months, followed by weekly sessions for the next three months. Continuation of GMT and RCS is allowed after that period, depending on local availability. Data on the resources related to the interventions will be measured (number of sessions attended by each participant, duration of each

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6 session, non-contact time spent by the intervention provider to prepare or follow up a session, recorded  
7  
8 by the provider). The components of standard care provided will also be recorded (see Outcomes).

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10  
11 GMT and RCS sessions will be 45 minutes each. In line with usual practice, GMT may be divided into  
12  
13 smaller groups (e.g. around 5 participants, but this may differ across local contexts), whereas RCS may  
14  
15 be conducted in larger groups (e.g. with all residents of the unit in one group).

16  
17  
18 *GMT.* A core principle of GMT is affect regulation through active, reciprocal music making with the  
19  
20 use of singing and musical instruments (Table 1). This facilitates the relationship between the music  
21  
22 therapist and the person living with dementia, and between participants in the group. Another core  
23  
24 principle of GMT is to meet the psychosocial needs of each individual resident, which in turn is  
25  
26 thought to reduce depressive symptoms and anxiety and to stimulate overall social and emotional  
27  
28 wellbeing.<sup>41 42 43</sup> GMT aims to work in the “here and now” by responding to participants’ immediate  
29  
30 emotional expressions, containing them, and incorporating them into meaningful musical expressions  
31  
32 for therapeutic gain.<sup>21</sup> GMT is provided by a trained music therapist, who is registered with the  
33  
34 appropriate professional association or registration body in his or her country and should also be skilled  
35  
36 as a musician. To facilitate individual relationship-building, the music therapist will offer each resident  
37  
38 an initial 20-minute assessment with the aim of determining their musical preferences and starting to  
39  
40 build individual rapport. The music therapist will also use other sources to determine the participants’  
41  
42 musical biography, cultural background, history, personal strengths, resources, and disabilities, and any  
43  
44 other information that could be useful to bring into GMT sessions.

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51 *RCS.* A core principle of RCS is to sing familiar songs and to provide a familiar musical environment  
52  
53 for participants (Table 1). Choral singing involves a combination of cognitive, physical, and  
54  
55 psychosocial engagement components.<sup>44</sup> Drawing on the psychosocial aspects of a choir setting, RCS  
56  
57 in this trial aims to foster connectedness in a group either with other older adults residing in the care  
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59

homes or family caregivers; emotional wellbeing; and enjoyment of music-making in a group.

Biographically and culturally grounded song materials are used with the central goal of stimulating positive experiences shared by groups of individuals. Where participants have engaged in music activities in their past, this may also enable the continuation, as far as possible, of the familiar social experience of music-making in everyday life. Sections of RCS sessions may vary in their focus; for example, sessions may focus on developing familiarity with well-known songs; learning and developing new material as a group; singing rounds to encourage listening to each other; or offering space for solo singing.<sup>45</sup> The materials can be familiar songs from a range of repertoires, including but not restricted to festive songs (e.g. birthday songs, Christmas carols), folk songs, traditional, classical, or popular songs. The selection of songs can vary from country to country, within and between choir leaders, and may also depend on seasonal and other circumstantial factors. RCS is provided by a skilled musician with choir leading skills.

*Training and assessment of treatment fidelity.* GMT and RCS providers will receive training and implement intervention guidelines developed in the initial phase of the study. Regular exchange and peer supervision for GMT and RCS providers will be organized in conjunction with guidelines and training. This will include monthly online or in-person meetings between researchers and intervention providers to ensure intervention quality and fidelity, to discuss potential threats that might undermine study quality, and to refine the guidelines accordingly. Intervention providers will also attend weekly staff meetings at intervention sites where possible, to maximise local knowledge transfer and benefit. Manuals for complex interventions need to standardize the quality of interventions to avoid unwarranted variation between therapists and countries while preserving the possibility for meaningful tailoring to local contexts and individuals.<sup>46</sup> This will be addressed by focusing on general principles rather than fixed behaviours. Both GMT and RCS should be tailored to fit the current situation/status of



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6 the group and its individual members. Interventionists will be trained at all sites, both through local in-  
7  
8 person meetings with all intervention providers at each site and through remote online training across  
9  
10 sites. The purpose of this training is to supplement rather than replace the existing training and  
11  
12 expertise of intervention providers. For assessment of adherence and competence, providers of GMT  
13  
14 and RCS will be video-recorded in 3-4 randomly selected sessions per unit. We will record and analyse  
15  
16 the entire session. To avoid performance bias due to the awareness of being videotaped in a selected  
17  
18 session, we will use sham video monitoring in other sessions where possible. Videos will be uploaded  
19  
20 and stored on a secure central server and will be available only to those who check treatment fidelity.  
21  
22 Two independent researchers will assess the different components used by intervention providers and  
23  
24 the degree of person-centeredness (i.e. tailoring of the intervention to the current situation/needs of the  
25  
26 group and its members). This process-related data will help us to understand the mechanisms or  
27  
28 effective ingredients of each intervention.  
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34 *Further development.* While the description above provides general guidance and will form the basis  
35  
36 for fidelity assessment in this study, no consensus guidelines exist for GMT and RCS. Descriptions in  
37  
38 the literature vary in many aspects such as: theoretical frame; session structure; specific therapeutic  
39  
40 goals; types of musical instruments and materials; inclusion of music listening in addition to active  
41  
42 music-making; structured versus improvisational techniques in active music-making; and  
43  
44 adaptation/tailoring to reach each person individually. Therefore, flexible manuals, including sets of  
45  
46 detailed principles and techniques for GMT and RCS, will be developed and agreed upon by scientific  
47  
48 and clinical experts from different countries using a modified Delphi consensus procedure.  
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### 53 **Outcomes**

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56 The study uses a broad array of resident-, staff-, and unit-level outcomes measured at 3 months, 6  
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58 months (primary), and 12 months after randomisation (Figure 3). A long-term extension with later  
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6 follow-ups is planned separately. Where possible, core outcomes ([www.comet-initiative.org](http://www.comet-initiative.org)) for  
7  
8 psychosocial intervention research in dementia care, that are widely used and available across the  
9  
10 languages of the trial, were selected.<sup>47</sup>

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12  
13 The primary endpoint will be change in the total score of the Montgomery-Åsberg Depression Rating  
14  
15 Scale (MADRS). The MADRS is a 10-item scale where each item is rated from 0 (no abnormality to 6  
16  
17 (severe)).<sup>48</sup> In the total sum score ranging from 0 to 60, higher scores indicate higher severity of  
18  
19 depressive symptoms. Assessment is based on an interview with the resident where possible, but where  
20  
21 definite answers cannot be elicited from them, all relevant clues as well as information from other  
22  
23 sources should be used as a basis for the rating, in line with usual clinical practice.<sup>49</sup> The total time of  
24  
25 administration is approximately 20 minutes. The MADRS has been used successfully in previous  
26  
27 studies of music interventions.<sup>16 50</sup> It has shown high reliability and validity, and its sensitivity to  
28  
29 change compares favourably to other scales evaluating depression severity in this population, such as  
30  
31 the Cornell Scale for Depression in Dementia (CSDD).<sup>49 51</sup>

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37 Secondary outcomes will include the following:

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40 • Dementia severity including cognitive and functional performance – Clinical Dementia Rating  
41  
42 (CDR), a standard assessment of dementia severity.<sup>52</sup> The CDR is used widely in clinical settings.  
43  
44 Its score is derived from a semi-structured interview with the person living with dementia and an  
45  
46 appropriate caregiver/relative. It rates impairment in each of 6 cognitive categories (memory,  
47  
48 orientation, judgment and problem solving, community affairs, home and hobbies, and personal  
49  
50 care). Its score is useful for characterising and tracking a person's level of impairment or dementia:  
51  
52 0 = normal; 0.5 = very mild or questionable dementia; 1 = mild dementia; 2 = moderate dementia; 3  
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54 = severe dementia.  
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6 • Neuropsychiatric symptoms – Neuropsychiatric Inventory (NPI), “a *de facto* standard for  
7 measuring neuropsychiatric symptoms in clinical trials”.<sup>47</sup> Developed to assess behaviour in people  
8 living with dementia, the NPI has substantial evidence of validity and reliability and has been  
9 translated into more than 40 languages.<sup>53 54</sup> The NPI uses a screening approach to minimise  
10 administration time, examining and scoring only the domains with positive responses to screening  
11 questions. In this study, the NPI – Questionnaire (NPI-Q)<sup>55</sup> will be used; another version specific  
12 for nursing homes (NPI-NH) was considered but rejected because it is not available across all  
13 languages. The NPI-Q includes 12 domains where if a symptom is present, both its severity (from  
14 1=mild to 3=severe) and the associated distress on caregivers (from 0=Not distressing at all to  
15 5=Extreme or very severe) are assessed by the professional carer who is most familiar with the  
16 resident’s behaviour. Item scores across the 12 domains are summed, leading to a total severity  
17 score from 0 to 36, where higher values represent higher severity. The additional total distress score  
18 can range from 0 to 60, also with higher values representing higher distress.<sup>55</sup>  
19  
20 • Generic quality of life – EuroQol (EQ-5D-5L), a generic health utility measure.<sup>47</sup> The standardized,  
21 non-disease-specific instrument for evaluating health-related quality of life was developed by the  
22 international EuroQol group and is used to derive quality-adjusted life-years (QALYs). It is based  
23 on a descriptive system that defines health in the five dimensions mobility, self-care, usual  
24 activities, pain/discomfort, and anxiety/depression. Each dimension has five response categories  
25 from “no problems” to “extreme problems”, which are combined using preference weights to form  
26 an overall quality of life score ranging from lower than 0 (worse than death) to 1 (best possible). An  
27 additional visual analogue scale indicates today’s health on a scale from 0 (“The worst health you  
28 can imagine”) to 100 (“The best health you can imagine”). As most residents will be unable to self-  
29 rate the EQ-5D-5L, the rating will rely on the judgment of the carer as a proxy. Careful selection of  
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6 assessment mode (self/proxy/both) and choice of appropriate proxies is important to ensure the  
7  
8 measure's validity in studies of people with dementia.<sup>56</sup>  
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11 • Disease-specific quality of life – Quality of Life in Alzheimer's Dementia (QOL-AD).<sup>47 57</sup> This 13-  
12  
13 item scale with a self-rating and proxy version has demonstrated sensitivity to psychosocial  
14  
15 intervention, correlates with health-utility measures, is widely translated and used internationally  
16  
17 and can be used by people with very low MMSE scores. Items such as "Physical health",  
18  
19 "Memory", or "Ability to do things for fun" are scored on a scale from 1 (poor) to 4 (excellent),  
20  
21 resulting in a total score ranging from 13 (worst) to 52 (best).  
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- 24  
25 • All-cause mortality (time to death), as recorded in official electronic registries.  
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29 • Any increase in psychotropic drug use: Data on type (ATC Codes N065, N06) of psychotropic  
30  
31 medication used and any increase or decrease over time will be collected from care staff using the  
32  
33 'medication profile' section of a tailored version of the Client Socio-Demographic and Service  
34  
35 Receipt Inventory (CSSRI).<sup>58</sup> Available electronic health registry data will be used where possible.  
36  
37 Psychotropic medications are sometimes used inappropriately to manage behavioural symptoms of  
38  
39 dementia.<sup>59 60 61</sup> An earlier study suggested that music therapy may help prevent increase in  
40  
41 medication.<sup>14</sup>  
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- 44  
45 • Costs: Total and component costs of the interventions will be assessed from a societal perspective,  
46  
47 including the cost of the intervention as well as statutory health and social care services used, using  
48  
49 a tailored version of the CSSRI.<sup>58</sup>  
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- 52  
53 • Any adverse events (safety): No adverse effects of music interventions are known from earlier  
54  
55 trials. Intervention providers are trained to work closely with and adapt their interventions to the  
56  
57 needs of participants in order to avoid adverse reactions. Because little knowledge exists about  
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6 what the potential adverse events could be, all types of adverse events and serious adverse events  
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8 (e.g. unexpected worsening of symptoms), whether related or unrelated to the interventions, will be  
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10 reported.  
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13 Staff-level outcomes will be as follows:  
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- 16 • Subjective perceived burden of care staff: Professional Care Team Burden Scale.<sup>62</sup> The 10-item  
17 scale provides a valid and reliable means of obtaining ratings of burden from formal care teams  
18 working in care homes in order to evaluate different interventions targeted at the reduction of  
19 burden in care teams. Items are scored on a 5-point scale from 0 (strongly disagree) to 4 (strongly  
20 agree), yielding a total sum score from 0 to 40, with higher scores indicating higher burden.  
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- 23 • Days on sick leave of care staff, as recorded monthly by the employer.  
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### 31 **Sample size and test power** 32 33

