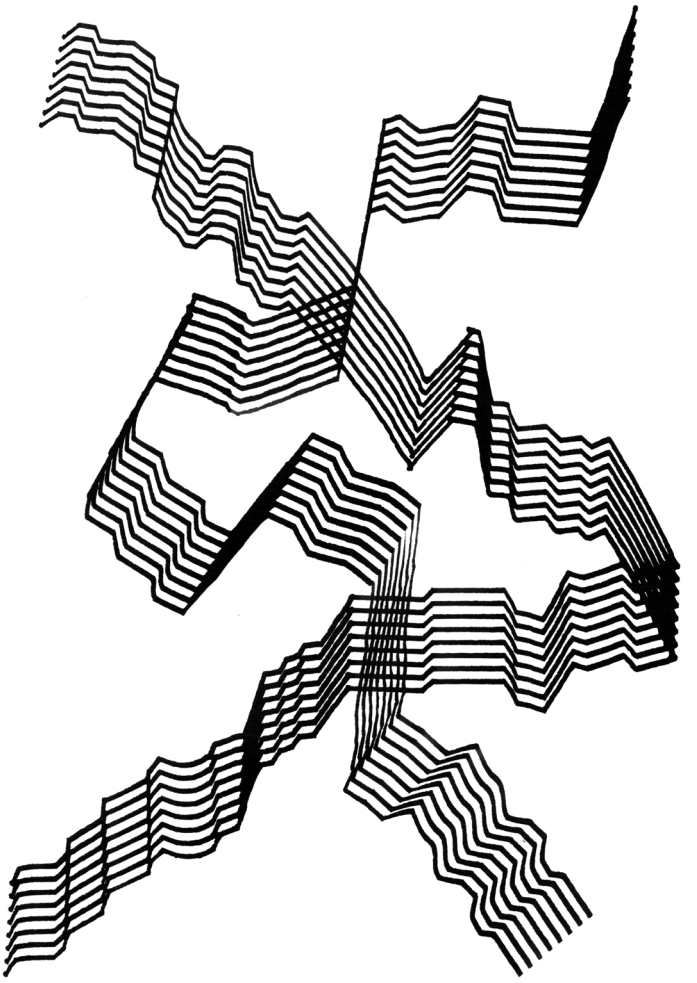
Music interventions for delirium in older adults

Jelena Golubovic



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Preface

Adjustments

This PhD project has emerged from an ongoing collaboration between the Centre for Research in Music and Health at the Norwegian Academy of Music and the Oslo Delirium Research Group at Oslo University Hospital. Both research centres share the long-term goal of advancing research concerning music, music therapy, delirium, dementia and personalised care for older adults. This PhD project focuses explicitly on delirium in older adults, exploring the potential of music interventions for its prevention and treatment.

This PhD project initially focused on developing feasible and effective single-session intervention protocols for clinically managing delirium symptoms. In addition to a systematic literature review, it was intended to include two interventional studies: one comparing different types of music interventions, such as live, recorded, active, receptive, movement to music, preference or improvisation-based, in a cross-over design, with a washout period, and the other one comparing different dosages. Single-session protocols were initially chosen based on the assumption that delivering the musical interventions over a longer period might not be feasible due to the short duration of patients' stays in the acute geriatric ward and the transient, unpredictable nature of delirium. However, the original single-session focus and overall design changed after knowledge emerged about the nature of delirium, the ward's routines, and the patients' average length of stay. Advancing knowledge about the acute, fluctuating nature of delirium as a condition also made it clear that a cross-over design with a washout period would not be feasible since it is more suited for stable, chronic conditions without fluctuations (Wellek & Blettner, 2012). The COVID-19 pandemic also influenced the planning and progression of this project since most ethical approvals and permissions were expected to take significantly longer time than usual to process, and all hospital wards were closed to all external visitors and researchers for almost seven months, including the acute geriatric ward where the clinical study was to be conducted. The COVID-19 pandemic-caused circumstances generally limited the time and resources available for completing this PhD project and affected the timeline for its intended clinical studies, resulting in significant design adjustments. The initially planned substudy comparing different dosages was omitted, and a more exploratory approach in the form of a pilot and feasibility study of two different music interventions was found to be most suitable.

Research roles and co-authorship

This project, spearheaded by the PhD candidate, Jelena Golubovic (JG), was developed in collaboration with her two primary supervisors: Prof Felicity Ann Baker (FAB) and Dr Med (PhD) Bjørn Erik Neerland (BEN). JG, FAB and BEN jointly formulated the protocols for the systematic review and the pilot and feasibility trial with input from statisticians Dagfinn Aune (DA) for the meta-analysis and Melanie Rea Simpson (MRS) for the clinical trial.

During the systematic review, JG, FAB and BEN were the primary reviewers, ensuring methodological quality and minimising bias. Discrepancies in the reviewers' decisions were resolved through a third reviewer. JG collected data from the selected studies, FAB and BEN checked the data for accuracy, and JG and DA conducted the meta-analysis. JG took the lead in drafting the manuscript, with BEN and FAB as co-authors, making corrections and contributing significantly to content and quality. DA also received co-authorship for his contribution to the meta-analysis section.

JG, FAB, BEN and MRS collaborated on the pilot and feasibility trial protocol. JG and FAB developed the intervention manuals and fidelity evaluation plan, BEN created the diagnostic algorithm, and MRS designed the statistical analysis plan. As the principal investigator, JG conducted participants' music preference assessments, tailored and delivered interventions, and was responsible for data management and overseeing data collection. FAB handled randomisation, while BEN trained assessors to perform pre-post delirium assessments and conducted the final delirium evaluations, where the results of the continuous variables were summarised into a dichotomous one (delirium: YES/NO). JG and MRS developed the statistical analysis plan and performed the analyses. Independent researcher Kjersti Johansson (KJ) assessed video recording for evaluating treatment fidelity, while JG scored the assessed items in checklists and calculated the percentage of satisfied fidelity. JG drafted the initial version of the manuscript, and BE, FAB, MRS and KJ oversaw manuscript development by providing feedback and making corrections along the way. MRS contributed significantly to formulating the statistical analysis sections, and KJ contributed to the sections on treatment fidelity evaluations.

All co-authors in all three publications satisfied the authorship criteria outlined in the Vancouver recommendations from the International Committee of Medical Journal Editors.

Academic voice(s)

Most sections of this PhD dissertation are written in the passive voice, consistent with the project's objectivist research paradigm. The project involved a team of researchers comprising co-reviewers, the project leader for the clinical trial, primary investigator and interventionist (PhD candidate), clinical assessors, supervisors, statisticians and others in nearly all its phases. Therefore, the third-person plural form ('our', 'us', and 'we') is also used throughout the text to reference the research team's decisions and processes. The first-person form is also used when relevant to more precisely articulate the values and reflections the PhD candidate individually contributed to the research process.

Acknowledgements

I am deeply grateful to the Norwegian Academy of Music (NMH), the Centre for Research in Music and Health (CREMAH), its director, Prof Karette Stensæth, and the PhD committee at NMH for recognising this PhD project as valuable and necessary for the music therapy field, and for providing me with both financial and moral support as a PhD candidate. Without their visionary views and faith that they put in the selection and the follow-up of the PhD candidates, none of this work would have been possible. Thank you for this opportunity!

I am also grateful to Oslo University Hospital and Oslo Delirium Research Group for taking this project under their wing, including me in their vibrant clinical and research milieu and for their availability, continuous engagement and generous feedback and support. The knowledge, enthusiasm, and practical assistance they provided me in all stages of this project are immeasurable! Prof Torgeir Bruun Wyller, Prof Leiv Otto Watne, Dr Marc Ahmed, Dr Nina Ommundsen, the nursing staff and the fantastic physicians from the Acute Geriatric ward who participated as assessors (Tora, Magnus, Alma, Georgios, Torgeir, Morten, Kim, Berit Sofie, Jan, Silje, Karianne, Siri, Birgitte, and Bjørn Erik), thank you for making my way into the medical field this fun and exciting!

Having superstar researchers such as Prof Felicity Baker and Dr Bjørn Erik Neerland as supervisors is a journey on its own. I have felt honoured and grateful beyond comprehension for the knowledge, wisdom, dedication and generosity they both brought into my supervision and the research process in general. They have made me feel safe, inspired, energised and empowered every step of this marathon while running shoulder to shoulder with me, allowing me to grow and explore my professional independence. I have loved every minute of it, and it did not feel like work for a second. Thank you for always being available! Thank you for always over-delivering when it comes to feedback! Most importantly, thank you for everything I have learned from you about being an extraordinary researcher while remaining an incredibly humble human being. Being a part of your team has been an honour and a privilege!

I am also grateful to collaborating researchers and statisticians Dagfinn Aune and Melanie Rea Simpson for their generous help and feedback regarding statistical analyses and to a dear colleague from CREMAH, Kjersti Johansson, for her assistance with the treatment fidelity evaluations and reviewing and providing feedback on kappa. My heated internal discussions with your comments have distilled clarity and improved the manuscript significantly! I would also like to thank the librarians, Marie Isachsen from the Medical Library at Oslo University Hospital and Johan Jørgensen at NMH, for their help with the searches for the systematic review.

I am also grateful to the two opponents on my midterm evaluation and my trial defence, Dr Alfredo Raglio and Dr Med Are Brean, for their valuable, constructive feedback and inspiring discussions. Your input at different stages of the process has improved the project significantly!

My family, dear colleagues from the PhD program at NMH, and friends (some old and some brand new) also deserve gratitude for their support, encouragement and inspiring conversations over the years! Tora, Damla, Guro, Runa, Kristi, Lillan, Ioannis, Bettina, Tuva, David, Ana C., Macak, Una, Nina, Bjørnar, Sasha, Stijn, Ana V., Visnja, Martina, Monica, my parents Momcilo and Vesna and my beautiful brother Miroslav, thank you!

I want to dedicate my PhD dissertation to my faithful, four-legged life companion and the love of my life, my irreplaceable Lola, who unfortunately cannot read (yet!) and mainly responds in barking, with most profound gratitude for keeping me sane and energised with her wild spirit and genuine joy of living, and for patiently putting up with me all these demanding years!

Thank you!

Jelena Golubovic

Oslo, 2024

Summary

Delirium is an acute confusional state, characterised by a sudden alteration in arousal, attention, cognition, emotions and psychomotor functions, highly prevalent in older, acutely hospitalised patients and patients with pre-existing dementia. An interplay between the underlying factors, such as old age or dementia, and precipitating factors, such as acute illness or surgery, contributes to the onset of delirium. The prognostic impact in the older population is poor, usually involving cognitive decline, onset or worsening of existing dementia, increased mortality risk, prolonged hospitalisation or need for long-term institutional care. Efficient pharmacological alternatives for clinically managing and preventing delirium are scarce, while non-pharmacological, multifactorial approaches, which sometimes include music, hold promise for preventing delirium. The continually emerging evidence supporting the use of music interventions in treating conditions similar to delirium, such as disorders of consciousness, dementia or psychosis, suggests that they could also be effective in managing delirium and warrant further exploration.

This PhD project explores the potential of music interventions for managing delirium in the older adults and encompasses two interrelated substudies published as three scientific articles. Its overarching aim was to generate the knowledge necessary for further efficacy testing of music interventions for delirium in older adults. Substudy 1 was a systematic review that aimed to synthesise the available published evidence, summarise effect-sizes and describe previously tested research designs, interventions, outcomes and psychometric tools. Substudy 2 was a pilot and feasibility trial that aimed to clinically explore the design and feasibility of two different music interventions for older patients with delirium in an acute geriatric ward and (2) provide a foundation for future conclusive trials. These substudies were intended to be complementary, with the systematic review informing the research design and planning of the clinical trial.

The systematic review (Article 1) included 12 quantitative effect trials on music and delirium in adults aged ≥18 years across clinical settings and care levels and included both narrative synthesis and a meta-analysis. The narrative synthesis provided an overview of the current efficacy trials. It highlighted strengths, weaknesses and biases regarding research designs, interventions, intervention protocols, theoretical rationales, selected outcomes, psychometric tools, follow-up plans and effect tendencies in eligible individual studies. The meta-analysis provided a non-robust summary estimate indicating an approximately 50% reduction in postoperative and intensive care unit delirium in older adults after exposure to music (music listening or interactive music therapy) based on data from six randomised controlled trials with small samples, moderate risk of bias, and substantial heterogeneity. These results

suggest that music interventions show potential for preventing and treating delirium and warrant further clinical exploration; they also provide recommendations for designing and planning future efficacy trials.

A study protocol for the pilot and feasibility trial (Article 2) was developed and published after completing the systematic review, describing the research design, assessment procedures, psychometric tools and intervention protocols. The intervention protocol specified the main components, mechanisms of change and theoretical rationale for comparing two music interventions: preferred live music (PLM) and preferred recorded music (PRM). Both interventions were to be based on the music preferences obtained from the family members and patients directly, in an interactive assessment session. The main therapeutic components expected to affect outcomes were live music and responsive musical and non-musical interactions with a trained music therapist in the PLM intervention, and synthetic, loud-speaker-delivered sound and original versions of the preferred music in the PRM intervention. The theoretical rationale described the PRM and PLM interventions' ability to modulate neurobiological processes, address psychological aspects, and optimise the socio-environmental context, providing a holistic and non-invasive approach to delirium management in older adults.

The pilot and feasibility trial (Article 3) was conducted in an acute geriatric ward at Oslo University Hospital. Patients aged ≥65 years, with delirium or subsyndromal delirium diagnosed within the last 72 hours and still present, were randomised to the PLM (n = 14) or PRM (n = 12) intervention. A trained music therapist delivered the music interventions for 30 minutes daily over three consecutive days. The primary feasibility outcomes included evaluating recruitment procedures, retention, adherence to interventions and assessments, and treatment fidelity. The secondary clinical outcomes were delirium symptom trajectory, delirium duration, hospitalisation length, and use of psychopharmacological medication. Its results indicated the feasibility of the recruitment procedures, interventions and assessments, as well as the fidelity and better acceptability of the PLM intervention. No significant pre-post intervention changes in clinical outcomes were observed among the participants or between the intervention groups. However, the sample sizes were small, and the confidence intervals were wide for most measures and comparisons, so the potential effect of the music interventions cannot be entirely discounted. The pilot and feasibility trial provided a foundation and recommendations for designing future conclusive trials of music interventions for treating delirium and suggested another pilot exploring a broader set of outcomes and intervention dosages is needed.

Sammendrag

Delirium er en akutt forvirringstilstand preget av en rask endring i våkenhet, oppmerksomhet, kognisjon, følelser og psykomotoriske funksjoner. Tilstanden er utbredt blant eldre pasienter som blir akuttinnlagt og blant pasienter med underliggende demens. Samspillet mellom underliggende faktorer som alderdom eller demens, og utløsende faktorer som akutt sykdom eller kirurgi, bidrar til utviklingen av delirium. Prognosen for den eldre befolkningen er vanligvis dårlig, med høy risiko for kognitiv svikt, nyoppstått eller forverring av demens, økt dødelighet, forlenget sykehusopphold eller behov for langtids institusjonell omsorg. Det finnes få effektive farmakologiske alternativer for behandling og forebygging av delirium. Ikke-farmakologiske og multi-komponent tilnærminger, som av og til inkluderer musikk, viser potensial til å forebygge delirium. Økende evidens støtter bruken av musikkintervensjoner i behandlingen av tilstander som er beslektet med delirium, for eksempel koma, demens eller psykose. Dette antyder at musikk også kan være effektiv i behandlingen av delirium og krever videre utforskning.

Dette doktorgradsprosjektet utforsker musikkintervensjonenes potensial for forebygging og behandlingen av delirium blant eldre personer og består av to sammenhengende delstudier som er presentert som tre vitenskapelige artikler. Prosjektets overordnede mål var å generere den nødvendige kunnskapen for videre testing av effektene av musikkintervensjoner for delirium blant eldre voksne. Delstudiet 1 omfattet en systematisk litteraturgjennomgang med formål å syntetisere tilgjengelig publisert evidens, oppsummere effektstørrelser og resultater, samt beskrive forskningsdesign, intervensjoner og kartleggings- og måleverktøy. Delstudiet 2 var en pilot- og gjennomførbarhetsstudie, hvor målet var å utforske gjennomførbarheten av designet og sammenligne to ulike musikkintervensjoner for delirium pasienter på en akutt geriatrisk sykehusavdeling. Overordnet mål var å legge grunnlaget for bedre design av fremtidige effektstudier. Delstudiene var utformet for å supplere hverandre, der den systematiske gjennomgangen informerte forskningsdesignet og planleggingen av den kliniske studien.

Den systematiske litteraturgjennomgangen (Artikkel 1) inkluderte 12 kvantitative effektstudier med fokus på musikk og delirium hos voksne pasienter fra ulike kliniske settinger og omsorgsnivåer. Analysen omfattet både narrativ syntese og metaanalyse. Den narrative syntesen ga en omfattende oversikt over de eksisterende effektstudiene og fremhevet styrker og svakheter knyttet til design, intervensjoner, intervensjonsprotokoller, intervensjonenes teoretiske forankring, vurderingsverktøy og oppfølgingsprotokoller, samt effekttendenser i de enkelte studiene. Metaanalysen resulterte i et ikke-robust effekt-estimat som indikerte 50% reduksjon i forekomsten av postoperativt og intensivavdelingsdelirium blant eldre voksne etter eksponering for musikk, enten gjennom musikklytting eller interaktiv musikkterapi. Estimatet er basert på data fra seks randomiserte kontrollerte studier, med små utvalg, moderat risiko

for bias og betydelig heterogenitet. Samlet sett indikerte resultatene at musikkintervensjoner har potensial til å forebygge og behandle delirium, og de understreket behovet for ytterligere forskning. Videre ga litteraturgjennomgangen anbefalinger for planleggingen og bedre design av fremtidige effektstudier på musikk og delirium.

Etter fullføring av den systematiske litteraturgjennomgangen, ble en studieprotokoll for den kliniske studien utviklet og publisert (Artikkel 2). Protokollen inneholdt detaljerte beskrivelser av studiedesign som omfattet: kartleggingsprosedyrer og verktøy for vurdering av delirium, intervensjonsprotokoller for to forskjellige musikkintervensjoner – Preferred Live Music (PLM) og Preferred Recorded Music (PRM), samt intervensjonenes endringsmekanismer og teoretisk grunnlag for sammenligning. Begge intervensjonene var basert på musikk-preferanser som ble kartlagt fra familiemedlemmer, og direkte fra pasienter i en interaktiv sesjon. Hovedkomponenter av PLM-intervensjonen omfattet levende musikk og musikalsk og ikke-musikalsk samspill med musikkterapeuten. I PRM-intervensjonen ble det forventet at syntetisk, høyttaler-levert lyd og originale versjoner av preferansemusikk skulle påvirke utfallsmålene. Det teoretiske rammeverket fremhevet PRM- og PLM-intervensjonenes potensial til å regulere deliriumsymptomer hos akutt syke eldre pasienter ved å påvirke nevrobiologiske prosesser, psykologiske aspekter, og optimalisere den psykososiale konteksten.

Vår pilot- og gjennomførbarhetsstudie (Artikkel 3) ble gjennomført ved en akutt geriatrisk avdeling ved Oslo Universitetssykehus (OUS), Ullevål, og inkluderte pasienter mellom 15. juni 2022 og 21. april 2023. Totalt 26 deltakere, 65 år eller eldre, med diagnostisert delirium eller subsyndromal delirium, ble randomisert til enten PLM (n=14) eller PRM (n=12) gruppe, med intervensjoner levert daglig i opptil 30 minutter over 3 påfølgende dager. Primære utfallsmål gjaldt gjennomførbarhet og omfattet vurdering av rekrutteringsprosedyrene, full-føring av intervensjonen og overholdelse av studieprotokollen, og evaluering av implementeringskvalitet (intervensjonsfidelitet). Sekundære, kliniske utfallsmål inkluderte: 1) endring i deliriumsymptomer, 2) varighet av delirium, 3) lengden på sykehusoppholdet, og 4) bruk av psykofarmakologisk medikasjon. Resultatene indikerte gjennomførbarhet av rekrutteringsprosedyrene, begge intervensjonene og kartleggingsprosedyrene for evaluering av delirium. Resultatene viste også bedre at PLM-intervensjonen var bedre akseptert og kunne leveres som beskrevet i protokollen. Ingen signifikante endringer i deliriumrelaterte utfallsmål ble funnet, hverken på før-og-etter målingene eller mellom intervensjonsgruppene, men utvalget var lite, og konfidensintervallene brede for de fleste målingene og sammenligningene. Den mulige effekten av musikkintervensjonene på delirium kan dermed ikke utelukkes. Den kliniske studien vår ga grunnlag og retningslinjer for utforming av fremtidige effektstudier av musikkintervensjoner for behandling av delirium, med større utvalg og statistisk styrke. Studien tydeliggjorde også behovet for en annen pilot som utforsker et bredere sett med utfallsmål og intervensjonsdoseringer.

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1 Introduction

1.1 Background and scope

The demographic landscape, particularly in industrialised societies, is undergoing a notable shift due to the progressively growing ageing population – a phenomenon popularly referred to as the 'Age Wave' (Dychtwald & Flower, 1989). Advanced age and genetic predisposition are acknowledged as key factors contributing to the development of cognitive impairments and neurological conditions in the ageing population, with dementia and delirium being the most common (Fong & Inouye, 2022). Forecasts based on data from 204 countries suggest a substantial increase in dementia cases by 2050, reaching around 153 million cases worldwide compared to the estimated 57 million in 2019 (Nichols et al., 2022). Patients with dementia are at high risk of developing delirium – a neurological syndrome also referred to as *acute confusion.*

Delirium is closely associated with dementia and may be both a risk factor for its onset and a symptom of its progression (Fong & Inouye, 2022). It is characterised by a sudden, transient alteration in mental status, resulting in various mental dysfunctions. It is often described as 'a failure of the vulnerable brain to show resilience in response to an acute stressor' (Wilson et al., 2020, p. 7). Delirium episodes in frail older adults, particularly after a fall or surgery, might contribute to the development of dementia. Conversely, a dementia diagnosis increases the individual's mental and physical vulnerability, making them highly predisposed to experiencing delirium, called delirium-predisposed dementia, which occurs in up to 49% of hospitalised patients with dementia (Fong & Inouye, 2022; Wilson et al., 2020). Therefore, preventing and managing delirium may also be viewed as a means of preventing dementia and other complications in the older adult (Nichols et al., 2022).

With almost one-fifth of in-hospital patients experiencing delirium, it is the most common hospital complication and syndrome today, most common in geriatric and emergency departments, intensive and palliative care units, orthopaedic departments and general wards (Bellelli et al., 2016; Wilson et al., 2020). While most prevalent among hospitalised older patients, delirium is also a common complication in younger patients in critical care, particularly those on mechanical ventilation in intensive care units (ICUs; Schubert et al., 2018), and even children (Bettencourt & Mullen, 2017). Ormseth et al. (2023) highlighted that the incidence of delirium among patients aged ≥75 years admitted to general medical departments was 29%–64%, reaching 50% after high-risk surgical interventions and nearly 75% among patients

on mechanical ventilation in ICUs (Ormseth et al., 2023). The prevalence of delirium was 15%–25% in emergency departments and 85% in palliative care settings (Inouye et al., 2014).

Patient reports indicate that they found experiencing delirium frightening (Kuusisto-Gussmann et al., 2021). Clinically managing delirium symptoms is challenging, and it often leads to prolonged hospitalisation, need for long-term institutional care and increased mortality risk (Gleason et al., 2015). Nonetheless, delirium remains overlooked in clinical settings, underdiagnosed and highly under-researched, with effective treatment and prevention alternatives lacking (Kington & Jenkinson, 2023; Wilson et al., 2020).