34 There is no consensus on the minimal clinically important difference (MCID)<sup>63</sup> on the MADRS.  
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36 Generally, effect sizes in the small- to medium range (i.e. between  $d = 0.20$  and  $0.50$ ) may be  
37 considered relevant.<sup>64</sup> Effect sizes in that range were also found in a previous trial on GMT and RCS ( $d$   
38 =  $0.33$  at 6 weeks and  $0.49$  at 12 weeks).<sup>16</sup> Studies of other depression scales have used anchor-based  
39 approaches to determine clinically important percent reductions;<sup>65</sup> we will not use such approaches for  
40 the primary analyses, but will include an additional responder analysis.<sup>63</sup>  
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48 The trial has the multiple aim of identifying main effects of GMT versus no GMT and RCS versus no  
49 RCS, interaction effects of GMT and RCS, and predictive effects of clinical characteristics including  
50 severity of dementia; severity of depression; gender; and socio-economic differences. (Although  
51 individual socio-economic differences tend to become more equal amongst residents in a given care  
52 home, they may still exist at the cluster level, as different homes may have different standards; we will  
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6 use the average cost of living in each care home unit as a cluster-based proxy measure for socio-  
7  
8 economic status.) Power for interaction effects and subgroup analyses is difficult to determine because  
9  
10 of the unknown distributions and effect sizes of the different variables. Therefore, the power  
11  
12 calculation for the primary outcome was based on the main comparisons of GMT versus no GMT and  
13  
14 RCS versus no RCS. This approach maximises power by fully exploiting the factorial design. A  
15  
16 general two-sided significance level of 5% will be used, leading with Bonferroni adjustment to a  
17  
18 marginal two-sided level of 2.5%. The power calculation was adjusted for cluster effects using the  
19  
20 intraclass correlation coefficient (ICC, between 0.01 and 0.10, Figure 4), assuming average cluster size  
21  
22 10. It was further assumed that attrition, which may occur due to death, moving to another care home,  
23  
24 or withdrawal from the study, will be no higher than 20% overall. With 100 clusters and 1000  
25  
26 participants randomised, 90% power is reached for effect sizes between 0.25 and 0.35 (Figure 4). Any  
27  
28 further increase beyond this sample size will serve heterogeneity of treatment effects analyses.  
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### 33 34 **Statistical analyses**

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37 The statistical analyses will use multivariate longitudinal statistical models, which make optimal use of  
38  
39 the data by using data from all time points at once and can account for the effects of clustering within  
40  
41 care home units and sites. We will use a modified intention-to-treat (ITT) approach using all available  
42  
43 data from all participants as randomised, regardless of the intervention actually received. Sensitivity  
44  
45 analyses using multiple imputation for missing data will enable a full ITT analysis. Additional per-  
46  
47 protocol analysis will address the effects of treatments as actually received and will complement the  
48  
49 ITT analyses. All tests in the study will be two-sided. The general significance level is set to 0.05.  
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51  
52 Since there are two comparisons in the primary analysis (GMT vs. no GMT, RCS vs. no RCS), we will  
53  
54 use a marginal Bonferroni level of 0.025. Continuous variables will be screened for normality. All  
55  
56 computations will be done using R.<sup>66</sup>  
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6 Sociodemographic and clinical baseline properties for the groups will be characterized by descriptive  
7 methods (mean (SD), median [range], n (%)) and presented in a table. A similar table will compare  
8 those who dropped out versus those who completed the primary outcome.  
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12  
13 The primary outcome, change of MADRS score from baseline to 6 months, will be assessed by a linear  
14 mixed-effects model (LME).<sup>67</sup> We will fit the unadjusted model for each treatment (RCS vs. no RCS)  
15 as well as the multivariate model containing both treatments as predictors both unadjusted and adjusted  
16 for the interaction between the treatments.  
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23 Secondary analyses of MADRS scores will include the following:  
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- 26 • The development of MADRS in the treatment groups over the entire study period will be  
27 assessed by a LME including time, treatment type and the interaction of time and treatment type  
28 as fixed effects, and participant nested within cluster as random effects. We will use both linear  
29 and simple contrasts in the time domain because it is not known whether there is a linear  
30 association in time. This will be illustrated by a figure showing the predicted mean of MADRS  
31 for each treatment type at each time point with confidence intervals.  
32  
33  
34
- 35 • The synergy of the two treatments will be assessed by the LME containing both treatments as  
36 well as their interaction as predictors. The interaction in the model will estimate the synergy  
37 effect.  
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- 40 • The predictive effect of several covariates (severity of dementia; severity of depression; gender;  
41 and socio-economic differences) will be assessed as odds ratios using LMEs for each covariate  
42 containing time, treatment type and their interaction as well as the covariate and the interaction  
43 between the covariate and the treatment type as predictors. The interaction in the model will  
44 estimate the predictive effect.  
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6 Secondary endpoints will be analysed as for the primary analysis, using LMEs for continuous outcomes  
7  
8 (both resident-level and staff-level). Special considerations apply for the following variables:  
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- 10  
11 • Binary outcomes, including response rates (the proportion of residents improved by at least  
12 50% from their baseline MADRS score), prevalence of medication use, and adverse events, will  
13 be assessed as odds ratios using generalised linear mixed models (GLMMs) with a logit link  
14 function. The predictive effect of several covariates (severity of dementia; severity of  
15 depression; gender; and socio-economic differences) will be assessed by GLMMs for each  
16 covariate containing time, treatment type and their interaction as well as the covariate and the  
17 interaction between the covariate and the treatment type as predictors. The interaction in the  
18 model will estimate the predictive effect.  
19
- 20 • Count data (days of sick leave) and cost data are more likely to follow a Poisson distribution  
21 than a normal distribution and will be analysed using the respective GLMMs.  
22
- 23 • Time-to-event data include mortality (time to death of any cause) and will be assessed by  
24 Kaplan-Meier and log-rank- or Breslow tests for differences between the treatment types and  
25 the hazard ratios at 12 months.  
26
- 27 • Loss to follow-up in all other outcomes can be influenced by mortality. Thus, if the survival  
28 analysis shows differences between the groups, it will be meaningful to use a joint modelling  
29 approach which combines the longitudinal models and the survival analysis.<sup>68</sup>  
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49 In addition to analysing effects of interventions as randomised, we will conduct mediator analyses to  
50 examine relations between elements of the therapy approach (mechanisms), direct and downstream  
51 outcomes, as depicted in Figure 1, using structural equation modelling (SEM).  
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### 55 56 57 **Cost-effectiveness analysis** 58



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6 Total and component costs of the interventions and the cost-effectiveness of alternative interventions  
7  
8 will be assessed from a societal perspective. This perspective will cover three categories of costs: the  
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10 cost of the intervention, statutory health and social care (and voluntary sector) service costs, and costs  
11  
12 of unpaid carer support. The cost per session for each of the interventions will be derived employing  
13  
14 established approaches used in a compendium of costs and in published studies.<sup>69 70 71</sup> Information on  
15  
16 the time inputs by GMT and RCS providers (for running sessions and for other activities) will be  
17  
18 obtained and valued using information on the midpoint of the salary scale and employer's national  
19  
20 insurance as well as superannuation contributions. The sum of the staffing contributions and allocations  
21  
22 for overheads for each session will then be summed, to derive a cost per session. To this cost per  
23  
24 session, the average number of sessions delivered as part of the intervention will be multiplied to derive  
25  
26 a cost per intervention. As there is no clear agreement on how the costs of group interventions should  
27  
28 be allocated, we will calculate the cost per session of each of the interventions on the basis of the  
29  
30 participants allocated to each of the groups, regardless of whether or not the participant attended,  
31  
32 because participants who miss a session are not replaced.  
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39 Data on statutory services used will be collected using a tailored version of the Client Socio-  
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41 Demographic and Service Receipt Inventory (CSSRI),<sup>58</sup> which contains data on the use of health and  
42  
43 other formal care resources and unpaid care. To service and support data we will attach unit costs  
44  
45 reflecting the long-run marginal opportunity costs drawn from available public sources. Costs per unit  
46  
47 of measurement for each service type will be taken from country-specific sources. We will adjust  
48  
49 country-specific costs to Euros using purchasing power parity methods. Costs and outcomes will be  
50  
51 compared for the comparators using extended dominance approaches. In this approach, the four  
52  
53 treatment combinations (GMT, RCS, GMT and RCS, no GMT or RCS) will be ranked by cost, and if  
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55 one is dominated (more expensive and less effective than another), it will be excluded from further  
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6 analysis, until two therapeutic groups are left on which to explore which of the two groups is most cost-  
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8 effective. The cost-effectiveness of one arm over another will be compared by calculating incremental  
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10 cost-effectiveness ratios (ICERs) defined as difference in mean costs (Euros spent) divided by  
11  
12 difference in mean effects (QALYs using the EQ-5D-5L; points improved on MADRS and QOL-AD).  
13  
14 Cost-effectiveness acceptability curves will be plotted for each cost-outcome combination to show the  
15  
16 likelihood of one treatment being seen as cost-effective relative to another for a range of values placed  
17  
18 on incremental outcome improvements. Using the net benefit approach, monetary values of incremental  
19  
20 effects and incremental costs will be combined, and net benefit (NB) derived as:  $NB = \lambda * (effect_b -$   
21  
22  $effect_a) - (cost_b - cost_a)$ , where  $\lambda$  is the willingness-to-pay for a unit improvement in effectiveness, and  
23  
24 subscript 'a' and 'b' denote two candidate treatment arms. There is no agreed cross-national  
25  
26 willingness-to-pay threshold, and in some countries there is no established threshold at all. Other  
27  
28 studies have used a threshold of Euros 50,000 per QALY, and we will consider this in the discussion of  
29  
30 the results.  
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36 Sensitivity analyses will be conducted to assess the robustness of the results to changes in key  
37  
38 parameters. One of the possible concerns is likely to be the sample size. If the sample size in some  
39  
40 participating countries is too small, their cost-effectiveness estimates are likely to be unreliable. We  
41  
42 shall therefore consider the added value of pooling the information on costs and outcomes in sensitivity  
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44 analyses.  
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### 48 **Patient and public involvement**

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51 The development of the research question and study design was informed by the priorities, experience  
52  
53 and preferences of residents and carers. Co-authors in Australia, Denmark, and the UK have been  
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55 actively involved in user and advocacy organisations in their countries for a long time and have  
56  
57 discussed interventions, outcomes and the need for research with them. Relatives and caregivers spoke  
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6 to the importance of music interventions as a help for carers and people with dementia, and to the need  
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8 for high-quality evidence on their effects. Relatives and caregivers are important for giving persons  
9  
10 with dementia a voice when they cannot speak for themselves.  
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13 Co-authors in Australia had significant involvement with residents, as well as with care staff and care  
14  
15 home managers, in discussing and piloting aspects of the study design. While the interventions were  
16  
17 generally perceived as pleasurable rather than burdening, some of the outcome measures were felt to be  
18  
19 burdening and too demanding due to their length or complexity. As a consequence, the longer Cornell  
20  
21 Scale for Depression in Dementia was replaced with the shorter MADRS, and a more extensive quality  
22  
23 of life scale was removed. Recruitment strategies were discussed and adapted in dialogue with care  
24  
25 home staff.  
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30 User representatives will continue to be actively involved throughout the conduct of the trial (see next  
31  
32 section). Results will be disseminated to residents, relatives, and care staff via care homes. Results will  
33  
34 also be disseminated to national user and advocacy organisations.  
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### 37 **Monitoring and oversight**

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40 One representative of each recruiting institution will be a member in the *Trial Steering Committee*  
41  
42 (*TSC*). They will be supplemented by other members who are independent of the investigators, their  
43  
44 organisations, funders and sponsors. The TSC will include service users or their relatives and  
45  
46 representatives of stakeholder organisations such as Alzheimer Europe and Dementia Australia. The  
47  
48 TSC will have regular meetings to closely supervise all aspects of the study, including any protocol  
49  
50 amendments, progress of recruitment, and publication plan.  
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54 *Data quality monitoring* will require a risk-based monitoring approach including remote monitoring  
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56 activities performed centrally and on-site monitoring as needed. The monitoring will be performed  
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6 according to the monitoring manual to be developed at the beginning of the project. Recruitment and  
7  
8 retention rates will be monitored closely to mitigate the risk of slow recruitment. The number of  
9  
10 participating care home units in total and in relation to care home units screened; the number of  
11  
12 participating care home residents in total and in relation to residents screened of potential participants;  
13  
14 and the retention of participants in the study over the trial period will be closely monitored.  
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17  
18 *A Data and Safety Monitoring Committee (DSMC)*, consisting of three people with strong  
19  
20 methodological and clinical expertise who are not otherwise affiliated with the project or its  
21  
22 institutions, will be appointed early in the international trial. The DSMC will receive regular updates on  
23  
24 recruitment, uptake of interventions, any unforeseen events, adverse events, and immediate information  
25  
26 on serious adverse events from the trial statistician. It will have unblinded access to study data.  
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29 Meetings with the DSMC will be on a biannual basis and will consist of an open and a closed part. In  
30  
31 the open part, the general progress of the trial will be discussed; in the closed part, the DSMC will  
32  
33 discuss any safety signals with the trial statistician. If issues arise, the DSMC will recommend to the  
34  
35 TSC on appropriate action.  
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39 All aspects of the study, from intervention fidelity through recruitment, outcome assessment, database  
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41 and data quality management, to data and safety monitoring, will be pilot-tested in one country  
42  
43 (Australia) before being rolled out internationally. The data of the pilot cohort will be included in the  
44  
45 main trial; no statistical adjustments are made because the decision depends only on feasibility, not on  
46  
47 an interim efficacy analysis. Patient-related documents such as the consent form will be tested because  
48  
49 they may influence how the study is perceived by potential participants, relatives and staff.  
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53 To ensure data quality, a trial database will be set up and maintained using a safe server hosted by Uni  
54  
55 Research (UHEADS) and OpenClinica software. UHEADS is a system for safely storing health  
56  
57 research data developed by Uni Research AS, that accommodates the safe upload, storage and retrieval  
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6 of any sensitive research data. OpenClinica is a web-based system for electronic data capture and  
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8 clinical data management for multicenter clinical trials, which conforms to relevant international  
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10 standards for health research. Uni Research AS runs an open source version of OpenClinica.  
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## 16 **ETHICS AND DISSEMINATION**

### 17 **Ethical aspects**

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19 Ethical approval has been obtained from the Medicine and Dentistry Human Ethics Sub-Committee at  
20  
21 the University of Melbourne, Australia (approval date: January 12, 2018) and will be obtained from the  
22  
23 relevant local institutional human research ethics committee at each international site. Local clinical  
24  
25 investigators will work on adaptation of study- and patient-related documentation to meet national  
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27 ethical requirements.  
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### 33 **Risk management**

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35 The main risks are: slow recruitment; low fidelity of interventions; and low reliability of outcome  
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37 measurements. Regarding recruitment, we will rely on clinical investigators with a track record of  
38  
39 successful recruitment. Slow recruitment at some sites can be compensated by other sites. Fidelity of  
40  
41 interventions will be ensured through clear guidance and ongoing monitoring. Reliability of outcomes  
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43 will be facilitated by the selection of widely used, recommended core outcome measures, and assessed  
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45 through tests of inter-rater reliability.  
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### 51 **Publication plan**

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53 The report on the main, pre-planned analyses of the primary endpoint and up until the 12-month  
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55 follow-up will be submitted to a leading medical journal. The report on the long-term extension will  
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57 also be submitted to a leading medical journal. Further publications may focus on recruitment and  
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6 retention strategies for international cluster-randomised multicentre trials of complex interventions in  
7 non-medical settings; development of an MCID for the MADRS based on an existing anchor question;  
8 inter-relations between outcomes and predictive value of early outcomes for later outcomes; clinical  
9 descriptions and qualitative research of therapy processes, including qualitative influences on care  
10 home staff, their perception of GMT and RCS and their potential “ripple effects”; barriers and  
11 facilitators for implementation, using qualitative interviews and surveys; and consensus guidelines for  
12 GMT and RCS. The data and meta-data will be stored in a public repository, such as that of the  
13 Norwegian Centre for Research Data (NSD).  
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### 25 **Relevance and benefit to society**

26  
27 Music interventions are widely used in care homes, and their effects are likely heterogeneous.  
28 MIDDEL is designed to provide reliable and generalisable knowledge about effectiveness,  
29 mechanisms, and heterogeneity of effects of music interventions. It will also fill knowledge gaps about  
30 potential long-term benefits and preconditions for achieving such sustained benefits. The results will  
31 drive changes in aged care and will contribute to our understanding of the relation between music and  
32 health.  
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### 42 **Implications for practice**

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44 If MIDDEL shows beneficial effects, differences in scalability need to be considered for successful  
45 implementation. GMT requires extensive, specialised music therapy training and is typically provided  
46 in small groups. The number of qualified music therapists is limited; it varies from country to country,  
47 but fluctuates around 1 in 100 000 (about 6000 in Europe, <http://emtc-eu.com>; 5000 in the USA,  
48 [www.cbmt.org](http://www.cbmt.org); 500 in Australia, [www.austmta.org.au](http://www.austmta.org.au)). RCS is more easily scalable as it can be  
49 provided by trained musicians and also in larger groups. There are about 1 million choirs and 37  
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6 million choir singers in Europe ([www.singingeurope.org](http://www.singingeurope.org)). MIDDEL will provide the knowledge  
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8 needed to identify the best targeting of both approaches, as well as contributing to their improvement  
9  
10 and standardisation. For example, GMT with its highly person-centred approach may be most  
11  
12 beneficial to those with neuropsychiatric symptoms, which are typical at late-stage dementia, whereas  
13  
14 the social engagement in RCS may help those at earlier stages, and the combination of both may be  
15  
16 best for another subset of residents with more complex needs. The knowledge generated by MIDDEL  
17  
18 will thus increase the impact of music interventions in care homes and potentially in related contexts,  
19  
20 such as day care centres for people still living at home.  
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### 25 **Implications for future research**

26  
27 As a strongly interdisciplinary project building on contributions from medicine, social sciences, and  
28  
29 humanities, this trial will contribute to strengthening the collaborations between these fields, which is  
30  
31 likely to stimulate new cross-disciplinary investigations. The study is unique in that it examines the  
32  
33 interaction of depressive symptoms, cognitive impairment, and dementia in an international sample of  
34  
35 participants. A critical feature of MIDDEL is its attention to interventions as applied within different  
36  
37 health systems. Results will be valid internationally and will contribute to establishing a model for  
38  
39 future research within different health systems.  
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44 In conclusion, MIDDEL will provide essential knowledge that will inform treatment guidelines aimed  
45  
46 at improving the lives of the rapidly rising number of people living with dementia across countries.

47 Building on previous small-scale randomised controlled trials, this large pragmatic effectiveness trial  
48  
49 will enhance the use of health technology assessment methodology in the area of non-pharmacological  
50  
51 interventions in this area. It is anticipated to have a significant positive impact on people living with  
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53 dementia, their caregivers, and the health system. Furthermore, it will also open several new lines of  
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research and development of personalised psychosocial interventions in an area of high and rising public health relevance.

For peer review only



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6 **Tables**  
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10 **Table 1. Differences and similarities of group music therapy and recreational choir singing**

	<b>Group music therapy</b>	<b>Recreational choir singing</b>
<b>Core principles</b>	Affect regulation and attunement Meet psychosocial needs Empathic relationship	Sing familiar songs, learn new songs Cognitive activation Focus on melody, lyrics, and rhythm
<b>Core intentions</b>	Facilitate and improve communication Reduce behavioural and psychological symptoms through regulation of emotions	Facilitate positive experience of self and others Stimulate expression, semantic autobiographic memory, and positive affect
<b>Shared principles and intentions</b>	Use and support remaining faculty of musical reminiscence Tailor to individuals Support social experience, stimulate social and emotional wellbeing	
<b>Proscribed</b>	Push participants to achieve goals	Instrumental improvisation
<b>Dementia inclusion criteria</b>	All levels of dementia, but may be divided to form homogeneous groups	All levels of dementia, but primarily mild to moderately severe dementia; mixed groups possible (inclusiveness)
<b>Group size</b>	Approx. 5	Approx. 10
<b>Qualification of intervention provider</b>	Music therapy degree; skilled musician; member of professional music therapy association or registration body	Skilled musician, choir leading skills and relevant further training

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6 **Figure captions**  
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9 **Figure 1. Mechanisms and outcomes of GMT and RCS**  
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11 *Note.* GMT – group music therapy; RCS – recreational choir singing.  
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14 **Figure 2. Flow of participants through the study: Illustration of the study design**  
15

16 *Note.* CDR – Clinical Dementia Rating; MADRS – Montgomery-Åsberg Depression Rating Scale;  
17 GMT – group music therapy; MMSE – Mini-Mental State Examination; MT – music therapy; RCS –  
18 recreational choir singing.  
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21 **Figure 3. Schedule of enrolment, interventions, and assessments**  
22

23 *Note.* CDR – Clinical Dementia Rating; CSSRI – Client Socio-Demographic and Service Receipt  
24 Inventory; d – day; ICD – International Classification of Diseases and Related Health Problems; m –  
25 month; MADRS – Montgomery-Åsberg Depression Rating Scale; MMSE – Mini-Mental State  
26 Examination; NPI – Neuropsychiatric Inventory; PCTB – Professional Care Team Burden Scale; QOL-  
27 AD – Quality of Life-Alzheimer Disease.  
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31 **Figure 4. Test power as a function of effect size and ICC.**  
32

33 *Note.* The intraclass correlation coefficient (ICC) describes the relative similarity of participants within  
34 units and is typically as low as 0.05 or 0.01;<sup>72</sup> we have added the pessimistic scenario of ICC = 0.10 for  
35 completeness only.  
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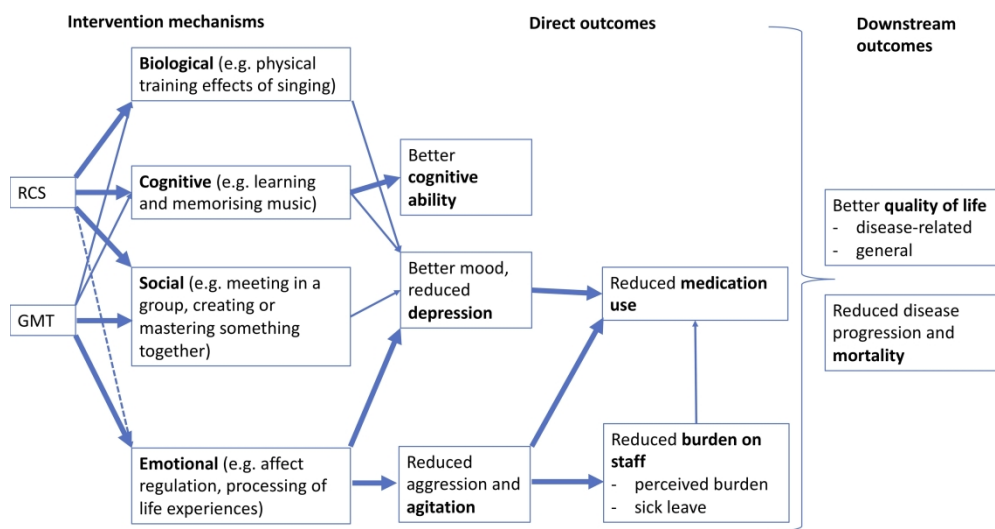


Figure 1. Mechanisms and outcomes of GMT and RCSNote. GMT – group music therapy; RCS – recreational choir singing.

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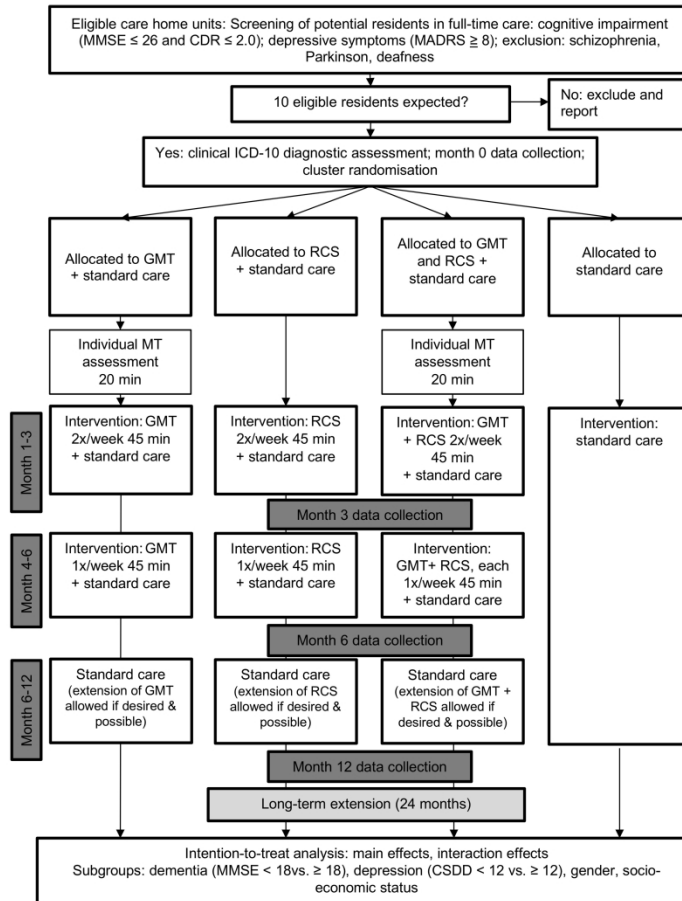


Figure 2. Flow of participants through the study: Illustration of the study design  
 Note. CDR – Clinical Dementia Rating; MADRS – Montgomery-Åsberg Depression Rating Scale; GMT – group music therapy; MMSE – Mini-Mental State Examination; MT – music therapy; RCS – recreational choir singing.

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TIMEPOINT	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
	-1d	0	1d	3m	6m	12m	...
<b>ENROLMENT:</b>							
Unit, residents: Eligibility screen	X						
Residents, staff: informed consent (or assent)	X						
Unit: allocation		X					
<b>INTERVENTIONS:</b>							
Group music therapy			←————→				
Recreational choir singing			←————→				
Standard care			←————→				
<b>ASSESSMENTS:</b>							
Unit baseline: Geographical area Size and costs (CSSRI part 3)	X						
Residents baseline: sociodemographic information (CSSRI part 1); MMSE; dementia diagnosis (ICD-10 code)	X						
Staff baseline: Age, sex	X						
Unit outcomes: Sick leave days			---	---	---	---	-----
Residents outcomes: MADRS; CDR; NPI; EQ-5D; QOL-AD; medication and service use (CSSRI part 2)	X			X	X	X	(X)
Residents outcomes: Adverse events; death			←————→				
Staff outcomes: PCTB; sick leave days	X			X	X	X	(X) X

Figure 3. Schedule of enrolment, interventions, and assessments

Note. CDR – Clinical Dementia Rating; CSSRI – Client Socio-Demographic and Service Receipt Inventory; d – day; ICD – International Classification of Diseases and Related Health Problems; m – month; MADRS – Montgomery-Åsberg Depression Rating Scale; MMSE – Mini-Mental State Examination; NPI – Neuropsychiatric Inventory; PCTB – Professional Care Team Burden Scale; QOL-AD – Quality of Life-Alzheimer Disease.