Pharmacological treatment and prevention alternatives have proven ineffective, whereas some non-pharmacological and multicomponent approaches show potential for preventing delirium (Krogseth et al., 2014; Witlox et al., 2010). Currently, available research evidence suggests that a promising avenue for addressing the complexities of delirium lies in exploring and implementing interdisciplinary, multicomponent interventions and approaches grounded in person-centred, psychosocial and environmentally focused frameworks (Abraha et al., 2015; Kim et al., 2022; Luther & McLeod, 2018).

In most countries, there remains little advancement in public understanding, national strategies or educational programs similar to those for dementia despite delirium being one of the most common risk factors and hospital complications related to dementia in older patients (Kmietowicz, 2012). Several national safety reports have highlighted delirium as one of the quality indicators for healthcare systems and one of the essential issues to address concerning care for older adults (Field & Wall, 2013; Inouye et al., 2014). Kington and Jenkinson (2023) stated that 'delirium remains the definitive test of whether our caring can match our technical care, both for those who suffer, and for those who look after them' (p. 398). Among the factors crucial for appropriately addressing this demanding condition, they highlighted placing the individual and their needs before the illness, family-centred care, and seeing the individual as a whole rather than merely the sum of their parts (Kington & Jenkinson, 2023). Further investigation and exploration of effective approaches based on these factors are warranted to enhance understanding and develop comprehensive strategies for managing delirium in an increasingly ageing society.

Currently, available research indicates that music interventions (MIs), including music therapy and music listening, positively affect the overall well-being of older adults. Specifically, these interventions have been shown to decrease agitated behaviours and improve engagement in individuals with dementia in long-term care settings (Ridder et al., 2013; Vink et al., 2014). In general hospital wards and ICUs, MIs effectively induced relaxation, reduced anxiety and

alleviated patients' pain (Bernatzky et al., 2011; Bradt et al., 2021). The effects observed in long-term care settings and general hospitals also suggest the potential effectiveness of MIs for delirium in older adults across clinical settings, highlighting the need for further exploration.

This project adopts an overall explorative approach to systematically evaluate MIs and their potential for preventing and treating delirium in older adults. It combines published evidence with primary empirical data collected in an acute geriatric clinical setting to establish a foundation and offer guidelines for more robustly designed clinical research trials in the future. It also seeks to add to the growing body of research on comprehensive, non-pharmacological, person-centred and holistic approaches to preventing and clinically managing delirium. Furthermore, it may be viewed as a contribution towards bridging the gap between art, humanities and the natural sciences/medicine, addressing the body-mind divide that is still widespread in Western medicine.

1.2 Key constructs and delimitations

1.2.1 Delirium

The etymology of the word delirium is associated with the Latin term *deliro-delirare,* which means 'to deviate from a straight line, to be crazy, deranged, out of one's wits, to be silly, to dote to rave' (Adamis et al., 2007, p. 461). This term and its alternative, *phrenitis*, appeared for the first time in the first century AD in the medical writings of Celsius and his descriptions of the mental disorders associated with head trauma or fever. *Phrenitis* had already been described by Hippocrates in 500 BC to denote fever-related sudden behavioural problems, sleep deprivation or cognitive disturbances, along with the term *lethargus*, referring to dulling of the senses and inertia, which he meant can fluctuate to *phrenitis* and vice versa. All these terms refer to fatal conditions with febrile or non-febrile causes and death as the common outcome (Adamis et al., 2007).

Delirium was associated with the clouding of consciousness for the first time in the early nineteenth century. In their unifying description from the 1950s, Engel and Romano first stated that disturbance of consciousness further affects cognitive performance and causes fluctuating awareness, psychomotor hypo- and hyperactivity, lethargy and agitation, emphasising that clinicians are not adequately trained to recognise it (Page & Ely, 2011). However, the most influential definition of delirium as a 'transient, global disorder of cognition, consciousness and attention' came from the Polish-born Irish physician Lipowski in 1990 (Lipowski, 1987; Page

& Ely, 2011, p. 6). Today, while delirium is defined and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2022), its main features are also described in the International Classification of Diseases (ICD; World Health Organization [WHO], 1992), both based on Lipowski's definition. Nonetheless, the core features and diagnostic criteria for delirium have varied between the different versions of DSM and ICD, leading to inconsistencies. This project was based mainly on the definitions from the fifth revision of the DSM (DSM-5) and the eleventh revision of the ICD (ICD-11).

While the term 'delirium' is gradually gaining acceptance, a certain degree of terminological diversity remains today, and over 30 different terms for delirium continue to be used. Examples include acute confusional state, altered mental status, acute psychosis, ICU psychosis and toxic metabolic encephalopathy (Francis et al., 1990). Today, delirium is classified as a neuropsychiatric syndrome characterised by a sudden alteration in mental status, followed by a suboptimal level of arousal (LoA), inattention, and cognitive, emotional and psychomotor disturbances (American Psychiatric Association, 2022). Some authors have argued that terminological and definitional ambiguities complicate the already complex epidemiology and diagnosis of delirium (Grover & Avasthi, 2018), leading to difficulties in its clinical recognition and underdiagnosing (Han et al., 2019). Others see delirium as a 'victim' of the persistent mind-body split in Western medicine, the fragmented, mechanistic approach to health in modern hospitals, and ageism – neglecting the issues mainly associated with or relevant to the older adults (Kington & Jenkinson, 2023). Delirium aetiology and pathophysiology will be thoroughly described in Chapter 2.

1.2.2 Differential diagnoses and conditions

While preparing this project, several preliminary searches were conducted to gain insights into the existing knowledge and evidence regarding MIs and delirium. While the research in this area is generally scarce, the preliminary searches revealed more published evidence supporting the efficacy of MIs in neurological conditions similar to delirium. Considering the relevance of this evidence for this project, particularly for defining its theoretical framework, it is crucial to provide an overview of these related conditions and highlight their distinctions and similarities to delirium.

Delirium, dementia and depression are often referred to as the 'three D's' of geriatric psychiatry (Downing et al., 2013). They have various overlapping symptoms and often co-occur. Delirium and dementia are connected and may be difficult to distinguish. Both are neurological disorders, with dementia primarily characterised by disturbed cognition and memory, with attention and arousal more intact, whereas delirium is mainly associated with attention and arousal

disturbances. While dementia is a progressive, neurodegenerative and chronic condition, delirium has an acute onset and a transient and fluctuating nature (Fong & Inouye, 2022). However, dementia and delirium have several intersections since delirium may be both a risk factor for and a symptom of dementia (Fong & Inouye, 2022; Wilson et al., 2021).

Patients with delirium and dementia are both highly predisposed to developing depression, while depression itself is a common predictor and risk factor for cognitive decline in older adults (Downing et al., 2013). Depression is associated with disturbances in circadian rhythm and sleep deprivation, which are also risk factors for developing delirium (Downing et al., 2013). Several studies have indicated that preventing delirium is an important strategy not only for reducing delirium incidence but also for preventing cognitive decline, dementia and depression, as well as falls, fractures, functional decline, and prolonged hospitalisation (Fong & Inouye, 2022).

Disorders of consciousness constitute a group of disorders characterised by altered consciousness and LoA, often ranging from coma and vegetative states to minimally conscious states, and associated with acquired brain injuries. These disorders share several similarities with the hypoactive delirium subtype, especially due to the suboptimal LoA (Eapen et al., 2017). Consequently, delirium is occasionally regarded as a disorder of consciousness (Mulkey, 2021).

While delirium is often associated with psychotic features such as hallucinations, delusions, disturbed perception, and disorganised thinking, it is sometimes considered one of the psychotic symptoms in older adults, referred to as acute psychosis caused by medical conditions (O'Connor, 2006). While both delirium and psychosis might have an acute onset, their main distinguishing characteristics are arousal and consciousness, which are generally unaffected in psychotic disorders (Wilson et al., 2021).

Delirium should also be differentiated from alcohol withdrawal delirium (delirium tremens), which is a severe symptom of alcohol abstinence, typically occurring approximately 48 hours after abrupt discontinuation of alcohol intake. Although somewhat similar, delirium and delirium tremens have different aetiologies and pathophysiologies and require different treatment approaches (Rahman & Paul, 2023). Therefore, delirium tremens is not within the scope of this project.

1.2.3 Music interventions

The collective term music intervention (MI) used in this project refers to any intentional and purposeful use of music to achieve specific treatment or prevention goals. It may include

activities such as singing, music making, or music listening (de Witte, 2021). It is usually associated with research in medical contexts and pertains to both music therapy and music medicine approaches (Dileo, 1999).

Music medicine approaches encompass receptive, recorded MIs facilitated by health practitioners other than trained music therapists, patients, and their family members (Haas & Brandes, 2009). While such approaches may involve beneficial therapeutic relationships, these relationships are rarely developed through music (Dileo, 1999). Music medicine interventions intend to address specific clinical objectives relevant to treating or preventing diseases, either as an adjunct to other medical approaches or alone. Trondalen and Bonde (2012) classify music medicine approaches as cognitive-behaviourally oriented. However, such approaches may still involve music therapists in supportive roles or the design of the interventions (Raglio & Oasi, 2015).

Music therapy is a dynamic and personalised approach. It involves (1) music and the musical experience, (2) a trained music therapist who tailors or facilitates the interventions (or both), (3) a therapeutic process and (4) a therapeutic relationship that develops through music (Bruscia, 2014). Trained music therapists use music and musical elements, such as melody, rhythm, tempo or harmony, to tailor structured interventions to promote well-being and achieve various therapeutic goals; they also actively use the therapeutic relationship as the healing agent (Dileo, 1999). According to Trondalen and Bonde (2012) therapeutic relationships in music therapy may be both *interpersonal* (patient-therapist) and *intermusical* (patient-therapist-music). Music therapy interventions may be active/expressive, with patients actively engaging and interacting with music and the therapist. They may also be receptive and involve listening to live or recorded music, which the therapist facilitates. In receptive music therapy interventions, the therapist may or may not engage with the patients by guiding them and verbally reflecting on their experiences during music-listening sessions (Bruscia, 2014; Wheeler, 2015).

The use of the term music intervention (MI) in this project and its design and delivery of MIs in the clinical phase reflects an intentional focus on investigating the potential of music for delirium management regardless of whether the interventions were administered within a music therapy or a music medicine framework. Using such inclusive terminology also expresses the authors' intention to recognise the significance of both approaches in addressing the comprehensive needs of older patients with delirium. The overall aim is to generate conclusions that could benefit both approaches. However, a more detailed elaboration of the project's positioning concerning music therapy and music medicine approaches will be provided in Subchapter 2.1.4.

1.3 Aims and objectives

This PhD project consists of two interrelated substudies, a systematic review and a pilot and feasibility trial, each with its own aims and objectives.

1. The systematic review with narrative synthesis and meta-analysis aimed to synthesise the published evidence on the effectiveness of MIs for preventing and treating delirium in adults across clinical settings and care levels.

The primary research question was: Are MIs effective in preventing and treating delirium in adults? The secondary questions were: (1) What MIs have been used in published studies?; (2) What standardised psychometric assessments have been used to measure their effect?; and (3) What health outcomes did they aim to effect, and what were their effect sizes?[1]

2. The randomised pilot and feasibility trial aimed to collect primary, empirical data to evaluate the design, feasibility, and preliminary efficacy of two MIs for delirium in an acute geriatric setting.

The feasibility objectives were to examine: (1) The feasibility of recruitment procedures and the recruitment rate in a given period; (2) The feasibility of assessments and follow-up procedures based on the proportion of fully completed pre-post-intervention assessments; (3) Adherence to the MIs and the success of treatment fidelity; (4) The MI's acceptability based on the number of the music sessions attended, refused, or not attended for other reasons; (5) The safety of the MIs based on monitoring and registering the minor and major adverse events they may have caused, such as non-specific treatment effects, or other identifiable adverse effects; and (6) The sensitivity and suitability of the effect outcomes (attention, cognition, and arousal) to assess the efficacy of the MIs.

The clinical objectives were to estimate (1) the preliminary efficacy of live and recorded MIs on the severity of delirium symptoms and (2) determine which specific delirium symptom domains are possibly most responsive to the MIs.