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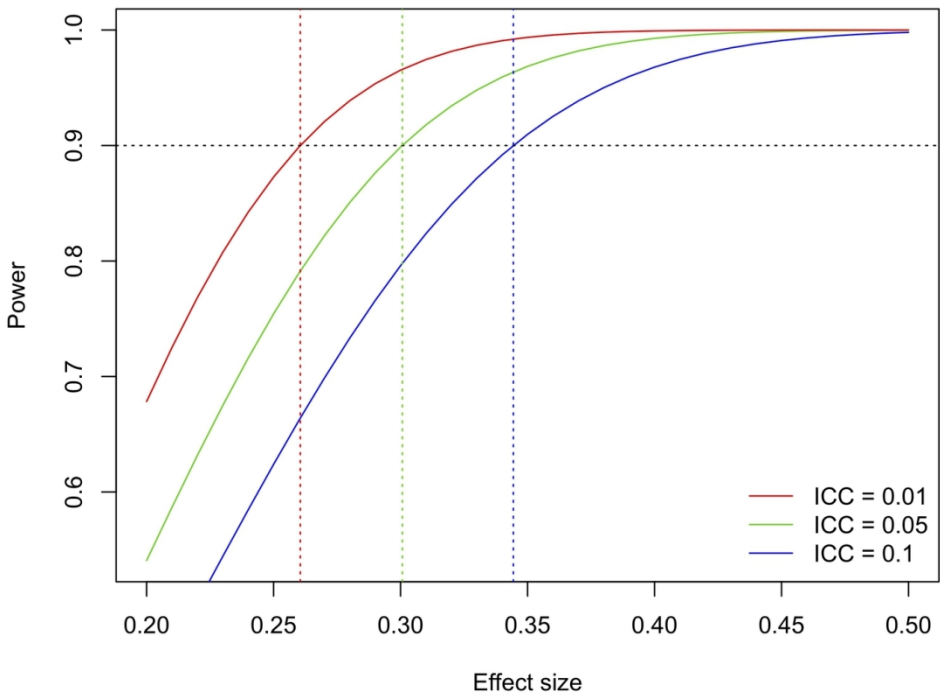


Figure 4. Test power as a function of effect size and ICC.  
Note. The intraclass correlation coefficient (ICC) describes the relative similarity of participants within units and is typically as low as 0.05 or 0.01;70 we have added the pessimistic scenario of ICC = 0.10 for completeness only.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____3
	2b	All items from the World Health Organization Trial Registration Data Set	_____3
Protocol version	3	Date and version identifier	_____NA (original)
Funding	4	Sources and types of financial, material, and other support	_____2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1-2
	5b	Name and contact information for the trial sponsor	_____2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____NA/2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____24

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**Introduction**

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____5-7
	6b	Explanation for choice of comparators	_____NA
Objectives	7	Specific objectives or hypotheses	_____8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8-10

**Methods: Participants, interventions, and outcomes**

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____11-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____14-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____Fig. 3

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3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including \_\_\_\_\_ 18  
4 clinical and statistical assumptions supporting any sample size calculations

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6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size \_\_\_\_\_ 24-26  
7

8 **Methods: Assignment of interventions (for controlled trials)**  
9

10 Allocation:

11  
12 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any \_\_\_\_\_ 9  
13 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction  
14 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants  
15 or assign interventions  
16

17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, \_\_\_\_\_ 9  
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  
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21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to \_\_\_\_\_ 9  
22 interventions  
23

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome \_\_\_\_\_ 9  
25 assessors, data analysts), and how  
26

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's \_\_\_\_\_ NA  
28 allocated intervention during the trial  
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31 **Methods: Data collection, management, and analysis**  
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33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related \_\_\_\_\_ 14-18  
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of  
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.  
36 Reference to where data collection forms can be found, if not in the protocol  
37

38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be \_\_\_\_\_ NA  
39 collected for participants who discontinue or deviate from intervention protocols  
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____24-25
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Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____19-23
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	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____20
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	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____20
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**Methods: Monitoring**

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____24-25
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	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA/24
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Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____17, 24-25
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Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____24
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**Ethics and dissemination**

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____25-26
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Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____24-25
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____10
4				
5				
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____24-25
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____2
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____NA
15				
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____11
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19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____24, 26-27
21				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____27
28				
29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____NA
32				
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34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA
35				
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
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# BMJ Open

## Music Interventions for Dementia and Depression in ELderly care (MIDDEL): Protocol and statistical analysis plan for a multinational cluster-randomised trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023436.R2
Article Type:	Protocol
Date Submitted by the Author:	26-Dec-2018
Complete List of Authors:	<p>Gold, Christian; NORCE Norwegian Research Centre, GAMUT Eickholt, Jasmin; Hochschule fur angewandte Wissenschaften Wurzburg-Schweinfurt Assmus, Jörg; NORCE Norwegian Research Centre, GAMUT Stige, Brynjulf; NORCE Norwegian Research Centre, GAMUT Wake, Jo; NORCE Norwegian Research Centre Baker, Felicity; Melbourne Conservatorium of Music Tamplin, Jeanette; Melbourne Conservatorium of Music Clark, Imogen; Melbourne Conservatorium of Music Lee, Young-Eun; Melbourne Conservatorium of Music Jacobsen, Stine; Alborg Universitet Institut for Kommunikation Ridder, Hanne Mette; Alborg Universitet Institut for Kommunikation Kreutz, Gunter; Carl von Ossietzky Universitat Oldenburg Institut fur Musik Muthesius, Dorothea; Universitat der Kunste Wosch, Thomas; Hochschule fur angewandte Wissenschaften Wurzburg-Schweinfurt Ceccato, Enrico; Universita degli Studi di Verona Dipartimento di Sanita Pubblica e Medicina di Comunita Raglio, Alfredo; Universita degli Studi di Pavia Sezione di Medicina Legale e Scienze Forensi Antonio Fornari Ruggeri, Mirella; University of Verona, Public Health and Community Medicine Vink, Annemieke; University Medical Centre Groningen, dept. of General Practice Zuidema, Sytse; University Medical Centre Groningen, dept. of General Practice Odell-Miller, Helen; Anglia Ruskin University - Cambridge Campus Orrell, Martin; Mental Health Sciences Schneider, Justine; University of Nottingham, Sociology &amp; Social Policy Kubiak, Christine; ECRIN Romeo, Renee; KCL, Geretsegger, Monika; NORCE Norwegian Research Centre, GAMUT</p>
<b>Primary Subject Heading</b>:	Geriatric medicine
Secondary Subject Heading:	Mental health, Neurology, Patient-centred medicine, Rehabilitation medicine



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Keywords:	Dementia < NEUROLOGY, Depression & mood disorders < PSYCHIATRY, Care homes, Music therapy, Music interventions, Old age psychiatry < PSYCHIATRY

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Manuscripts

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6 **Music Interventions for Dementia and Depression in ELderly care (MIDDEL): Protocol and**  
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8 **statistical analysis plan for a multinational cluster-randomised trial**  
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#### 39 40 41 **Autors' contributions:**

42 CG took the initiative for the study; CG, JE, JA, BS, HMOR, SZ and RR developed the concept and  
43 design; FAB, JT, IC, YCL, GK, DM, TW, EC, AR, MR, AV, HOM, MO, JS, and MG helped to  
44 revise the concept and design. CG drafted the manuscript; JE, JA, RR, and MG helped drafting the  
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46 HOM, MO, JS, CK revised the manuscript for important intellectual content. CG, FAB, JT, IC,  
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48 MR, AV, SZ, HOM, and MG were involved in setting up the study conduct in each site. JDW,  
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## Abstract

*Introduction:* In older adults, dementia and depression are associated with individual distress and high societal costs. Music interventions such as group music therapy (GMT) and recreational choir singing (RCS) have shown promising effects, but their comparative effectiveness across clinical subgroups is unknown. This trial aims to determine effectiveness of GMT, RCS, and their combination for care home residents and to examine heterogeneity of treatment effects across subgroups.

*Methods and analysis:* This large, pragmatic, multinational cluster-randomised controlled trial with a 2x2 factorial design will compare the effects of GMT, RCS, both, or neither, for care home residents aged 65 years or older with dementia and depressive symptoms. We will randomise 100 care home units with  $\geq 1000$  residents in total across 8 countries. Each intervention will be offered for 6 months (3 months 2x/week followed by 3 months 1x/week), with extension allowed if locally available. The primary outcome will be the change in the Montgomery-Åsberg Depression Rating Scale score at 6 months. Secondary outcomes will include depressive symptoms, cognitive functioning, neuropsychiatric symptoms, psychotropic drug use, caregiver burden, quality of life, mortality, and costs over at least 12 months. The study has 90% power to detect main effects and is also powered to determine interaction effects with gender, severity, and socio-economic status.

*Ethics and dissemination:* Ethical approval has been obtained for one country and will be obtained for all countries. Results will be presented at national and international conferences and published in scientific journals.

*Trial registration numbers:* NCT03496675, ACTRN12618000156280

**Keywords:** group music therapy, recreational choir singing, depression, dementia, non-pharmacological interventions, psychosocial interventions, randomised controlled trial

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## Strengths and limitations of this study

- As a multinational trial, this study will provide internationally generalisable results concerning the effects of music interventions in older adults with dementia and depression.
- Based on previous small-scale studies, this trial will have adequate power to determine clinical effects as well as to explain variation in treatment effects in relation to patient characteristics.
- A comprehensive set of core outcomes will be measured, including long-term effects in key variables, with assessor blinding where relevant.
- The trial will also enable modelling of trajectories of change and will thereby contribute to an improved understanding of the mechanisms of music interventions.
- Limitations include the potential bias inherent in cluster-randomised studies if recruitment within clusters is incomplete. Due to the nature of the intervention, care providers and participants cannot be blinded, which may bias measures that rely on their reports.

## Glossary of terms

- Site: an organisational or geographical entity containing several units, for example a care home/residential care facility.
- Unit (or care home unit; also ‘cluster’): the smallest organisational unit within a site, where residents live together and are cared for together by staff; each unit is randomised.
- Participant: staff or residents within units who have consented to participate.

## INTRODUCTION

Dementia and depression are highly prevalent and comorbid conditions in older adults and are associated with individual distress and high and rising societal costs. Globally, around 50 million people were living with dementia in 2017; this number is predicted to reach 82 million in 2030 and 152 million in 2050.<sup>1</sup> The societal costs of dementia are increasing from a total estimated worldwide amount of US\$ 818 billion in 2015, about 1.1% of global gross domestic product,<sup>1</sup> to US\$ 1 trillion in 2018.<sup>2</sup> Further, the disease's ramifications for families and carers are significant with respect to financial outlay and carer burden.<sup>3</sup> Dementia is highly prevalent among care home residents; more than half of all Australian care home residents in 2016-2017 had dementia.<sup>4</sup>

Depression is the leading cause of disability worldwide.<sup>5</sup> In older adults, it co-occurs and interacts with dementia in complex ways. Depression can cause cognitive impairment and may increase the risk of developing dementia;<sup>6,7</sup> conversely, depression is very common in the early stages of dementia<sup>6</sup> and often exacerbated by admission to a long-term care facility.<sup>8</sup> Psychotropic medication is only a second-line intervention due to limited efficacy and severe adverse effects, including increased mortality from antipsychotics,<sup>9</sup> but is in practice often used to reduce challenging behaviours in later stages of dementia. Non-pharmacological interventions are available and have some supporting evidence, but further research is needed.<sup>10</sup> Among the most promising non-pharmacological approaches to depression and dementia are music interventions, and in the following section we scope out this evidence.

Music interventions for older adults are based on the notion that music elicits emotional responses and helps to retrieve memories,<sup>11</sup> with recent support from research suggesting that brain regions responsible for processing music, particularly known familiar songs, may be spared even in late-stage dementia.<sup>12,13</sup> They are offered in individual,<sup>14,15</sup> group,<sup>16,17</sup> and community settings<sup>18</sup>

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6 and range from targeted clinical interventions offered by trained music therapists to broader  
7  
8 recreational activities, which may be facilitated by choir leaders or nursing staff. However, overlaps  
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10 between the levels of targeting and training do exist. The most common group-based music  
11  
12 interventions may be described as group music therapy (GMT) and recreational choir singing  
13  
14 (RCS), where GMT is offered by a music therapist and may use a variety of activities ranging from  
15  
16 singing through instrumental music making to music listening, whereas RCS is often facilitated by a  
17  
18 choir leader and focuses centrally on singing. Putative mechanisms of GMT and RCS can be  
19  
20 described as a combination of biological, psychological (cognitive and emotional), and social  
21  
22 mechanisms (Figure 1, left part), however with strong overlaps:  
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- 26  
27 • Among the *psychological mechanisms, emotional processing*, such as using musical  
28  
29 interactions to regulate affects and to reflect on relationships, may be most important in  
30  
31 GMT, but is also present to some extent in RCS. *Cognitive processing*, for example through  
32  
33 learning and memorising music pieces, is a central mechanism in RCS and less pronounced  
34  
35 in GMT, although this may vary between cases, groups, or therapists.<sup>16 19 20</sup>  
36  
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- 38  
39 • *Social mechanisms* are important in both GMT and RCS. The function of the group in itself  
40  
41 may be relatively more important in RCS, whereas GMT to a greater extent also relies on  
42  
43 the one-to-one relationship between the therapist and each group member. Another  
44  
45 important part of the social mechanisms is developing a shared sense of mastery and  
46  
47 achievement through learning and performing music pieces, which is more central in RCS  
48  
49 than in GMT but may again vary from case to case.<sup>21</sup>  
50  
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- 52  
53 • *Biological mechanisms* include physical training effects of singing and other music-related  
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55 activities, which may include movement. They are important in both GMT and RCS but  
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57 may be more central in RCS.<sup>18 22</sup>  
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6 Systematic reviews of the clinical effects of GMT and RCS have reported mixed results,<sup>10 17 19 20 23</sup>  
7  
8 <sup>24 25 26 27</sup> possibly owing to the heterogeneity of treatment effects across types of participants and  
9  
10 music interventions. One small trial comparing GMT and RCS directly suggested that the  
11  
12 comparative effects of these music interventions may depend on the comorbidity of dementia and  
13  
14 depressive symptoms.<sup>16</sup> Process-outcome relations of music interventions may be described as  
15  
16 follows (Figure 1, right part):  
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20 • *Emotional processing* in a therapist-client relationship may lead to finding meaning and  
21  
22 regaining orientation, and thereby to reduced *agitation* and related *neuropsychiatric*  
23  
24 *symptoms*. Such effects have been suggested in some systematic reviews,<sup>17 26</sup> but not in  
25  
26 others.<sup>19</sup> Reduced agitation may in consequence reduce *burden on staff*<sup>15</sup> and consequently  
27  
28 *sick leave*. This may also help to reduce inappropriate use of *medication*,<sup>14</sup> which is a  
29  
30 concern in care homes.<sup>28</sup>  
31  
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- 33  
34 • *Cognitive processing* through practicing music may promote or maintain *cognitive*  
35  
36 *functioning* in older adults. Such effects have been shown for active music therapy, but not  
37  
38 music listening, for people with dementia.<sup>20</sup>  
39  
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- 41  
42 • *Emotional processing*, but also social, biological, and cognitive mechanisms may be  
43  
44 associated with improved mood and reduced *depressive symptoms*. Systematic reviews have  
45  
46 suggested effects of music therapy on depressive symptoms in older adults in general<sup>29</sup> and  
47  
48 in people with dementia.<sup>19</sup>  
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- 51  
52 • As downstream outcomes of all four mechanisms and of the intermediate outcomes above,  
53  
54 one may expect improved *quality of life*, and possibly reduced *mortality*, although these  
55  
56 effects may be small<sup>30 31</sup> and indirect.<sup>9</sup> Music interventions may also reduce costs by  
57  
58 reducing time spent on treating neuropsychiatric symptoms and reducing absence by staff.  
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## Hypotheses



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6 Through these different pathways of GMT and RCS, one may hypothesise differential effects for  
7  
8 different outcomes, and therefore for different subgroups of care home residents. Specifically:  
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- 10  
11 • GMT may be more effective than no GMT, and RCS may be more effective than no RCS,  
12 with respect to reducing depression symptoms and other outcomes shown in Figure 1.  
13
- 14 • GMT and RCS may differ in the pattern of effects across outcome domains, which may be  
15 explained by their different mechanisms. For example, GMT may be more effective than  
16 RCS for reducing aggression and agitation and may therefore be more beneficial for people  
17 with late-stage dementia who often present with these neuropsychiatric symptoms.<sup>32 33</sup> RCS  
18 may be more effective than GMT with respect to cognitive functioning. Effects on  
19 depression symptoms may be achieved through different pathways (Figure 1), and the  
20 strength of those effects may therefore depend on severity or comorbidity.<sup>16</sup>  
21
- 22 • When offered together, synergistic effects of GMT and RCS may occur through activation  
23 of different pathways.  
24
- 25 • Cost-effectiveness may differ accordingly across interventions and subgroups. As RCS is  
26 likely to be associated with lower intervention costs, it may have better cost-effectiveness  
27 ratio in areas where clinical effects are similar; however, this will depend also on each  
28 intervention's effects on use of other treatments and services.  
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## 50 51 **METHODS AND ANALYSIS**

### 52 53 **Design**

54  
55 This large, multinational cluster-randomised controlled trial will be conducted in care homes in  
56 Australia, Denmark, Germany, Italy, Netherlands, Norway, Poland, and the UK. The list of study  
57 sites is provided in the trial registration record. MIDDEL uses a 2x2 factorial design to examine the  
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6 effects of GMT, RCS, both, or neither, for elderly care home residents with dementia and  
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8 depressive symptoms (Figure 2). This design enables investigating the effects of two music  
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10 interventions as well as potential synergy effects between them. These may occur between  
11  
12 intervention providers on the cluster level (GMT and RCS providers learning from each other) and  
13  
14 through residents on the individual or cluster level (participants gaining in different ways from the  
15  
16 combination). We will randomise 100 or more care home units (clusters) in eight countries for a  
17  
18 total of 1000 or more participants. Recruitment started in July 2018, and primary completion is  
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20 anticipated for April 2020.  
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25 Block randomisation (block size 4 clusters) will be used to ensure that each site will have a  
26  
27 balanced distribution between the interventions. The computer-generated randomisation list will be  
28  
29 created and kept concealed at the central study office. Only after the eligibility of a care home unit  
30  
31 is confirmed and eligible participants (residents and staff) within that unit have formally consented  
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33 and completed baseline assessment, will site investigators be informed of the randomisation result  
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35 for that unit. Where possible, a number of care home units will be randomised at the same time,  
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37 which will further ensure allocation concealment.  
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42 Blinding will be difficult to achieve. Intervention providers and study participants cannot be blinded  
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44 to the intervention they receive or provide. However, participants may be unaware of the specific  
45  
46 differences between GMT and RCS. Plain language summaries and consent forms will use neutral  
47  
48 wording to maintain equipoise and to avoid expectancy effects. Blinding of assessors (those  
49  
50 evaluating outcomes) will be attempted by using assessors external to the care homes, but this may  
51  
52 be incomplete because they will have to rely on information from proxy informants (care staff who  
53  
54 know the participant well) due to the inability of most residents to report on themselves. Assessors  
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56 will remind informants not to reveal the unit's allocation to them. At the time of the last assessment,  
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58 success of blinding will be verified by asking assessors whether they inadvertently discovered the  
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60 unit's allocation.

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6 GMT and RCS may entail “ripple effects” beyond the individual participants by leading to changes  
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8 of the local milieu/culture at the care home unit.<sup>15 34</sup> These will be assessed by measuring objective  
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10 and perceived burden on care staff. The cluster design is ideally suited for that situation because it  
11  
12 facilitates application in a naturalistic setting and avoids some of the problems of individually  
13  
14 randomised trials (such as treatment contamination); it also minimises the additional workload for  
15  
16 care staff. Trial procedures will be tested in the Australian cohort before applying them in the other  
17  
18 countries. The trial will be conducted and reported in accordance with relevant legal frameworks  
19  
20 and research guidelines.<sup>35 36 37 38</sup>

## 24 25 **Participants**

26  
27 Eligibility is defined on two levels, care home units and individual participants. Participating care  
28  
29 home units will be those that are expected to have at least 10 eligible and consenting residents. Care  
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31 home units that are currently providing music-based interventions as part of their usual care  
32  
33 programme will be excluded. Eligible participants will meet all of the following inclusion criteria:

- 34  
35 • aged 65 years or older, resident (full-time, 24h/day) at a participating care home;
- 36  
37 • dementia as indicated by a Clinical Dementia Rating score of 0.5 to 2 and a Mini-Mental  
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39 State Examination (MMSE) score of 26 or less;
- 40  
41 • at least mild depressive symptoms, as indicated by a Montgomery-Åsberg Depression  
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43 Rating Scale (MADRS) score of at least 8;
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45 • a clinical diagnosis of dementia according to ICD-10 research criteria;
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47 • have given written informed consent (may be assent by proxy for those unable to provide  
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49 consent themselves).

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Clinical diagnosis will be ascertained by a clinician or researcher, based on the ICD-10 dementia  
criteria of memory decline; decline in other cognitive abilities; impairment in activities of daily

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6 living; preserved awareness of the environment; decline in emotional control or motivation or  
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8 change in social behaviour; and more than 6-month duration of memory decline and other cognitive  
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10 symptoms.<sup>39</sup> People with a known diagnosis of schizophrenia or Parkinson's disease or those who  
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12 are known to be severely hearing-impaired, in short-term care, or unable to tolerate sitting in a chair  
13  
14 for at least part of the sessions, will be excluded. People may however have other clinical diagnoses  
15  
16 such as pre-morbid substance use disorders or anxiety disorders. The list of exclusion criteria is  
17  
18 intentionally short to ensure generalisability.<sup>38</sup> Residents will always be provided information about  
19  
20 the study, and their ability for consent will be assessed directly, before turning to proxies (next of  
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22 kin/legal representative/carer) for written informed assent. In case of doubt, consent/assent will be  
23  
24 provided by both resident and proxy. Residents unable to provide written consent will still be asked  
25  
26 if they agree to the interventions and assessments when these begin.<sup>40</sup>  
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### 31 **Interventions**

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33 Units in all intervention arms will continue with standard care as locally available. In the units  
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35 allocated to music interventions, GMT, RCS, or both will be provided twice weekly for the first  
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37 three months, followed by weekly sessions for the next three months. Continuation of GMT and  
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39 RCS is allowed after that period, depending on local availability. Data on the resources related to  
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41 the interventions will be measured (number of sessions attended by each participant, duration of  
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43 each session, non-contact time spent by the intervention provider to prepare or follow up a session,  
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45 recorded by the provider). The components of standard care provided will also be recorded (see  
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47 Outcomes).  
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53 GMT and RCS sessions will be 45 minutes each. In line with usual practice, GMT may be divided  
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55 into smaller groups (e.g. around 5 participants, but this may differ across local contexts), whereas  
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57 RCS may be conducted in larger groups (e.g. with all residents of the unit in one group).  
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6 *GMT*. A core principle of GMT is affect regulation through active, reciprocal music making with  
7  
8 the use of singing and musical instruments (Table 1). This facilitates the relationship between the  
9  
10 music therapist and the person living with dementia, and between participants in the group. Another  
11  
12 core principle of GMT is to meet the psychosocial needs of each individual resident, which in turn  
13  
14 is thought to reduce depressive symptoms and anxiety and to stimulate overall social and emotional  
15  
16 wellbeing.<sup>41 42 43</sup> GMT aims to work in the “here and now” by responding to participants’  
17  
18 immediate emotional expressions, containing them, and incorporating them into meaningful musical  
19  
20 expressions for therapeutic gain.<sup>21</sup> GMT is provided by a trained music therapist, who is registered  
21  
22 with the appropriate professional association or registration body in his or her country and should  
23  
24 also be skilled as a musician. To facilitate individual relationship-building, the music therapist will  
25  
26 offer each resident an initial 20-minute assessment with the aim of determining their musical  
27  
28 preferences and starting to build individual rapport. The music therapist will also use other sources  
29  
30 to determine the participants’ musical biography, cultural background, history, personal strengths,  
31  
32 resources, and disabilities, and any other information that could be useful to bring into GMT  
33  
34 sessions.  
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41 *RCS*. A core principle of RCS is to sing familiar songs and to provide a familiar musical  
42  
43 environment for participants (Table 1). Choral singing involves a combination of cognitive,  
44  
45 physical, and psychosocial engagement components.<sup>44</sup> Drawing on the psychosocial aspects of a  
46  
47 choir setting, RCS in this trial aims to foster connectedness in a group either with other older adults  
48  
49 residing in the care homes or family caregivers; emotional wellbeing; and enjoyment of music-  
50  
51 making in a group. Biographically and culturally grounded song materials are used with the central  
52  
53 goal of stimulating positive experiences shared by groups of individuals. Where participants have  
54  
55 engaged in music activities in their past, this may also enable the continuation, as far as possible, of  
56  
57 the familiar social experience of music-making in everyday life. Sections of RCS sessions may vary  
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59 in their focus; for example, sessions may focus on developing familiarity with well-known songs;  
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6 learning and developing new material as a group; singing rounds to encourage listening to each  
7  
8 other; or offering space for solo singing.<sup>45</sup> The materials can be familiar songs from a range of  
9  
10 repertoires, including but not restricted to festive songs (e.g. birthday songs, Christmas carols), folk  
11  
12 songs, traditional, classical, or popular songs. The selection of songs can vary from country to  
13  
14 country, within and between choir leaders, and may also depend on seasonal and other  
15  
16 circumstantial factors. RCS is provided by a skilled musician with choir leading skills.