1 The aims and the research questions from the two substudies are presented in the same format as in the published articles.

1.4 Literature review

Preparatory searches for this project identified a limited number of published trials investigating MIs for preventing and treating delirium and a small number of systematic and narrative reviews. To summarise the research landscape preceding the project's initiation, this subchapter will highlight the findings of pertinent prior systematic reviews and notable individual studies not included in our subsequent systematic review.

1.4.1 Previous systematic reviews

The Google Scholar and PubMed databases were searched for currently available systematic reviews using the terms delirium, acute confusion, music, music therapy and systematic review. Five relevant systematic reviews were identified, of which four included studies investigating music therapy and music-based interventions (Garcia Guerra et al., 2019; Khan et al., 2018; Sibanda et al., 2019; Sousa et al., 2020) and one specifically targeted music therapy studies but did not ultimately include any (Sherriff et al., 2017).

Sousa et al. (2020) included qualitative and quantitative studies involving older acute care patients with dementia and/or delirium. Sibanda et al. (2019) included mainly quantitative studies involving adult patients with postoperative delirium, particularly those undergoing hip-knee surgery. Garcia Guerra et al. (2019) included only randomised controlled trials (RCTs) with critically ill adult hospitalised patients experiencing sedation, analgesia and delirium. Khan et al. (2018) intended to include RCTs involving adults with delirium but later reformulated their inclusion criteria and focused on inflammatory biomarkers correlated with delirium due to only one study meeting the initial inclusion criteria. Sherriff et al. (2017) aimed to include trials on patients with dementia and/or delirium in general hospitals but did not identify any trials that met their inclusion criteria. Instead, they descriptively reported the results of the trials that were close to meeting their inclusion criteria.

Most trials included in the previous systematic reviews enrolled patients with both delirium and dementia, as well as other conditions. Consequently, the available data for drawing conclusions specifically relevant to delirium were limited. Since each review included a limited number of heterogeneous studies, characterised by small sample sizes and a relatively high risk of bias, no meta-analysis was feasible, and they only conducted narrative synthesis. Despite the limitations, their narrative syntheses consistently indicated that MIs were feasible and safe. Some highlighted trends towards positive effects, particularly in individual studies conducted within the postoperative and critical care or acute care settings (Garcia Guerra et al., 2019; Sibanda et al., 2019; Sousa et al., 2020). All the systematic reviews recommended

further exploration of MIs and music therapy for treating and preventing delirium across diverse patient populations and clinical settings.

Evaluating previous systematic reviews showed that methodological challenges regarding inclusion were common, resulting in high heterogeneity among the included clinical trials. This evaluation also highlighted that, due to the generally limited number of published trials, those included mainly had small sample sizes and high risks of bias, emphasising the need for further and better-designed trials.

1.4.2 Significant individual studies

In some individual studies, [2] music listening was integrated as a component of non-pharmacological and multicomponent, non-pharmacological interventions (MNIs) for delirium (Guo et al., 2016; Sahawneh & Boss, 2021). Luther and McLeod (2018) emphasized that complex MNIs with music integrated, may be particularly effective in enhancing circadian rhythms and prevent delirium in ICUs. Guo et al. (2016) also reported statistically significant improvements in this regard. These studies indicate that music listening, whether used independently or integrated within complex MNIs, shows the potential to prevent delirium incidence and thus should be further investigated.

1.5 Structure of the dissertation

Chapter 1 has briefly introduced this project's topic, focus, and key constructs and summarised the state-of-the-art research conducted before its initiation. Next, Chapter 2 describes its main philosophical assumptions, including the author's and the project's epistemological, methodological and axiological stances, where relevant. Chapter 3 highlights the relevant theoretical perspectives on delirium aetiology, clinical features, subtyping and pathophysiology, and the theoretical framework for the MIs explored in this project. Chapter 4 describes the methods and procedures used in this project, with a short critical discussion of the ethical considerations. Chapter 5 briefly summarises the results from each of the articles. Chapter 6 discusses the design and results, emphasising strengths, limitations and implications for further research and practice. Finally, Chapter 7 presents the main conclusions of the entire project and the recommendations for further research.

2 The reasons for omitting such studies from our systematic review will be described in Chapter 4.

2 Philosophical assumptions

Philosophy has traditionally provided intellectual resources for critical reflection by asking questions about the nature of reality (ontological), knowledge and ways of knowing (epistemological), reason and reasoning (logical), moral choices and actions (ethical), and the nature of art and beauty (aesthetic) and values (axiological; Grayling, 2019). The historical split between philosophy and science resulted in several philosophical inquiries being overtaken by the autonomous scientific disciplines. However, despite their shared pursuit of clarity and certainty, the independent sciences remain susceptible to conceptual confusion, inevitably prompting questions that the scientific method alone cannot address (Hacker, 2013). Therefore, the need for philosophical reflections remains.

The research approach used to address the main aims of a scientific project is usually shaped by the researcher's worldview and grounded in a set of philosophical assumptions and paradigms, which further influence the choice of design, interventions, methods and procedures for data collection and analysis. This PhD project is situated at the intersection of art, humanities and natural sciences. Such a multidisciplinary position and its resulting challenges necessitate comprehensive clarification and critical reflection. Therefore, giving an account of the philosophical foundation of a health research project such as this one involves the following: (1) Elucidating the researcher's ontological stance and describing their view of the nature of health, music, illness, healthcare paradigms, and the nature of the approaches within which MIs are implemented; (2) Outlining the epistemological stance that underlies methods and procedures, and conceptualising the view of knowledge and the ways it is acquired; (3) Clarifying the researcher's axiological stance and the steps taken to uphold the participants' rights, adhere to ethical principles, and minimise risks (Alele & Malau-Aduli, 2023).

2.1 Ontological stance and conceptual foundation

The overarching ontological stance of this project is realist, positing that reality exists objectively and independently of our awareness and can be studied (Hiller, 2016). Various aspects of this project also align with the ontological perspectives of critical realism, which combines positivist ontology with social-constructivist epistemology (Bhaskar et al., 1998). Critical realism contends that our comprehension of reality is shaped and constructed by our interpretative process and critical examination, leading to a nuanced understanding of its intricate nature beyond simple causality. It also advocates for transcending broad, generalisable statements

and emphasises the importance of scrutinising the process, structures, and mechanisms underlying observed phenomena in the real world (Bhaskar et al., 1998).

Consistent with critical realism, this project is grounded in the biopsychosocial understanding of health and the biopsychosocial approach to medicine and healing. It is also grounded in a critical realist view of music. Viewing music through critical realist lenses assumes it exists as an objective fact with underlying mechanisms and structures. Consistent with critical realism, the role of human perception and interpretation in understanding music must be acknowledged. Such a view also recognises that our understanding of music is mediated by our sensory perceptions, cultural background, and personal experiences (McConnell & Porter, 2017). Therefore, music may also be understood as a biopsychosocial phenomenon in the context of a critical realist perspective. These ontological stances will be further expounded upon in the subsequent subchapters.

2.1.1 Biomedical model of healthcare

This project was conducted within the medical context, with its clinical part conducted in an acute geriatric medical ward. As mentioned in the previous subchapter, it is grounded in a biopsychosocial framework, which emerged as a reaction to the biomedical model that has dominated industrialised societies since the mid-twentieth century (Engel, 1977). Given the biopsychosocial model, incorporating MIs into medical care may be interpreted as an attempt to 'humanise' biomedicine and broaden its understanding of human nature and needs. However, a thorough description of the biopsychosocial model and its main pillars is needed before further elaboration on this project's positioning.

Biomedicine is a complex and multifaceted construct. While it is a post-World War II, contemporary, global, social institution inseparable from Western culture and its power structures and dynamics, it represents an epistemological framework for research and practice and a set of philosophical assumptions and commitments; it is also considered the dominant theoretical framework for the health practices and healthcare systems of the West (Valles, 2020). Therefore, the terms medicine, biomedicine, contemporary medicine and Western medicine are often used interchangeably (Lock & Nguyen, 2018). Contemporary biomedicine is also referred to as 'technomedicine' since it involves various biomedical technologies developed through practice and research, involving activities in various contexts such as hospitals, clinics, doctors' offices, laboratories, research institutes, technological units, and public health sites (Lock & Nguyen, 2018).

The mandate of biomedicine is to promote and protect human health, and its concern is as much maintenance as it is prevention, alleviation and cure of diseases (Lock & Nguyen, 2018). The biomedical framework has traditionally been grounded in understanding health phenomena as physical or biochemical entities and processes and a reductionist ontology that views human bodies as a collection of subsidiary parts and processes (biological, chemical, and physical). A positivist epistemology has also dominated, emphasising the scientific, quantitative research methods that can produce reliable evidence and experimental techniques and technologies as the preferred means of acquiring and assessing health-related knowledge (Krieger, 2011).

However, the nature of evidence and knowledge within the biomedical framework has been criticised over the years, resulting in various changes and adjustments with consequences for both research and practice. The criticism emerged due to the crisis instigated by the scientific triumphalism of the twentieth century. The proliferation of hyper-specialism and the escalating reliance on technology gradually eroded the doctor-patient relationship. Furthermore, the biomedical model failed to effectively address the epidemiological shift occurring during that period, as acute and infectious diseases gave way to chronic and degenerative pathologies, leaving patients dissatisfied with the healthcare system and increasingly seeking alternative forms of medicine and a more humane, compassionate approach from their therapists (Borrell-Carrió et al., 2004).

The Alma-Ata Health Declaration made by the WHO defined health as follows:

> (…) health, which is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, is a fundamental human right, and the attainment of the highest possible level of health is a most important world-wide social goal whose realisation requires the action of many other social and economic sectors in addition to the health sector (WHO, n.d., para. 1; Larson, 1996, p. 736)

This broad definition of health by the WHO was intended to be a guideline for governments worldwide to organise their healthcare systems so that they are available to potential users at all levels of society (Oleribe et al., 2018). Therefore, biomedicine must also be understood as inseparable from society, politics and the health policies of those in charge. Lock and Nguyen (2018) characterised biomedicine as a 'sociotechnical system' (p. 1) and described biomedical technologies resulting from biomedical research and practices as the primary tools governments and development agencies use to prevent illness and improve health outcomes.

However, the WHO definition of health has been widely criticised for being absolute and representing an unattainable conceptualisation, hence the phrase 'complete physical, mental

and social well-being' (Oleribe et al., 2018). The definition also accurately suggests that health not only refers to the absence of illness but also encompasses physical, mental and social dimensions. Therefore, it reflects a more holistic, salutogenic perspective in which health is understood as a continuum rather than an either/or condition (Schramme, 2023). Schramme (2023) defended the WHO definition, arguing that the term 'complete' might also be understood as an expression of such holistic perspective, where 'complete well-being' is interpreted as 'exhaustive well-being', the kind that contains all its constitutive features, rather than a perfect, unattainable condition. Such an interpretation also aligns with this project's stance on health.

2.1.2 The biopsychosocial model and systemic perspectives

As an alternative to the biomedical model, Georg Engel (1977) proposed a holistic approach to health and medicine, advocating that clinicians must simultaneously consider the biological, psychological and social aspects of the illness to understand and address a patient's needs. As Borrell-Carrió et al. (2004) highlighted, formulated as a biopsychosocial model, this approach was intended to be both a philosophy of clinical care and a practical guide in clinical settings. The WHO reintroduced this model in 1980 in an attempt to rehumanise medicine and reverse the disempowerment of patients (Borrell-Carrió et al., 2004). It incorporates general systems theory (Von Bertalanffy, 1968), which embraces a complex view and acknowledges that different levels in the biopsychosocial hierarchy can interact and influence each other. The rules governing these interactions are considered emergent properties, highly dependent on the individuals involved and the initial conditions (Borrell-Carrió et al., 2004; Von Bertalanffy, 1968).

Borrell-Carrió et al. (2004) argued that, while clinical medicine must undeniably be rooted in scientific knowledge, technology, problem-solving and decision-making, it should also involve profound relationships between individuals, encompassing both the physical and emotional aspects and avoiding the body-mind dualism, and a mechanistic body view. The biopsychosocial perspective contributes to an understanding of the patients not only as biological entities but also as individuals with feelings, expectations, and fears, emphasising the need for adopting holistic and empathetic approaches in clinical practice tailored to meet the unique needs of each patient (Borrell-Carrió et al., 2004). Borrell-Carrió et al. (2004) also advocated for clinical practice grounded in the biopsychosocial approach. They highlighted the following fundamental principles: (1) fostering self-awareness among the clinicians, (2) actively nurturing trust in relationships with patients, (3) developing an empathetic curiosity-driven emotional approach, (4) continuously self-adjusting to counteract biases, (5) leveraging emotional intelligence in diagnosing and forming therapeutic bonds, (6)

using informed intuition, and (7) using clinical evidence to facilitate open dialogue instead of rigidly applying protocols.

2.1.3 The nature and therapeutic value of music

Defining music as a phenomenon[3] and its nature has been challenging. Various attempts to conceptualise it have arisen from the fields of philosophy, physics, psychology and sociology (Bruscia, 2014; Hillecke, 2005). Such attempts differ in their views of whether music should be considered as only sound, or if silence and noise are contained in music; whether it exists only in the human experience or also in the work itself; if it is an activity, a thing, or form of communication; if it refers to the sound organised in time or the motion unfolding in time; and whether the definitions of music are always socially and culturally constructed (Bruscia, 2014).

The idea of using music to affect and promote health, well-being and behaviour is not new. It can be found in the early work of Greek philosophers such as Plato and Aristotle. However, the first explicit references to using music as therapy and descriptions of its therapeutic value stem from the 1800s (American Music Therapy Association, [AMTA], 2002). The therapeutic use of music traditionally derives from the social science concepts: (1) The connection between music and emotions and the ways music has been used to express feelings, thoughts and ideas throughout human history; (2) The social roles it plays in our personal lives and socio-cultural interactions, both bringing people together and structuring our interactions; (3) The function of music, and art in general, in expressing and supporting the social values and marking pivotal life-events; (4) The communicative role of music and arts in religious and ritual contexts or in expressing political ideas (Thaut, 2005). Linked to our personal and collective lives, the qualities of music are often described as both emotional and motivational (Thaut, 2005). However, besides being a cultural and interpersonal phenomenon influencing humans via sociocultural pathways, music is, as Thaut (2005) emphasised, also a biological fact with neurobiological and neurocognitive impacts. Music has both a physical and a cognitive-perceptual nature, and it relates to human perception and expression simultaneously. Music's form and meaning-making structure have, in the broadest terms, been defined throughout history as a symbolic, abstract language and a medium for communicating and exchanging meaningful information (Thaut, 2005).

3 This subchapter is intended to provide a general overview of music's multifacetedness as a universal phenomenon and to highlight the complexity and multitude of its possible conceptualisations and definitions. It does not situate music within the music therapy framework or define it according to this framework, which will first be introduced in Subchapter 2.1.4. Consequently, the references used in this subchapter are not meant to reflect only the music therapy perspective on the nature of music and its therapeutic value.

Driven by cutting-edge technological advancements such as neuro-imaging (e.g. functional magnetic resonance imaging) and brain wave recording (e.g. electroencephalograms), contemporary cognitive neuroscience research continuously provides valuable insights into the intricate processes and perception of music within the brain (González et al., 2020; Koelsch, 2014). This research has also shed light on how music acts as a catalyst for neuroplasticity, influencing the brain's ability to reorganise and adapt (Brancatisano et al., 2020). This understanding opens limitless possibilities for using music in therapeutic interventions to achieve goals that extend beyond general well-being but do not undermine the importance of well-being as a therapeutic objective. The emerging insights reveal diverse pathways through which music can impact intricate brain processes, influencing arousal, attention, emotions, cognition, and psychomotor and behavioural functions (Brancatisano et al., 2020). Such insights are highly relevant for treating and preventing neurocognitive conditions such as delirium and warrant further exploration and testing of music as an intervention in clinical contexts and within patient groups with high delirium prevalence.

2.1.4 The music therapy approach

In the clinical part of this project, two MIs were designed and implemented by a trained music therapist, incorporating a specific therapeutic process and a unique therapeutic relationship. Both MIs were based on individual music preferences, assessed beforehand in an interactive session with each participant. The preferred live music (PLM) intervention involved the music therapist delivering live music using their voice and guitar and included improvisation and musical and verbal interactions between the participants and the therapist. Conversely, the preferred recorded music (PRM) intervention involved the music therapist delivering original recordings of selected music through a loudspeaker and otherwise refraining from active engagement with the participants either verbally or musically (Golubovic et al., 2023).

Despite the differences in the music therapist's engagement, the nature and intensity of the therapeutic relationship in the two tested MIs were both broadly classified as music therapy in this project. While PLM may be viewed as an active/expressive intervention, PRM could be described as a receptive or a music-listening intervention. However, this categorisation is not without complexity and requires a thorough discussion about the connections and relevance of the PLM and PRM interventions to music therapy and music medicine approaches. This topic is discussed in detail in Chapter 6. However, this subchapter will concentrate on elucidating the basic principles and conceptual foundation of the music therapy approach within which the MIs were situated and implemented in this project

The theoretical rationale for our classification of PRM and PLM interventions as music therapy is informed by Dileo-Maranto's (1992) perspective which highlighted that, while music and the therapeutic relationship are always present in the music therapy process, they may be emphasised in different ways and to varying degrees (Dileo-Maranto, 1992). Bruscia's (2014) perspectives on different levels and intensity of music therapy practice have also been relevant in this respect, particularly his description of the augmentative, complementary levels of practice, during which music experiences and therapeutic relationships are used in a supportive way to address symptoms and undesired behaviours, and thus emphasized in different ways (Bruscia, 2014).

2.1.4.1 Music therapy discipline and process

Integrating the terms 'music' and 'therapy' within a contemporary discipline and research field poses various challenges since music traditionally belongs to the arts and humanities disciplines, while therapy is more often associated with the sciences and healthcare disciplines (Aigen, 2013). However, music therapy theory and practice were developed by integrating knowledge from disciplines such as medicine, psychology, sociology, anthropology, evolutionary biology and musicology. Such development embedded music therapy practice and research with an inherent multidisciplinary nature (Hillecke, 2005). The overarching goal of each music therapy process is to actively use music experiences and therapeutic relationships formed through music to facilitate transformative change towards optimising the client's potential for psychophysiological and ecological wholeness (Bruscia, 2014).[4] The nature of this change and the processes leading to it are usually conceptualised according to the theoretical framework of the employed music therapy approach and the dominant therapeutic strategies it is based on (Bruscia, 2014). However, perspectives on the ontology of music and musical experiences, the conceptualisation of therapeutic change, and the stance on the nature of music therapy as a process can vary widely among music therapists (Hillecke et al., 2005). These differing viewpoints influence their approach to both clinical practice and research resulting in a variety of methods, techniques, models, traditions and approaches, which are not always strictly delineated (Bruscia, 2014; Trondalen & Bonde, 2012).

4 Health can be perceived as either an absence of illness (pathogenic perspective) or as various degrees of health on a continuum (salutogenic perspective; Bruscia, 2014). Similarly, promoting or improving health may be understood as minimising the risk factors and managing the symptoms of an illness or as contextualising health within the patient's relationship and engagement with their socio-cultural context and environment, expressing different degrees of health along a continuum (Bruscia, 2014).

2.1.4.2 "Our" approach – nature and characteristics

In our clinical trial, music is intentionally implemented as a means for improving specific aspects of participants' health. Our music therapy approach may thus be viewed as instrumental. It also aligns to some degree with what Aigen (2013) defined as the reductionist perspective on the ontology of music, which suggests that the individual components of music influence and drive changes in specific aspects of an individual. Such a perspective contrasts with a holistic view, which considers music as a reflection of the individual as a whole (Aigen, 2013). However, while focusing on the individual music components and their ability to influence targeted health outcomes, our music therapy approach also acknowledges the potential for collective and more holistic effects of music and its inherent qualities on the participants' health. Moreover, in our approach, music is also acknowledged as a biopsychosocial phenomenon capable of instigating changes at the biological, psychological, and social levels, simultaneously integrating the critical realist view in which the role of our sensory perception of music and our culturally and personally conditioned interpretative process is highlighted[5] (McConnell & Porter, 2017).

The therapeutic strategies within our music therapy approach can also be characterised as outcome-oriented, following the framework outlined by Bruscia (2014), in which music context and experiences are viewed as stimuli intended to induce targeted health outcomes in patients. Such strategies have traditionally been associated with the cognitive-behavioural music therapy (CBMT) model (Bruscia, 2014; Trondalen & Bonde, 2012), although our approach does not entirely align with the CBMT discourse. According to Bruscia (2014), outcome-oriented strategies can induce change at personal, interpersonal, or ecological levels, and these changes may be evident in both musical and non-musical events (outcomes), manifesting within or outside the music therapy context. Such view is also aligned with the general biopsychosocial positioning of our music therapy approach. Some changes are externally observable and measurable, while others are subjective and internal, requiring operationalisation or personal reports from patients themselves (Bruscia, 2014). Our clinical investigation mainly focused on detecting personal changes within or outside the therapy setting (pre-post-intervention), primarily reflected in measurable non-musical outcomes (symptom improvement). However, it is essential to note that, despite the specific set of outcomes formulated in our trial, the influence of music on its participants may have extended beyond the measured outcomes, encompassing broader and more holistic effects and influences. Although such influences were not within the scope of the current project, they might be worth exploring in the future.

5 A critical realist view of music acknowledges the role of our sensory perception and of our culturally and personally conditioned interpretative process (McConnell & Porter, 2017).

2.1.4.1 The Norwegian context

The music therapy approach used in our clinical trial was also influenced by the interventionist's music therapy training from the Norwegian Academy of Music in Oslo, which is primarily grounded in humanistic values and social perspectives (Ruud, 1998, 2011). Norwegian music therapy approaches inherently prioritise relational perspectives, resource orientation and adaptability to the patient's needs and emphasise patient participation in interpersonal musical interactions and relationships (Garred, 2006; Rolvsjord, 2004, 2010; Ruud, 2020; Trondalen, 2008) [6]. Such perspectives were mainly reflected in the music therapist's approach to the patients and her inherent knowledge, skills and professional sensitivity. Therefore, besides the outcomes, the music therapy approach applied in this trial was also significantly focused towards the therapy process, with the music therapist ensuring the ongoing adaptation of the process to participants' needs and fostering their sense of security. While the components of the MIs in our clinical trial were strictly protocolised to be consistently implemented, standardised and controlled, challenges arose due to the music therapist's intuitive, relational skills and the naturally flexible, adaptable and empathetic music therapy approach, which does not readily align with strict intervention protocols. Chapter 6 thoroughly discusses the implications of these challenges on the trial results.

2.2 Epistemological considerations and methodological positioning

Given its medical context, this research project has adopted its dominant positivist epistemology and focused mainly on quantitative research methods, experimental procedures, and objective observational measurements to produce reliable evidence (Krieger, 2011). However, since the project's main aim was to explore the feasibility and gain new knowledge relevant to further research rather than generate conclusive effectiveness findings and claims, it also involved a certain amount of interpretation and narrative descriptions.

Quantitative methodology is associated with the objectivist paradigm, which is based on (1) the previously described realist ontology, which assumes that reality and meaning exist independent of our consciousness of it, and (2) epistemological objectivism, which assumes that it is possible to know reality through repeated, systematic observations and the scientific

6 The challenges arising from the intersection between the current authors' professional identity as a Norwegian-practicing music therapist and her researcher identity grounded in the objectivist paradigm and quantitative methodology, will be thoroughly described and reflected upon in Subchapter 2.3 devoted to elucidating the projects' axiological stance.

method (Hiller, 2016). This project's methodology is mainly grounded in the two main theoretical perspectives within this paradigm: positivism and its upgraded, postmodern alternative, postpositivism (Zammito, 2004). The positivistic philosophical system values measurable and observable empirical experiences of reality and assumes that reality can be studied objectively and that causational relationships and laws exist in nature and can be uncovered by applying scientific methods.