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20 *Training and assessment of treatment fidelity.* GMT and RCS providers will receive training and  
21  
22 implement intervention guidelines developed in the initial phase of the study. Regular exchange and  
23  
24 peer supervision for GMT and RCS providers will be organized in conjunction with guidelines and  
25  
26 training. This will include monthly online or in-person meetings between researchers and  
27  
28 intervention providers to ensure intervention quality and fidelity, to discuss potential threats that  
29  
30 might undermine study quality, and to refine the guidelines accordingly. Intervention providers will  
31  
32 also attend weekly staff meetings at intervention sites where possible, to maximise local knowledge  
33  
34 transfer and benefit. Manuals for complex interventions need to standardize the quality of  
35  
36 interventions to avoid unwarranted variation between therapists and countries while preserving the  
37  
38 possibility for meaningful tailoring to local contexts and individuals.<sup>46</sup> This will be addressed by  
39  
40 focusing on general principles rather than fixed behaviours. Both GMT and RCS should be tailored  
41  
42 to fit the current situation/status of the group and its individual members. Interventionists will be  
43  
44 trained at all sites, both through local in-person meetings with all intervention providers at each site  
45  
46 and through remote online training across sites. The purpose of this training is to supplement rather  
47  
48 than replace the existing training and expertise of intervention providers. For assessment of  
49  
50 adherence and competence, providers of GMT and RCS will be video-recorded in 3-4 randomly  
51  
52 selected sessions per unit. We will record and analyse the entire session. To avoid performance bias  
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54 due to the awareness of being videotaped in a selected session, we will use sham video monitoring  
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56 in other sessions where possible. Videos will be uploaded and stored on a secure central server and  
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6 will be available only to those who check treatment fidelity. Two independent researchers will  
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8 assess the different components used by intervention providers and the degree of person-  
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10 centeredness (i.e. tailoring of the intervention to the current situation/needs of the group and its  
11  
12 members). This process-related data will help us to understand the mechanisms or effective  
13  
14 ingredients of each intervention.  
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17  
18 *Further development.* While the description above provides general guidance and will form the  
19  
20 basis for fidelity assessment in this study, no consensus guidelines exist for GMT and RCS.  
21  
22 Descriptions in the literature vary in many aspects such as: theoretical frame; session structure;  
23  
24 specific therapeutic goals; types of musical instruments and materials; inclusion of music listening  
25  
26 in addition to active music-making; structured versus improvisational techniques in active music-  
27  
28 making; and adaptation/tailoring to reach each person individually. Therefore, flexible manuals,  
29  
30 including sets of detailed principles and techniques for GMT and RCS, will be developed and  
31  
32 agreed upon by scientific and clinical experts from different countries using a modified Delphi  
33  
34 consensus procedure.  
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### 38 39 **Outcomes**

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42 The study uses a broad array of resident-, staff-, and unit-level outcomes measured at 3 months, 6  
43  
44 months (primary), and 12 months after randomisation (Figure 3). A long-term extension with later  
45  
46 follow-ups is planned separately. Where possible, core outcomes ([www.comet-initiative.org](http://www.comet-initiative.org)) for  
47  
48 psychosocial intervention research in dementia care, that are widely used and available across the  
49  
50 languages of the trial, were selected.<sup>47</sup>  
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54 The primary endpoint will be change in the total score of the Montgomery-Åsberg Depression  
55  
56 Rating Scale (MADRS). The MADRS is a 10-item scale where each item is rated from 0 (no  
57  
58 abnormality to 6 (severe)).<sup>48</sup> In the total sum score ranging from 0 to 60, higher scores indicate  
59  
60 higher severity of depressive symptoms. Assessment is based on an interview with the resident

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6 where possible, but where definite answers cannot be elicited from them, all relevant clues as well  
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8 as information from other sources should be used as a basis for the rating, in line with usual clinical  
9  
10 practice.<sup>49</sup> The total time of administration is approximately 20 minutes. The MADRS has been  
11  
12 used successfully in previous studies of music interventions.<sup>16 50</sup> It has shown high reliability and  
13  
14 validity, and its sensitivity to change compares favourably to other scales evaluating depression  
15  
16 severity in this population, such as the Cornell Scale for Depression in Dementia (CSDD).<sup>49 51</sup>  
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19  
20 Secondary outcomes will include the following:  
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- 22  
23 • Dementia severity including cognitive and functional performance – Clinical Dementia Rating  
24  
25 (CDR), a standard assessment of dementia severity.<sup>52</sup> The CDR is used widely in clinical  
26  
27 settings. Its score is derived from a semi-structured interview with the person living with  
28  
29 dementia and an appropriate caregiver/relative. It rates impairment in each of 6 cognitive  
30  
31 categories (memory, orientation, judgment and problem solving, community affairs, home and  
32  
33 hobbies, and personal care). Its score is useful for characterising and tracking a person's level of  
34  
35 impairment or dementia: 0 = normal; 0.5 = very mild or questionable dementia; 1 = mild  
36  
37 dementia; 2 = moderate dementia; 3 = severe dementia.  
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- 40  
41 • Neuropsychiatric symptoms – Neuropsychiatric Inventory (NPI), “a *de facto* standard for  
42  
43 measuring neuropsychiatric symptoms in clinical trials”.<sup>47</sup> Developed to assess behaviour in  
44  
45 people living with dementia, the NPI has substantial evidence of validity and reliability and has  
46  
47 been translated into more than 40 languages.<sup>53 54</sup> The NPI uses a screening approach to  
48  
49 minimise administration time, examining and scoring only the domains with positive responses  
50  
51 to screening questions. In this study, the NPI – Questionnaire (NPI-Q)<sup>55</sup> will be used; another  
52  
53 version specific for nursing homes (NPI-NH) was considered but rejected because it is not  
54  
55 available across all languages. The NPI-Q includes 12 domains where if a symptom is present,  
56  
57 both its severity (from 1= mild to 3=severe) and the associated distress on caregivers (from  
58  
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60



0=Not distressing at all to 5=Extreme or very severe) are assessed by the professional carer who is most familiar with the resident's behaviour. Item scores across the 12 domains are summed, leading to a total severity score from 0 to 36, where higher values represent higher severity. The additional total distress score can range from 0 to 60, also with higher values representing higher distress.<sup>55</sup>

- Generic quality of life – EuroQol (EQ-5D-5L), a generic health utility measure.<sup>47</sup> The standardized, non-disease-specific instrument for evaluating health-related quality of life was developed by the international EuroQol group and is used to derive quality-adjusted life-years (QALYs). It is based on a descriptive system that defines health in the five dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response categories from “no problems” to “extreme problems”, which are combined using preference weights to form an overall quality of life score ranging from lower than 0 (worse than death) to 1 (best possible). An additional visual analogue scale indicates today's health on a scale from 0 (“The worst health you can imagine”) to 100 (“The best health you can imagine”). As most residents will be unable to self-rate the EQ-5D-5L, the rating will rely on the judgment of the carer as a proxy. Careful selection of assessment mode (self/proxy/both) and choice of appropriate proxies is important to ensure the measure's validity in studies of people with dementia.<sup>56</sup>
- Disease-specific quality of life – Quality of Life in Alzheimer's Dementia (QOL-AD).<sup>47 57</sup> This 13-item scale with a self-rating and proxy version has demonstrated sensitivity to psychosocial intervention, correlates with health-utility measures, is widely translated and used internationally and can be used by people with very low MMSE scores. Items such as “Physical health”, “Memory”, or “Ability to do things for fun” are scored on a scale from 1 (poor) to 4 (excellent), resulting in a total score ranging from 13 (worst) to 52 (best).

- All-cause mortality (time to death), as recorded in official electronic registries.
- Any increase in psychotropic drug use: Data on type (ATC Codes N065, N06) of psychotropic medication used and any increase or decrease over time will be collected from care staff using the 'medication profile' section of a tailored version of the Client Socio-Demographic and Service Receipt Inventory (CSSRI).<sup>58</sup> Available electronic health registry data will be used where possible. Psychotropic medications are sometimes used inappropriately to manage behavioural symptoms of dementia.<sup>59 60 61</sup> An earlier study suggested that music therapy may help prevent increase in medication.<sup>14</sup>
- Costs: Total and component costs of the interventions will be assessed from a societal perspective, including the cost of the intervention as well as statutory health and social care services used, using a tailored version of the CSSRI.<sup>58</sup>
- Any adverse events (safety): No adverse effects of music interventions are known from earlier trials. Intervention providers are trained to work closely with and adapt their interventions to the needs of participants in order to avoid adverse reactions. Because little knowledge exists about what the potential adverse events could be, all types of adverse events and serious adverse events (e.g. unexpected worsening of symptoms), whether related or unrelated to the interventions, will be reported.

Staff-level outcomes will be as follows:

- Subjective perceived burden of care staff: Professional Care Team Burden Scale.<sup>62</sup> The 10-item scale provides a valid and reliable means of obtaining ratings of burden from formal care teams working in care homes in order to evaluate different interventions targeted at the reduction of burden in care teams. Items are scored on a 5-point scale from 0 (strongly disagree) to 4 (strongly agree), yielding a total sum score from 0 to 40, with higher scores indicating higher burden.

- Days on sick leave of care staff, as recorded monthly by the employer.

### Sample size and test power

There is no consensus on the minimal clinically important difference (MCID)<sup>63</sup> on the MADRS.

Generally, effect sizes in the small- to medium range (i.e. between  $d = 0.20$  and  $0.50$ ) may be considered relevant.<sup>64</sup> Effect sizes in that range were also found in a previous trial on GMT and RCS ( $d = 0.33$  at 6 weeks and  $0.49$  at 12 weeks).<sup>16</sup> Studies of other depression scales have used anchor-based approaches to determine clinically important percent reductions;<sup>65</sup> we will not use such approaches for the primary analyses, but will include an additional responder analysis.<sup>63</sup>

The trial has the multiple aim of identifying main effects of GMT versus no GMT and RCS versus no RCS, interaction effects of GMT and RCS, and predictive effects of clinical characteristics including severity of dementia; severity of depression; gender; and socio-economic differences. (Although individual socio-economic differences tend to become more equal amongst residents in a given care home, they may still exist at the cluster level, as different homes may have different standards; we will use the average cost of living in each care home unit as a cluster-based proxy measure for socio-economic status.) Power for interaction effects and subgroup analyses is difficult to determine because of the unknown distributions and effect sizes of the different variables.

Therefore, the power calculation for the primary outcome was based on the main comparisons of GMT versus no GMT and RCS versus no RCS. This approach maximises power by fully exploiting the factorial design. A general two-sided significance level of 5% will be used, leading with Bonferroni adjustment to a marginal two-sided level of 2.5%. The power calculation was adjusted for cluster effects using the intraclass correlation coefficient (ICC, between 0.01 and 0.10, Figure 4), assuming average cluster size 10. It was further assumed that attrition, which may occur due to death, moving to another care home, or withdrawal from the study, will be no higher than 20% overall. With 100 clusters and 1000 participants randomised, 90% power is reached for effect sizes

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6 between 0.25 and 0.35 (Figure 4). Any further increase beyond this sample size will serve  
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8 heterogeneity of treatment effects analyses.  
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## 10 **Statistical analyses**

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14 The statistical analyses will use multivariate longitudinal statistical models, which make optimal  
15  
16 use of the data by using data from all time points at once and can account for the effects of  
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18 clustering within care home units and sites. We will use a modified intention-to-treat (ITT)  
19  
20 approach using all available data from all participants as randomised, regardless of the intervention  
21  
22 actually received. Sensitivity analyses using multiple imputation for missing data will enable a full  
23  
24 ITT analysis. Additional per-protocol analysis will address the effects of treatments as actually  
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26 received and will complement the ITT analyses. All tests in the study will be two-sided. The general  
27  
28 significance level is set to 0.05. Since there are two comparisons in the primary analysis (GMT vs.  
29  
30 no GMT, RCS vs. no RCS), we will use a marginal Bonferroni level of 0.025. Continuous variables  
31  
32 will be screened for normality. All computations will be done using R.<sup>66</sup>  
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37 Sociodemographic and clinical baseline properties for the groups will be characterized by  
38  
39 descriptive methods (mean (SD), median [range], n (%)) and presented in a table. A similar table  
40  
41 will compare those who dropped out versus those who completed the primary outcome.  
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44  
45 The primary outcome, change of MADRS score from baseline to 6 months, will be assessed by a  
46  
47 linear mixed-effects model (LME).<sup>67</sup> We will fit the unadjusted model for each treatment (RCS vs.  
48  
49 no RCS) as well as the multivariate model containing both treatments as predictors both unadjusted  
50  
51 and adjusted for the interaction between the treatments.  
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54 Secondary analyses of MADRS scores will include the following:  
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57 • The development of MADRS in the treatment groups over the entire study period will be  
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59 assessed by a LME including time, treatment type and the interaction of time and treatment  
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type as fixed effects, and participant nested within cluster as random effects. We will use

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6 both linear and simple contrasts in the time domain because it is not known whether there is  
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8 a linear association in time. This will be illustrated by a figure showing the predicted mean  
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10 of MADRS for each treatment type at each time point with confidence intervals.

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13 • The synergy of the two treatments will be assessed by the LME containing both treatments  
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15 as well as their interaction as predictors. The interaction in the model will estimate the  
16  
17 synergy effect.  
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- 20  
21 • The predictive effect of several covariates (severity of dementia; severity of depression;  
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23 gender; and socio-economic differences) will be assessed as odds ratios using LMEs for  
24  
25 each covariate containing time, treatment type and their interaction as well as the covariate  
26  
27 and the interaction between the covariate and the treatment type as predictors. The  
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29 interaction in the model will estimate the predictive effect.  
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33 Secondary endpoints will be analysed as for the primary analysis, using LMEs for continuous  
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35 outcomes (both resident-level and staff-level). Special considerations apply for the following  
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37 variables:  
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41 • Binary outcomes, including response rates (the proportion of residents improved by at least  
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43 50% from their baseline MADRS score), prevalence of medication use, and adverse events,  
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45 will be assessed as odds ratios using generalised linear mixed models (GLMMs) with a logit  
46  
47 link function. The predictive effect of several covariates (severity of dementia; severity of  
48  
49 depression; gender; and socio-economic differences) will be assessed by GLMMs for each  
50  
51 covariate containing time, treatment type and their interaction as well as the covariate and  
52  
53 the interaction between the covariate and the treatment type as predictors. The interaction in  
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55 the model will estimate the predictive effect.  
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- 58  
59 • Count data (days of sick leave) and cost data are more likely to follow a Poisson distribution  
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than a normal distribution and will be analysed using the respective GLMMs.

- Time-to-event data include mortality (time to death of any cause) and will be assessed by Kaplan-Meier and log-rank- or Breslow tests for differences between the treatment types and the hazard ratios at 12 months.
- Loss to follow-up in all other outcomes can be influenced by mortality. Thus, if the survival analysis shows differences between the groups, it will be meaningful to use a joint modelling approach which combines the longitudinal models and the survival analysis.<sup>68</sup>

In addition to analysing effects of interventions as randomised, we will conduct mediator analyses to examine relations between elements of the therapy approach (mechanisms), direct and downstream outcomes, as depicted in Figure 1, using structural equation modelling (SEM).

### **Cost-effectiveness analysis**

Total and component costs of the interventions and the cost-effectiveness of alternative interventions will be assessed from a societal perspective. This perspective will cover the cost of the intervention, statutory health and social care (and voluntary sector) service costs, and costs of unpaid carer support. The cost per session for each of the interventions will be derived employing established approaches used in a compendium of costs and in published studies.<sup>69 70 71</sup> Information on the time inputs by GMT and RCS providers (for running sessions and for other activities) will be obtained and valued using information on the midpoint of the salary scale and employer's national insurance as well as superannuation contributions. The sum of the staffing contributions and allocations for overheads for each session will then be summed, to derive a cost per session. The average number of sessions delivered as part of the intervention will be multiplied to derive a cost per intervention. As there is no clear agreement on how the costs of group interventions should be allocated, we will calculate the cost per session of each intervention on the basis of the participants allocated to each of the groups, regardless of whether or not the participant attended.

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6 Data on statutory services used will be collected using a tailored version of the Client Socio-  
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8 Demographic and Service Receipt Inventory (CSSRI),<sup>58</sup> which contains data on the use of health  
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10 and other formal care resources and unpaid care. To service and support data we will attach unit  
11  
12 costs reflecting the long-run marginal opportunity costs drawn from available public sources. Costs  
13  
14 per unit of measurement for each service type will be taken from country-specific sources. We will  
15  
16 adjust country-specific costs to Euros using purchasing power parity methods. Costs and outcomes  
17  
18 will be compared for the comparators using extended dominance approaches. In this approach, the  
19  
20 four treatment combinations (GMT, RCS, GMT and RCS, no GMT or RCS) will be ranked by cost,  
21  
22 and if one is dominated (more expensive and less effective than another), it will be excluded from  
23  
24 further analysis, until two therapeutic groups are left on which to explore which of the two groups is  
25  
26 most cost-effective. The cost-effectiveness of one arm over another will be compared by calculating  
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28 incremental cost-effectiveness ratios (ICERs) defined as difference in mean costs (Euros spent)  
29  
30 divided by difference in mean effects (QALYs using the EQ-5D-5L; points improved on MADRS  
31  
32 and QOL-AD). Cost-effectiveness acceptability curves will be plotted for each cost-outcome  
33  
34 combination to show the likelihood of one treatment being seen as cost-effective relative to another  
35  
36 for a range of values placed on incremental outcome improvements. Using the net benefit approach,  
37  
38 monetary values of incremental effects and incremental costs will be combined, and net benefit  
39  
40 (NB) derived as:  $NB = \lambda * (effect_b - effect_a) - (cost_b - cost_a)$ , where  $\lambda$  is the willingness-to-pay for a  
41  
42 unit improvement in effectiveness, and subscript 'a' and 'b' denote two candidate treatment arms.  
43  
44 There is no agreed cross-national willingness-to-pay threshold, and in some countries there is no  
45  
46 established threshold at all. Other studies have used a threshold of Euros 50,000 per QALY, and we  
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48 will consider this in the discussion of the results.  
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57 Sensitivity analyses will be conducted to assess the robustness of the results to changes in key  
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59 parameters. One of the possible concerns is likely to be the sample size. If the sample size in some  
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participating countries is too small, their cost-effectiveness estimates are likely to be unreliable. We

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6 shall therefore consider the added value of pooling the information on costs and outcomes in  
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8 sensitivity analyses.  
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### 10 **Patient and public involvement**

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14 The development of the research question and study design was informed by the priorities,  
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16 experience and preferences of residents and carers. Co-authors in Australia, Denmark, and the UK  
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18 have been actively involved in user and advocacy organisations in their countries for a long time  
19  
20 and have discussed interventions, outcomes and the need for research with them. Relatives and  
21  
22 caregivers spoke to the importance of music interventions as a help for carers and people with  
23  
24 dementia, and to the need for high-quality evidence on their effects. Relatives and caregivers are  
25  
26 important for giving persons with dementia a voice when they cannot speak for themselves.  
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29  
30 Co-authors in Australia had significant involvement with residents, as well as with care staff and  
31  
32 care home managers, in discussing and piloting aspects of the study design. While the interventions  
33  
34 were generally perceived as pleasurable rather than burdening, some of the outcome measures were  
35  
36 felt to be burdening and too demanding due to their length or complexity. As a consequence, the  
37  
38 longer Cornell Scale for Depression in Dementia was replaced with the shorter MADRS, and a  
39  
40 more extensive quality of life scale was removed. Recruitment strategies were discussed and  
41  
42 adapted in dialogue with care home staff.  
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47 User representatives will continue to be actively involved throughout the conduct of the trial (see  
48  
49 next section). Results will be disseminated to residents, relatives, and care staff via care homes.

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51 Results will also be disseminated to national user and advocacy organisations.  
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### 53 **Monitoring and oversight**

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57 One representative of each recruiting institution will be a member in the *Trial Steering Committee*  
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59 (*TSC*). They will be supplemented by other members who are independent of the investigators, their  
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organisations, funders and sponsors. The TSC will include service users or their relatives and



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6 representatives of stakeholder organisations such as Alzheimer Europe and Dementia Australia. The  
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8 TSC will have regular meetings to closely supervise all aspects of the study, including any protocol  
9  
10 amendments, progress of recruitment, and publication plan.  
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13 *Data quality monitoring* will require a risk-based monitoring approach including remote monitoring  
14  
15 activities performed centrally and on-site monitoring as needed. The monitoring will be performed  
16  
17 according to the monitoring manual to be developed at the beginning of the project. Recruitment  
18  
19 and retention rates will be monitored closely to mitigate the risk of slow recruitment. The number of  
20  
21 participating care home units in total and in relation to care home units screened; the number of  
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23 participating care home residents in total and in relation to residents screened of potential  
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25 participants; and the retention of participants in the study over the trial period will be closely  
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27 monitored.  
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32 A *Data and Safety Monitoring Committee (DSMC)*, consisting of three people with strong  
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34 methodological and clinical expertise who are not otherwise affiliated with the project or its  
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36 institutions, will be appointed early in the international trial. The DSMC will receive regular  
37  
38 updates on recruitment, uptake of interventions, any unforeseen events, adverse events, and  
39  
40 immediate information on serious adverse events from the trial statistician. It will have unblinded  
41  
42 access to study data. Meetings with the DSMC will be on a biannual basis and will consist of an  
43  
44 open and a closed part. In the open part, the general progress of the trial will be discussed; in the  
45  
46 closed part, the DSMC will discuss any safety signals with the trial statistician. If issues arise, the  
47  
48 DSMC will recommend to the TSC on appropriate action.  
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53 All aspects of the study, from intervention fidelity through recruitment, outcome assessment,  
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55 database and data quality management, to data and safety monitoring, will be pilot-tested in one  
56  
57 country (Australia) before being rolled out internationally. The data of the pilot cohort will be  
58  
59 included in the main trial; no statistical adjustments are made because the decision depends only on  
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6 feasibility, not on an interim efficacy analysis. Patient-related documents such as the consent form  
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8 will be tested because they may influence how the study is perceived by potential participants,  
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10 relatives and staff.

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13 To ensure data quality, a trial database will be set up and maintained using a safe server hosted by  
14  
15 Uni Research (UHEADS) and OpenClinica software. UHEADS is a system for safely storing health  
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17 research data developed by Uni Research AS, that accommodates the safe upload, storage and  
18  
19 retrieval of any sensitive research data. OpenClinica is a web-based system for electronic data  
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21 capture and clinical data management for multicenter clinical trials, which conforms to relevant  
22  
23 international standards for health research. Uni Research AS runs an open source version of  
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25 OpenClinica.  
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## 33 **ETHICS AND DISSEMINATION**

### 34 **Ethical aspects**

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38 Ethical approval has been obtained from the Medicine and Dentistry Human Ethics Sub-Committee  
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40 at the University of Melbourne, Australia (approval date: January 12, 2018) and will be obtained  
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42 from the relevant local institutional human research ethics committee at each international site.

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45 Local clinical investigators will work on adaptation of study- and patient-related documentation to  
46  
47 meet national ethical requirements.  
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### 49 **Risk management**

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53 The main risks are: slow recruitment; low fidelity of interventions; and low reliability of outcome  
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55 measurements. Regarding recruitment, we will rely on clinical investigators with a track record of  
56  
57 successful recruitment. Slow recruitment at some sites can be compensated by other sites. Fidelity  
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59 of interventions will be ensured through clear guidance and ongoing monitoring. Reliability of  
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6 outcomes will be facilitated by the selection of widely used, recommended core outcome measures,  
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8 and assessed through tests of inter-rater reliability.  
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### 10 11 **Publication plan**

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14 The report on the main, pre-planned analyses of the primary endpoint and up until the 12-month  
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16 follow-up will be submitted to a leading medical journal. The report on the long-term extension will  
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18 also be submitted to a leading medical journal. Further publications may focus on recruitment and  
19  
20 retention strategies for international cluster-randomised multicentre trials of complex interventions  
21  
22 in non-medical settings; development of an MCID for the MADRS based on an existing anchor  
23  
24 question; inter-relations between outcomes and predictive value of early outcomes for later  
25  
26 outcomes; clinical descriptions and qualitative research of therapy processes, including qualitative  
27  
28 influences on care home staff, their perception of GMT and RCS and their potential “ripple effects”;  
29  
30 barriers and facilitators for implementation, using qualitative interviews and surveys; and consensus  
31  
32 guidelines for GMT and RCS. The data and meta-data will be stored in a public repository, such as  
33  
34 that of the Norwegian Centre for Research Data (NSD).  
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### 40 **Relevance and benefit to society**

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42 Music interventions are widely used in care homes, and their effects are likely heterogeneous.  
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44 MIDDEL is designed to provide reliable and generalisable knowledge about effectiveness,  
45  
46 mechanisms, and heterogeneity of effects of music interventions. It will also fill knowledge gaps  
47  
48 about potential long-term benefits and preconditions for achieving such sustained benefits. The  
49  
50 results will drive changes in aged care and will contribute to our understanding of the relation  
51  
52 between music and health.  
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### 56 **Implications for practice**

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59 If MIDDEL shows beneficial effects, differences in scalability need to be considered for successful  
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implementation. GMT requires extensive, specialised music therapy training and is typically

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6 provided in small groups. The number of qualified music therapists is limited; it varies from  
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8 country to country, but fluctuates around 1 in 100 000 (about 6000 in Europe, <http://emtc-eu.com>;  
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10 5000 in the USA, [www.cbmt.org](http://www.cbmt.org); 500 in Australia, [www.austmta.org.au](http://www.austmta.org.au)). RCS is more easily  
11  
12 scalable as it can be provided by trained musicians and also in larger groups. There are about 1  
13  
14 million choirs and 37 million choir singers in Europe ([www.singingeurope.org](http://www.singingeurope.org)). MIDDEL will  
15  
16 provide the knowledge needed to identify the best targeting of both approaches, as well as  
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18 contributing to their improvement and standardisation. For example, GMT with its highly person-  
19  
20 centred approach may be most beneficial to those with neuropsychiatric symptoms, which are  
21  
22 typical at late-stage dementia, whereas the social engagement in RCS may help those at earlier  
23  
24 stages, and the combination of both may be best for another subset of residents with more complex  
25  
26 needs. The knowledge generated by MIDDEL will thus increase the impact of music interventions  
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28 in care homes and potentially in related contexts, such as day care centres for people still living at  
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30 home.  
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### 36 **Implications for future research**