However, our [7] approach to studying music and delirium, including both a systematic review with narrative synthesis and meta-analysis and a clinical pilot and feasibility trial, reflects our overall explorative focus and acknowledges the limitations to obtaining robust conclusive claims on effectiveness at this time point. This stance is aligned with postpositivist naturalised/evolutionary epistemology, which challenges the idea of absolute truth and introduces the idea of truth and knowledge as circumstantial and situated (Phillips & Burbules, 1986). Since the human capacity to obtain knowledge is fallible, the obtainable knowledge is incomplete, contextualised in time and society, and not isolated from human influence. Therefore, scientific knowledge can, at best, be highly probable or approximate rather than absolute. The positivist idea of one ideal scientific method was also challenged, and methodological pluralism was proposed as necessary to identify valid knowledge (Zammito, 2004). Both the narrative synthesis in our systematic literature review and our focus on evaluating feasibility had an interpretative component, which originates from social constructivist epistemology and the idea that meaning is constructed via the meaning-making process in human interactions (Lincoln & Guba, 2016).

2.2.1 Evidence-based medicine and narrative evidence

Due to its focus on collecting objective, measurable data, this project also belongs within the evidence-based medicine paradigm.

There has been a notable shift in the approach to medicine since the 1990s, known as evidence-based medicine, which involved moving away from depending solely on the intuition of physicians and unsystematic clinical experiences toward a greater emphasis on a structured and scientific method to assessing the effectiveness of medical treatments in studies on a diverse population of patients (Greenhalgh, 1999; Misak, 2010) The outcomes of well-designed and controlled studies, particularly RCTs, are crucial in this paradigm. When summarised in meta-analyses and systematic reviews, these outcomes become robust empirical evidence that serves as the groundwork for developing clinical practice guidelines, protocols and standing orders, influencing the decision-making process in medical practice (Misak, 2010).

7 Pronouns 'our', 'us' and 'we' are used in the text to refer to the research team's decisions and processes.

Despite the positive aspects of evidence-based medicine, exclusively relying on RCTs may not be universally applicable or feasible for all medical situations, and there is a recognised need for a greater balance between empirical evidence, clinical expertise and patients' values (Greenhalgh, 1999; Misak, 2010).

Several authors have advocated for supplementing empirical evidence with subjective, narrative accounts (Greenhalgh, 1999; Meadows, 2021; Misak, 2010). These accounts are often referred to as narrative evidence and comprise listening to the patients' experiences of their conditions, their psycho-emotional environments, and the procedures and interventions they undergo, particularly in contexts with complex health challenges and needs, such as the acute, critical, or intensive care of older patients (Misak, 2010). Delirium care has been specifically highlighted as an area where evidence-based practice is insufficient and must be supplemented with more subjective approaches (Misak, 2010). While we have not formally collected data regarding participants' experiences of their condition and the interventions, the music therapist has observed and recorded participants' responses and engagement during the sessions, using checklists and notes. Some of these narrative data were valuable supplements to evaluating acceptability of the interventions.

2.3 Axiological stance – a personal interlude

The axiological stance of a project refers to the set of values and perspectives that the researcher brings into the research process. These values and perspectives make each research project inherently subjective, regardless of the methodology used. The axiological stance influences both the epistemological and methodological positioning and choices, as well as decisions regarding participant consent, confidentiality, data management and potential harm mitigation (Alele & Malau-Aduli, 2023). Clarifying the axiological stance of a research project is essential for critically evaluating its methods, results and implications.

2.3.1 Subjectivity and objectivity

The question of subjectivity is particularly relevant for objectivist research projects such as this one since they essentially aim for objectivity to avoid bias. However, since research generally relies on human choices and decisions, a certain level of subjectivity is always presented and reflected in the researcher's decisions and choices. This research project was designed and conducted by a team of researchers whose professional expertise is rooted in both the humanistic context and the natural sciences and medicine context, where my role was that

of a co-designer, principal investigator, co-reviewer, and interventionist (music therapist) in the study.

My motivation for this PhD project stems from my broader interest in the potential of music to promote and improve the health and well-being of older adults. Drawing on my experience as a clinical music therapist in long-term care settings and acute geriatric hospital wards, I have gained insights into this group's specific needs, challenges and diagnoses. This exposure has also allowed me to explore the potential of music and MIs for promoting health at different levels of geriatric care. My music therapy training at the Norwegian Academy of Music was grounded in humanistic values and systemic, relational, and resource-oriented perspectives (Ruud, 2020). These perspectives are incorporated into my professional identity as a clinician and are reflected in my generally holistic approach to patients, which focuses on their resources and personal and social contexts and building safe, supportive relationships with healing potential. In my professional approach, I highly value its flexibility and adaptability to the patient's needs, participation, and interpersonal musical and non-musical interactions.

My identity as a researcher has also been shaped by the objectivist paradigm, quantitative methodology and search for evidence-based knowledge. My research interests encompass investigating the impacts of music and MIs on biological, psychological, and ecological aspects of older adults' health by exploring both objectively measurable and subjective clinical outcomes (particularly patient reports). I am particularly interested in enhancing the quality of effect-testing of MIs and developing intervention protocols for experimental testing that preserve fidelity to the nature of the interventions. My focus on establishing a robust evidence base is driven by the recognition that it could catalyse policy changes and facilitate the integration of music therapy and MIs into a broader spectrum of clinical settings. Broader implementation of music therapy interventions across clinical settings would also open possibilities for more pragmatic trial designs in which the effectiveness of interventions could be tested within real-world settings, allowing for greater flexibility and balance between strict protocols and adaptation to the context. This approach also ensures greater fidelity to the nature of music therapy interventions (Holtrop et al., 2022; Macpherson, 2004; Patsopoulos, 2011)

In this project, my professional and researcher identities have intersected through my roles as the co-developer of the research design and intervention protocols, principal investigator and interventionist. While presenting some ethical challenges, such a dual role has allowed my identities to influence each other and contributed to a more nuanced approach to both research and clinical practice. The challenges mainly arose from attempting to confine a relational, empathetic and flexible approach, such as music therapy, to a strictly structured intervention protocol. This tension has prompted valuable reflections for future research and

will be elaborated on in the discussion in Chapter 6. Nonetheless, adhering to strict interventions and study protocols increased my awareness and sensitivity to the therapeutic process and the correlation between the interventions and the desired outcomes, further improving my efficiency as a clinician. Therefore, I believe that my two roles have significantly enhanced each other, and their synergy has fostered a more comprehensive and refined approach to both.

2.3.2 Overarching ethical considerations and social impact

The ethical principles that I bring into this research process as both a professional music therapist, a researcher and a person are rooted in my firm beliefs in (1) universally available healthcare, and health-promotion as the government's responsibility; (2) social justice and equal distribution of resources, benefits and opportunities for health promotion; (3) the responsibility of research to advocate for universally available healthcare by accumulating evidence and driving policy changes, (4) autonomy and respect for each individual's rights to make their own choices and influence their life-situation insofar as possible; (5) beneficence and the obligation to promote well-being and avoid causing harm; (6) the importance of reflexivity, accountability, and transparency of research decisions and choices; (7) the balance between effectiveness, acceptability, and ethical justifiability of interventions aimed at health-promotion; and (8) the potential of music as a safe, accessible, public health resource to contribute to both social justice and fostering autonomy of all groups, regardless of age, sex, disabilities, or social status (Green, 1998; Vaillancourt, 2012). The specific steps undertaken to uphold participants' rights and autonomy, adhere to overarching ethical principles, and minimise risks in this project will be thoroughly described in Subchapters 4.1.2 and 4.2.8.

3 Theoretical framework

A thorough description of delirium's aetiology, pathogenesis, and pathophysiology is essential for designing clinical studies and developing detailed, comprehensive intervention protocols since potential interventions may target risk factors, biomarkers and underlying pathophysiological mechanisms and concentrate on mitigating clinical symptoms. Treatment strategies may also be directed at mitigating patients' subjective experiences, enhancing their engagement and acceptance of other treatments and influencing environmental factors. Particularly relevant for experimental studies such as the one conducted in this project is clarifying the nature and working factors of the examined interventions and how and where their assumed influences and health effects are expected to be reflected and identified. Therefore, the objective of the subsequent subchapters is to delve into the pertinent aspects of delirium and MIs implemented within this PhD project.

3.1 Delirium characteristics

3.1.1 Diagnostic criteria, aetiology and management

The DSM defines delirium as a neurocognitive disorder and an umbrella construct highlighting its following core features – (1) acute and fluctuating disturbances in attention (i.e. ability to direct, focus sustain attention), (2) awareness (i.e. orientation to the environment), and (3) cognitive functions (e.g. memory, language, and perception) – that cannot be associated with another underlying neurocognitive disorder or condition with severely reduced arousal, such as coma (American Psychiatric Association, 2022; Marcantonio, 2017).

The risk factors for delirium can be either predisposing, such as older age, frailty, cognitive decline, dementia, functional disabilities, depression, poor vision/hearing, male sex, alcohol abuse and comorbidities, or precipitating, related to sudden triggers such as medication, surgery, anaesthesia, pain, anaemia, infections, acute medical illness, trauma or psychological distress (Marcantonio, 2017; Wilson et al., 2020). Delirium arises through the interplay between the predisposing and precipitating factors; the more predisposing factors present, the fewer precipitating factors are needed for delirium to be triggered (Marcantonio, 2017).

Patients' self-reported experiences of delirium indicate that they find it highly distressing. It usually involves records of perceptual disturbances such as hallucinations and visions; emotional disturbances in the form of feelings of fear, panic, anxiety, loss of control and

shame; and disorientation in space and time, with mixed memories and confusion about what is and is not real (Kuusisto-Gussmann et al., 2021). The distressing experience reflects the patient's ability to relate to and interact with relatives and medical staff, making them ambivalent about receiving help and support and challenging to manage, particularly in acute care settings (Kuusisto-Gussmann et al., 2021). The duration and the severity of delirium vary widely, from cases lasting for a few days to those lasting for weeks or even months (Maldonado, 2017; Wilson et al., 2020). Despite the common assumptions of its transience and reversibility, the emerging literature shows that delirium in older patients may persist throughout the hospital stay in 45% of cases and up to one month after discharge in 33% of cases (Marcantonio, 2017).

The outcomes and prognoses in the older adults are also poor and usually involve a cognitive decline, with the onset of dementia or the worsening of existing dementia (Siddiqi et al., 2006; Wilson et al., 2020). Recent studies have shown that delirium is common in patients with coronavirus disease 2019 (COVID-19), particularly in older patients admitted to emergency departments (Shao et al., 2021; Tyson et al., 2022), and can cause complications and longer hospital stays in these patients (Kennedy et al., 2020). The COVID-19 pandemic has created ideal conditions for delirium to be triggered in older adults thanks to their social isolation, leading to a lack of physical exercise, depression, greater frailty and more frequent falls and hospitalisations. Consequently, delirium cases have risen drastically, creating a 'silent epidemic' in patients with COVID-19 (Han et al., 2010).

A longitudinal cohort study at a Swiss university hospital, analysing data from 29 278 eligible patients admitted over a period of 12 months, showed that patients with delirium in acute care settings had significantly higher mortality rates, longer hospital and ICU stays and required significantly more nursing resources, generating significantly higher costs than patients without delirium (Schubert et al., 2018). Since delirium also leads to an increased need for costly long-term care (Gleason et al., 2015; Zhang et al., 2013), it represents a major burden for the local communities and the healthcare system in general (Krogseth et al., 2014; Witlox et al., 2010). Despite its consequences being difficult for affected individuals and their relatives and costly for society, delirium remains highly understudied (Wilson et al., 2023).