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39 As a strongly interdisciplinary project building on contributions from medicine, social sciences, and  
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41 humanities, this trial will contribute to strengthening the collaborations between these fields, which  
42  
43 is likely to stimulate new cross-disciplinary investigations. The study is unique in that it examines  
44  
45 the interaction of depressive symptoms, cognitive impairment, and dementia in an international  
46  
47 sample of participants. A critical feature of MIDDEL is its attention to interventions as applied  
48  
49 within different health systems. Results will be valid internationally and will contribute to  
50  
51 establishing a model for future research within different health systems.  
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56 In conclusion, MIDDEL will provide essential knowledge that will inform treatment guidelines  
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58 aimed at improving the lives of the rapidly rising number of people living with dementia across  
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60 countries. Building on previous small-scale randomised controlled trials, this large pragmatic

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6 effectiveness trial will enhance the use of health technology assessment methodology in the area of  
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8 non-pharmacological interventions in this area. It is anticipated to have a significant positive impact  
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10 on people living with dementia, their caregivers, and the health system. Furthermore, it will also  
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12 open several new lines of research and development of personalised psychosocial interventions in  
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14 an area of high and rising public health relevance.  
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For peer review only

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6 **Tables**  
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10 **Table 1. Differences and similarities of group music therapy and recreational choir singing**

	<b>Group music therapy</b>	<b>Recreational choir singing</b>
<b>Core principles</b>	Affect regulation and attunement Meet psychosocial needs Empathic relationship	Sing familiar songs, learn new songs Cognitive activation Focus on melody, lyrics, and rhythm
<b>Core intentions</b>	Facilitate and improve communication Reduce behavioural and psychological symptoms through regulation of emotions	Facilitate positive experience of self and others Stimulate expression, semantic autobiographic memory, and positive affect
<b>Shared principles and intentions</b>	Use and support remaining faculty of musical reminiscence Tailor to individuals Support social experience, stimulate social and emotional wellbeing	
<b>Proscribed</b>	Push participants to achieve goals	Instrumental improvisation
<b>Dementia inclusion criteria</b>	All levels of dementia, but may be divided to form homogeneous groups	All levels of dementia, but primarily mild to moderately severe dementia; mixed groups possible (inclusiveness)
<b>Group size</b>	Approx. 5	Approx. 10
<b>Qualification of intervention provider</b>	Music therapy degree; skilled musician; member of professional music therapy association or registration body	Skilled musician, choir leading skills and relevant further training

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6 **Figure captions**  
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9 **Figure 1. Mechanisms and outcomes of GMT and RCS**

10 *Note.* GMT – group music therapy; RCS – recreational choir singing.  
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14 **Figure 2. Flow of participants through the study: Illustration of the study design**

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16 *Note.* CDR – Clinical Dementia Rating; MADRS – Montgomery-Åsberg Depression Rating Scale;  
17 GMT – group music therapy; MMSE – Mini-Mental State Examination; MT – music therapy; RCS  
18 – recreational choir singing.  
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21 **Figure 3. Schedule of enrolment, interventions, and assessments**

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23 *Note.* CDR – Clinical Dementia Rating; CSSRI – Client Socio-Demographic and Service Receipt  
24 Inventory; d – day; ICD – International Classification of Diseases and Related Health Problems; m  
25 – month; MADRS – Montgomery-Åsberg Depression Rating Scale; MMSE – Mini-Mental State  
26 Examination; NPI – Neuropsychiatric Inventory; PCTB – Professional Care Team Burden Scale;  
27 QOL-AD – Quality of Life-Alzheimer Disease.  
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31 **Figure 4. Test power as a function of effect size and ICC.**

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33 *Note.* The intraclass correlation coefficient (ICC) describes the relative similarity of participants  
34 within units and is typically as low as 0.05 or 0.01;<sup>72</sup> we have added the pessimistic scenario of ICC  
35 = 0.10 for completeness only.  
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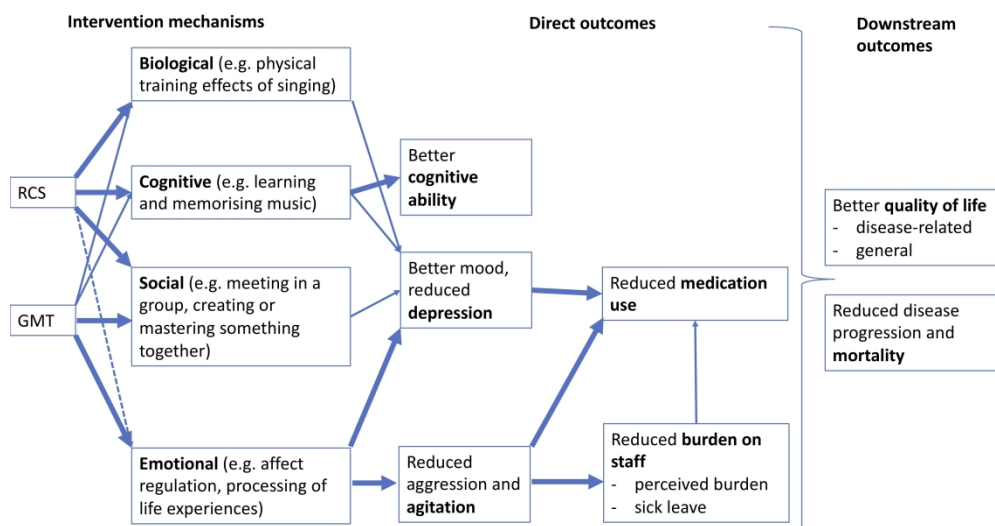


Figure 1. Mechanisms and outcomes of GMT and RCSNote. GMT – group music therapy; RCS – recreational choir singing.

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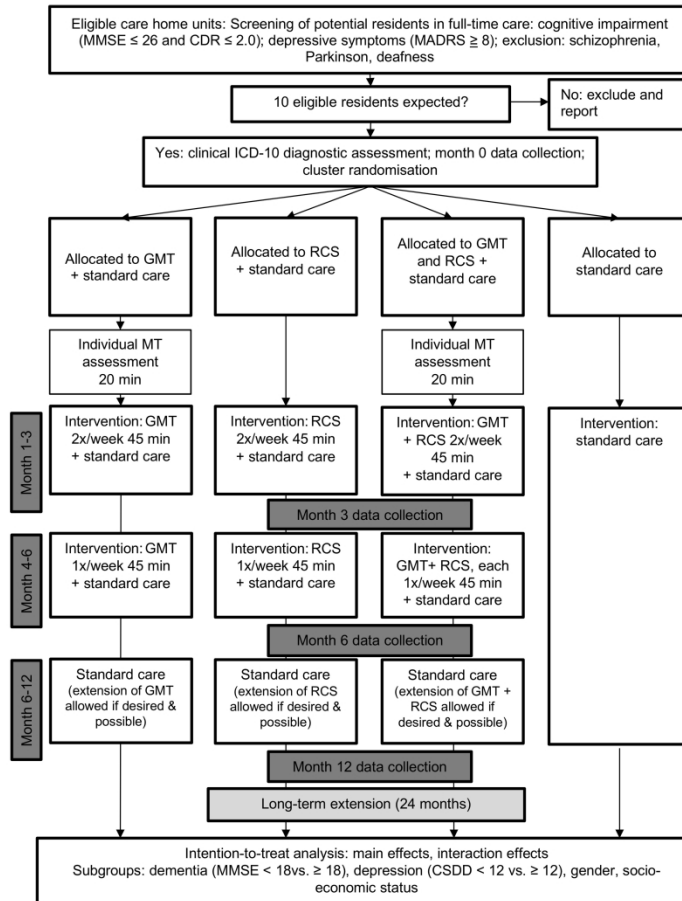


Figure 2. Flow of participants through the study: Illustration of the study design  
 Note. CDR – Clinical Dementia Rating; MADRS – Montgomery-Åsberg Depression Rating Scale; GMT – group music therapy; MMSE – Mini-Mental State Examination; MT – music therapy; RCS – recreational choir singing.

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TIMEPOINT	STUDY PERIOD							Close-out
	Enrol-ment	Alloca-tion	Post-allocation					
	-1d	0	1d	3m	6m	12m	...	
<b>ENROLMENT:</b>								
Unit, residents: Eligibility screen	X							
Residents, staff: informed consent (or assent)	X							
Unit: allocation		X						
<b>INTERVENTIONS:</b>								
Group music therapy			←————→					
Recreational choir singing			←————→					
Standard care			←————→					
<b>ASSESSMENTS:</b>								
Unit baseline: Geographical area Size and costs (CSSRI part 3)	X							
Residents baseline: sociodemographic information (CSSRI part 1); MMSE; dementia diagnosis (ICD-10 code)	X							
Staff baseline: Age, sex	X							
Unit outcomes: Sick leave days			---	---	---	---	---	-----
Residents outcomes: MADRS; CDR; NPI; EQ-5D; QOL-AD; medication and service use (CSSRI part 2)	X			X	X	X	(X)	
Residents outcomes: Adverse events; death			←————→					
Staff outcomes: PCTB; sick leave days	X			X	X	X	(X)	X

Figure 3. Schedule of enrolment, interventions, and assessments

Note. CDR – Clinical Dementia Rating; CSSRI – Client Socio-Demographic and Service Receipt Inventory; d – day; ICD – International Classification of Diseases and Related Health Problems; m – month; MADRS – Montgomery-Åsberg Depression Rating Scale; MMSE – Mini-Mental State Examination; NPI – Neuropsychiatric Inventory; PCTB – Professional Care Team Burden Scale; QOL-AD – Quality of Life- Alzheimer Disease.

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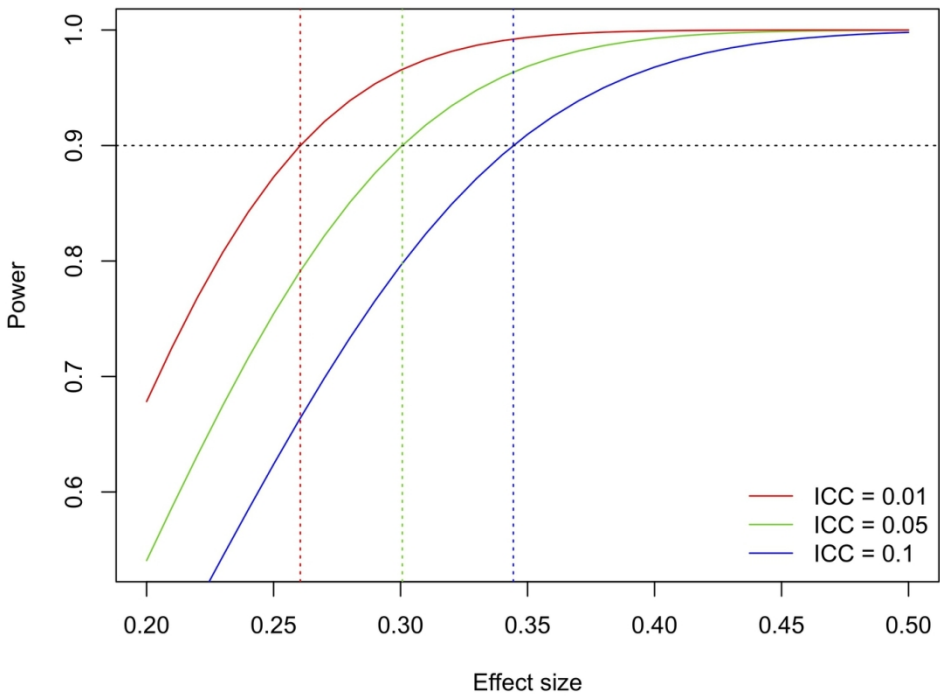


Figure 4. Test power as a function of effect size and ICC.  
Note. The intraclass correlation coefficient (ICC) describes the relative similarity of participants within units and is typically as low as 0.05 or 0.01;70 we have added the pessimistic scenario of ICC = 0.10 for completeness only.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____3
	2b	All items from the World Health Organization Trial Registration Data Set	_____3
Protocol version	3	Date and version identifier	_____NA (original)
Funding	4	Sources and types of financial, material, and other support	_____2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1-2
	5b	Name and contact information for the trial sponsor	_____2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____NA/2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____24



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47**Introduction**

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____5-7
	6b	Explanation for choice of comparators	_____NA
Objectives	7	Specific objectives or hypotheses	_____8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____8-10

**Methods: Participants, interventions, and outcomes**

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____10-11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____11-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____11-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____14-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____Fig. 3

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3	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____18
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5	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____24-26
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### 8 **Methods: Assignment of interventions (for controlled trials)**

#### 9 Allocation:

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12	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____9
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17	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9
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21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____9
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA
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### 31 **Methods: Data collection, management, and analysis**

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33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____14-18
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38		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA
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Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol \_\_\_\_\_24-25

Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol \_\_\_\_\_19-23

20b Methods for any additional analyses (eg, subgroup and adjusted analyses) \_\_\_\_\_20

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) \_\_\_\_\_20

**Methods: Monitoring**

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed \_\_\_\_\_24-25

21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial \_\_\_\_\_NA/24

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct \_\_\_\_\_17, 24-25

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor \_\_\_\_\_24

**Ethics and dissemination**

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval \_\_\_\_\_25-26

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) \_\_\_\_\_24-25

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2				
3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____10
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA
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9	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____24-25
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____2
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15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____NA
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18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____11
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21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____24, 26-27
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	_____NA
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____27
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29	<b>Appendices</b>			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____NA
32				
33				
34	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA
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37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
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