Delirium has a complex, multifactorial, and incompletely understood pathogenesis and is also difficult to recognise and diagnose clinically (Wilson et al., 2020). Early detection and treatment of underlying causes may reverse delirium, and it can, in some cases, also be prevented. However, clinical management of its symptoms remains challenging, and new and effective treatment and prevention alternatives are urgently needed (Wilson et al., 2023). Common pharmacological agents (e.g. benzodiazepines and antipsychotic medication) show poor

efficacy and can, in some cases, trigger or worsen delirium (Wu et al., 2019). Newer network meta-analyses have shown that multi-factorial approaches combining environmental and clinical adjustments, reorientation, cognitive and sensory stimulation (sometimes including music), early mobilisation and family involvement significantly reduced the incidence and duration of delirium in older patients in the ICU, making them the most promising non-pharmacological approach in this setting (Chen et al., 2022).

3.1.2 Subtyping

The clinical manifestation of delirium is heterogeneous regarding both the number and intensity of its presenting features. Therefore, subtyping of delirium is highly recommended for advancing research on alternative treatments and interventions. It enables a focused examination of specific symptoms and outcomes with proposed treatments instead of evaluating delirium as a whole (Wilson et al., 2020). Abraha et al. (2015) highlight that the limited efficiency of existing interventional studies might be attributed to their dichotomising of delirium (focusing only on its presence or absence) and overlooking its specific symptoms and subtypes. We have attempted to address this limitation in our clinical trial design. We have also ascertained the degree to which delirium was subtyped in the trials included in our systematic literature review.

The predominant psychomotor subtypes of delirium include (1) hypoactive delirium, with abnormal drowsiness, lethargy and reduced motor activity as the main features; (2) hyperactive delirium, recognised by agitation, restlessness, rapid mood changes, hallucinations and refusal to cooperate with care; and (3) mixed delirium, with fluctuations between the hyperactive and hypoactive symptoms (Maldonado, 2017). Extreme manifestations are also observed, such as the 'catatonic type' characterised by catatonic retardation (severe immobility and unresponsiveness) and the 'excited type' characterised by catatonic excitement (severe agitation and motoric restlessness; Maldonado, 2017). The medical literature also recognises subsyndromal delirium, where only one or a few core symptoms are present (Sepulveda et al., 2016).

The assessment of delirium subtypes traditionally relies on evaluating psychomotor functioning, encompassing observational measures of motor activity, speech and LoA (Meagher et al., 2008). Frequently considered a robust predictor of delirium (Tieges et al., 2013), Neerland et al. (2018) proposed arousal as the lowest-level diagnostic criterion, influencing all others. Directly contingent on arousal and awareness, attention and consciousness constitute middle-level criteria. Dependent on both arousal and attention, cognition is regarded as the highest-level diagnostic criterion. This hierarchical model suggests that individuals with disturbed LoA may experience challenges in focusing attention, awareness of their surroundings, and

performance on cognitive tests, often resulting in additional emotional and psychomotor disturbances (Neerland et al., 2018).

Chester et al. (2012) asserted that assessing the LoA proved particularly valuable in subtyping delirium and emphasised correlations between decreased arousal and the hypoactive subtype and increased arousal and the hyperactive subtype. Han et al. (2019) also emphasised the importance of arousal-based subtyping of delirium, deeming it more feasible and efficient than subtyping based on psychomotor functioning, particularly in critically ill patients in acute care settings with numerous risk factors and severe outcomes. Han et al. (2019) partly challenged the notion of arousal being the primary indicator of delirium by noting instances, especially among older patients in emergency departments, where patients met delirium criteria, such as inattention and disrupted awareness, while still exhibiting a normal LoA.

The correlation between delirium subtypes and outcome severities usually depends on the clinical setting. Hypoactive delirium was reported to be associated with the highest one-year mortality in patients receiving palliative and post-acute care (Han et al., 2019) but the lower mortality in patients with hip fractures (Marcantonio et al., 2002). As previously mentioned, the less common delirium with normal LoA led to the worst six-month outcomes, including the greatest mortality and cognitive decline, in older patients in emergency departments (Han et al., 2019). However, further research is necessary to establish the exact correlations between the specific delirium subtypes and the severity of short- and long-term outcomes.

3.1.3 Pathophysiology and pathogenesis

The primary objectives of exploring the pathophysiology of delirium were to formulate relevant outcomes for patients with delirium in an acute geriatric hospital setting and devise potentially effective MI protocols highlighting specific underlying mechanisms of change. The pathophysiological process associated with delirium is essentially characterised as a 'failure of the vulnerable brain to show resilience in response to an acute stressor' (Wilson et al., 2020, p. 4). The brain's vulnerability is caused by several intricate neurobiological mechanisms, making understanding its pathogenesis challenging. Despite emerging unifying themes, formulating a common pathway for delirium pathogenesis remains difficult (Maldonado, 2017). Current theories are mostly hypotheses associated with specific patient groups, risk factors and delirium subtypes (Echeverría et al., 2022; Wilson et al., 2020). Kennedy et al. (2020) proposed the following common contributors to delirium development: (1) Delirium may be associated with a transient disturbance in the brain's oxidative metabolism, which can be reversed; (2) Imbalances in various neurotransmitters, with a particular emphasis on reduced cholinergic activity, may play a role in delirium development; (3) The presence of inflammatory markers

such as C-reactive protein (CRP), interleukin (IL)-1β and IL-6, and tumour necrosis factor (TNF)-α, suggests an inflammatory component in the pathophysiology of delirium; (4) Any stress can increase sympathetic tone and decrease parasympathetic tone, disrupting cholinergic function and contributing to the onset of delirium. Older adults are particularly susceptible to reduced cholinergic transmission, heightening their vulnerability to delirium.

Currently, the most relevant hypotheses on delirium pathophysiology, as listed by Echeverría et al. (2022), are: (1) Neuro-inflammation arising from peripheral inflammatory insults disrupts the blood-brain barrier and causes central nervous system inflammation and damage; (2) Reactive oxygen species, implicated in cellular damage, pose a particular threat to the central nervous system due to its lipid-rich and antioxidant-poor nature; (3) Neurotransmitter imbalances, specifically decreased acetylcholine and increased dopamine activity, contribute to delirium; (4) The release of neuroendocrine factors (glucocorticoids) in response to physiological stress heightens neuronal vulnerability and influences gene transcription, cellular signalling, and glial cell behaviour.

Regardless of the specific causes, delirium seems to be associated with impaired functioning of the cerebral hemispheres and disruptions in the arousal mechanisms of the thalamus and the reticular activating system, with these central nervous system alterations collectively contributing to the clinical manifestation of delirium (Kennedy et al., 2020; Wilson et al., 2020). Building upon the understanding of these pathways, in our clinical trial, we hypothesised that MIs could provide neurophysiological stimulation, influencing arousal and further regulating various aspects of delirium, such as attention and cognition (Golubovic et al., 2023). The following subchapter will describe the theoretical rationale for the MIs used to regulate delirium symptoms in our clinical trial.

3.2 Theoretical rationale for the implemented interventions

This subchapter elaborates on the short version of the theoretical rationale for the two tested MIs previously published in Article 2.

Our pilot and feasibility trial investigated PLM and PRM interventions, both designed and administered by a trained music therapist. The hypothesis posited that they would benefit acutely ill patients with delirium and act through some shared and specific therapeutic mechanisms based on which they could be compared. The structure of our theoretical framework was based on the heuristic model of working factors in music therapy (Hillecke, 2005) and

the theoretical music capacities model (TMCM) for neurological disorders similar to delirium (Brancatisano et al., 2020). The TMCM emphasises the importance of defining the context for music delivery (protocolised MIs), the specific music capacities that the chosen interventions provide, the mechanisms through which they impact health and well-being, and the specific outcomes and health benefits resulting from them (Brancatisano et al., 2020). The model by Hillecke (2005) highlights factors at play in music therapy interventions and the particular functions that they can modulate.

3.2.1 Shared therapeutic features of PLM and PRM interventions

As a multisensory phenomenon and a stimulus, music can stimulate various brain regions (Peretz & Zatorre, 2005) and has unique capacities relevant to treating neurologic conditions similar to delirium: (1) The capacity to engage a myriad of functions simultaneously; (2) The capacity to modulate, induce and communicate emotions; (3) The capacity to stimulate spontaneous physical movement; (4) The capacity to build personal connections and evoke personal associations; (5) The capacity to facilitate meaningful social interaction and bonding; (6) The capacity to be persuasive and interact with religious and non-religious belief-systems; and (7) The capacity to afford synchronisation of movement and singing to the external rhythm or melody (Brancatisano et al., 2020). These capacities of music generally afford MIs the potential to modulate both neurocognitive, perceptual, behavioural, physiological and psychosocial functions (Hillecke, 2005), such as attention, memory, learning, motivation, emotions, planning, expectation, heart rate, breathing, communication, social interaction, and (in)voluntary movement (Brancatisano et al., 2020). Underpinning these therapeutic capacities are mutually overlapping biological (neurological), psychological (cognitive-emotional), and socio-environmental (ecological) mechanisms, and pathways such as neuroplasticity, neurochemistry, mirror-neuronal, auditory-motor coupling and neural entrainment, arousal-mood, autobiographical and implicit memory, and affect attunement (Brancatisano et al., 2020; Gold et al., 2019; Koelsch, 2014; O'Kelly et al., 2013; Park et al., 2016; Vuilleumier & Trost, 2015). Most capacities, working factors and mechanisms described above are expected to be at play in the PRM and PLM interventions (Figure 3.1.).

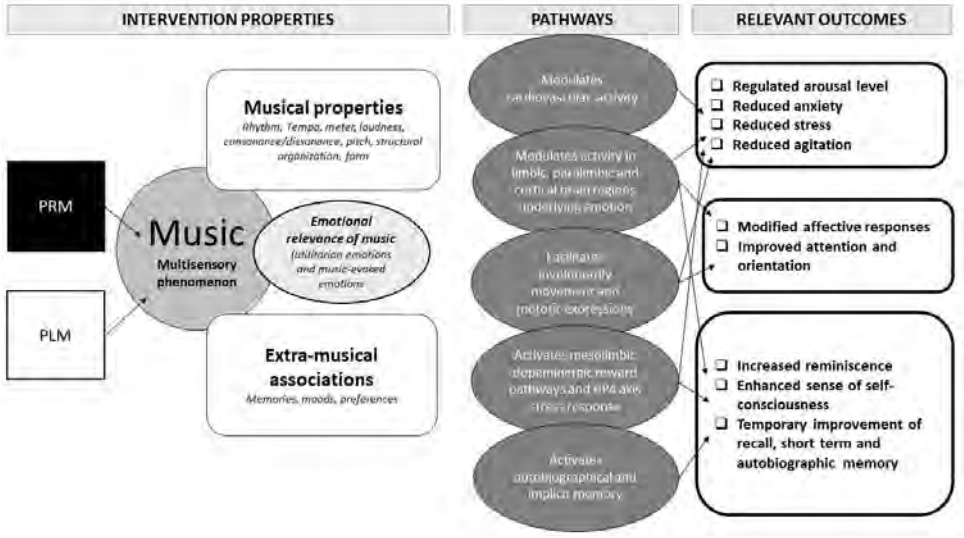


Figure 3.1: The shared therapeutic mechanisms of PRM and PLM.

Note. Reprinted from the Article 2 (Golubovic et al., 2023).

3.2.1.1 Psychological mechanisms

Music can create the experience of anticipation, expectation, predictability, novelty, surprise and importance, establishing a specific auditory environment that can influence and modulate arousal (Thaut et al., 2014). Music properties such as rhythmical patterns, metre, pitch, intensity, tempo, form, and structural organisation, as well as extra-musical associations, such as memories and moods, contribute to creating the state of readiness and motivation, which modulate both arousal and attention, thus eliciting various therapeutic outcomes (Ellsworth & Scherer, 2003; Thaut et al., 2014; Figure 3.1.).

Music's arousal-regulating potential is reflected in its ability to raise energy levels, reduce tension and increase wakefulness, and it has been associated particularly with improvements in retrieving memory, increased reminiscence (Hirokawa, 2004; Lim & Park, 2018), reduced anxiety (Bradt & Dileo, 2014), agitation (Baker, 2001) and increased relaxation (Bernatzky et al., 2011) in older adults. In addition to subjective feelings, motoric expressions (e.g. smiling), and motor-action tendencies (e.g. foot-tapping, clapping, and dancing), arousal is considered an essential component of emotions, and the evidence shows that music can evoke changes in all these areas (Koelsch, 2014). An additional factor relevant to regulating delirium symptoms is music's environmental component, reflected in its ability to influence and modify the

experience of the surroundings and potentially induce relaxation, pleasantness and coherence, thus regulating arousal (Franěk et al., 2020; Yamasaki et al., 2015). Conversely, inappropriate music choices may adversely affect the environmental experience and arousal.

3.2.1.2 Neurobiological mechanisms

The therapeutic potential of music for treating neurological conditions such as delirium also lies in its ability to modulate activity in limbic and paralimbic structures underlying emotion, such as the amygdala, nucleus accumbens, hypothalamus, hippocampus, insula, cingulate cortex and orbitofrontal cortex, that are usually affected (Koelsch, 2014). Music can elicit every day, utilitarian emotions that are important for adaptation, survival and thriving, such as joy, fear or surprise. However, music can also evoke more complex aesthetic/epistemic emotions related to its intrinsic qualities, thus affecting more profound behavioural and psychological changes (Ellsworth & Scherer, 2003; Koelsch, 2014). Such music-evoked emotions are further associated with music's ability to stimulate involuntary movement and various entrainment effects (Thaut & Hoemberg, 2014). Rhythmic entrainment is a process in which brain activity or heart rate is modified by and gradually synchronised with the tempo or rhythmic structure of the stimulating music (Vuilleumier & Trost, 2015). Metrical rhythms can facilitate movement (Grahn & Brett, 2007), induce emotions, cognitive processes (Sakai et al., 1999) and attention (Jones & Boltz, 1989), and musical meter might, through neural synchronisation, entrain the attention process and synchronise attention with the musical beat (Jones & Boltz, 1989).

3.2.1.3 Music preferences and psychosocial mechanisms

The therapeutic qualities of preferred music derive both from its social and auditory characteristics (Rentfrow et al., 2011). Music preferences are closely related to personal, social and cultural identity and musical memory, which is usually intact (Baird & Samson, 2015), even in neurological conditions such as dementia and delirium. Preferred music is hypothesised to be able to modify affective responses (Baird & Samson, 2015), enhance the sense of self-consciousness (Arroyo-Anlló et al., 2013), and even temporarily improve some cognitive functions, such as autobiographic memory (Thaut & Hoemberg, 2014). Furthermore, integrating music into care settings contributes to a therapeutic milieu by alleviating environmental stressors and enhancing ambience, thereby regulating LoA for effective delirium management (Iyendo, 2016).

3.2.1.4 Summary of the shared therapeutic impacts

The theoretical rationale for using PLM and PRM interventions in delirium management lies in their shared abilities to modulate neurobiological processes, address psycho-emotional aspects, and optimise the socioenvironmental context, providing a holistic and non-invasive approach to delirium management (Hillecke, 2005; Vuilleumier & Trost, 2015). Neurobiologically, music engages brain regions associated with emotion, memory and attention, influencing neurotransmitter activity and neural connectivity linked to delirium-related cognitive processes. Music's rhythmic and melodic components may also synchronise with neural oscillations, fostering coherence in brain function and potentially ameliorating delirium-related disarray. Psychologically, music elicits emotional responses, induces relaxation, and facilitates communication, addressing disturbances in perception and affect commonly observed in delirium. While the psychosocial/ecological perspective is not directly reflected in our choice of outcome measures, the potential impacts of MIs on mitigating ecological stressors and modulating arousal by enhancing ambience may not be excluded and might still contribute to the effectiveness of the tested MIs.

3.2.2 Theoretical rationale for comparing PRM and PLM

The main differentiating components of the PLM intervention were live sound delivered by a human voice, the presence of a musical instrument (guitar) and improvisation elements. The PRM intervention involved synthetic sound delivered from the loudspeakers and original versions of the preferred music. While both MIs were delivered within the context of a therapeutic relationship, the nature and intensity of this relationship differed; it was more intensive and interactive in the case of PLM and supportive and non-interactive in the case of PRM. In the PLM intervention, the music therapist actively engaged in responsive musical and non-musical interactions with the participants, aiming to tune into their emotional and psychological state, meet their needs and foster safety. During this musical and emotional attunement process, both verbal and non-verbal cues and expressions were used to establish a connection with the participants, as well as musical elements such as rhythm, tempo, dynamics, melody, and harmony (Krøier et al., 2022; Krøier et al., 2021; Metzner et al., 2018). Conversely, in the PRM intervention, the music therapist only introduced and facilitated the music-listening session, otherwise attempting to remain inactive.

The principal agents for change in the PLM intervention were the music and the therapeutic relationship with the trained music therapist, within which musical interactions and attunement occur (Sihvonen et al., 2017). Since the music therapist can respond dynamically and adapt the intervention to the participant's changing needs, it was anticipated that the PLM

intervention would be more suitable than the PRM intervention to address the fluctuating, multifaceted nature of delirium. Since the patient's subjective experience of delirium is usually frightening and distressing, collaborative musical interactions with the music therapist during the PLM intervention were expected to enhance feelings of safety, foster emotional connectedness, and regulate stress levels and agitation (McDermott et al., 2014). Elements such as live performance and improvisation in the PLM intervention were hypothesised to be more engaging for patients with delirium and to be able to assist in synchronising their internal physiological rhythms to the external ones in music, thus mitigating anxiety and stress (Bush et al., 2021; Cheong et al., 2016). The physical presence of a musical instrument, human voice and sound vibrations during the PLM intervention was expected to introduce visual and sound-localisation components, thus providing additional sensory stimulation that could impact attention, orientation, reminiscence and recall better than the PRM intervention (Lee et al., 2021). Furthermore, due to the number of sensory and social stimuli, the PLM intervention was expected to enhance the environmental effects of music and modify the participant's experience of the environment and arousal more than the PRM intervention, which had fewer such stimuli (Figure 3.2; Yamasaki et al., 2015).

Without a musical interaction with the music therapist and fewer stimulating sensory elements, the PRM intervention was expected to afford participants a more direct engagement with the music and a more soothing and relaxing experience (Dileo, 1999). Therefore, the PRM intervention was expected to better suit participants exhibiting symptoms of hyperactive delirium than the PLM intervention. Recorded music has been previously shown to positively affect cognitive functions, orientation, recall, anxiety reduction and aggression mitigation (Clare & Camic, 2020). As Baker (2001) emphasised, recognising the unique 'sound' of an original song version may also be expected to contribute to enhanced orientation and biographical recall. However, prolonged exposure to complex music featuring multiple instruments, such as bands or orchestras, may also lead to habituation and boredom in the participants (Figure 3.2; Szpunar et al., 2004;).

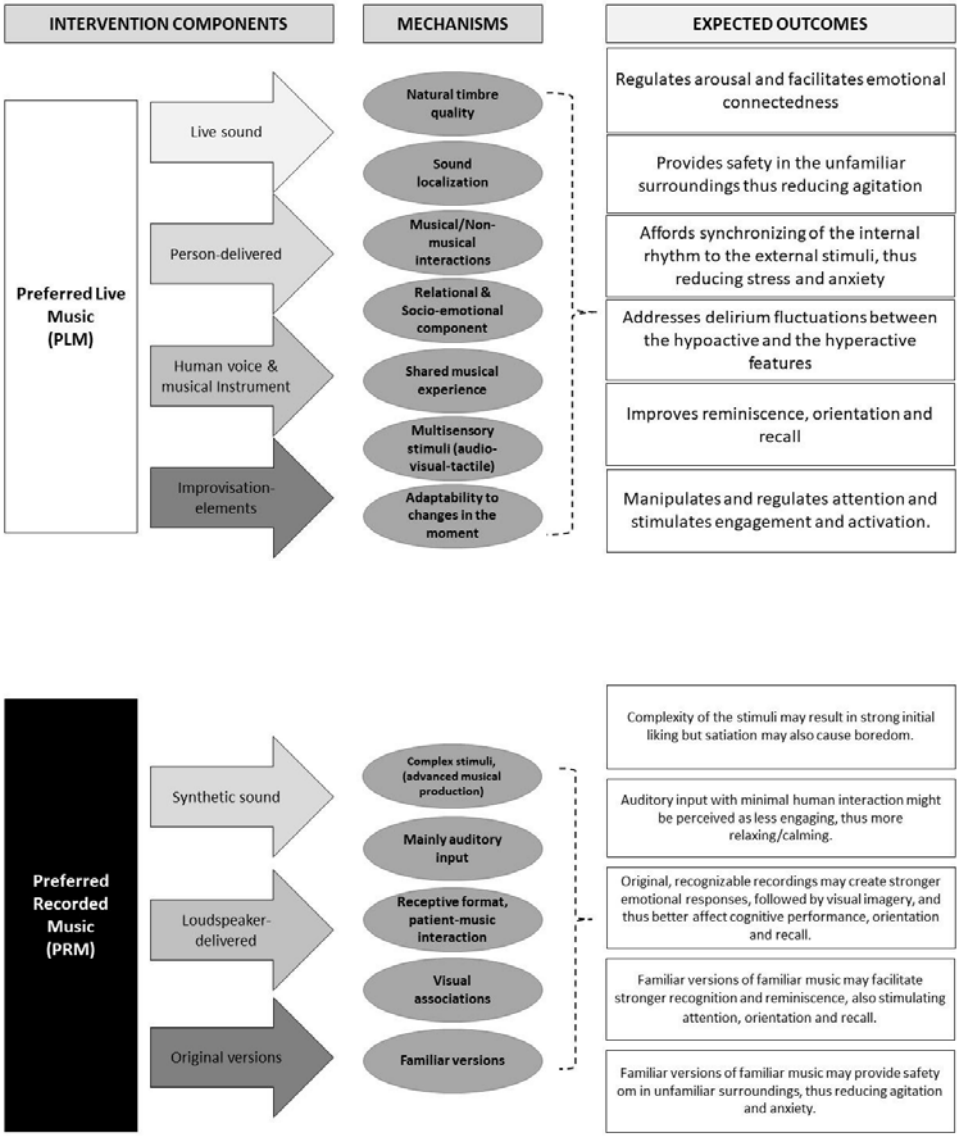


Figure 3.2: The rationale for comparison.

Note. Reprinted from the Article 2 (Golubovic et al., 2023) with permission.

4 Design, methods and procedures

This thesis comprised two mutually related substudies: (1) a systematic literature review with narrative synthesis and meta-analysis, and (2) a pilot and feasibility trial conducted in an acute geriatric clinical context. This chapter describes the design, methods and procedures used in the substudies.

4.1 Systematic review

A systematic review is a meticulous, methodological approach to identifying, examining and synthesising published data to answer a specific research question. Systematic reviews, particularly those including statistical meta-analysis, focus on replicability, minimising bias, and generating reliable conclusions that can inform clinical practice, policy changes and decision-making in healthcare and identify areas for further research. Quantitative findings generated in systematic reviews with meta-analyses are considered the highest level of evidence on the evidence pyramid (Burns et al., 2011).

Systematic reviews are protocol-based and revolve around predefined key questions, which are equivalent to hypotheses in primary research studies. Since they define the scope of the review, the key questions must be clear, focused and structured in a specific way, usually following the PICO framework, where 'P' stands for the population and/or the health challenge of interest; 'I' for the intervention(s), treatments and exposures in focus; 'C' for comparators, such control groups or alternative interventions; and 'O' for expected outcomes and what had been measured. In some cases, when study designs other than RCTs are relevant to include, an additional "S" specifying study design might be added (Linares-Espinós et al., 2018).

Our systematic review's primary and secondary research questions were formulated according to the PICOS standard and were previously presented in Subchapter 1.3. In our review, 'P' represents adults (age ≥18 years) with or at risk of delirium across clinical settings and care levels; 'I' represents the MIs, both delivered by a music therapist and others; 'C' represents usual care, another pharmacological/non-pharmacological intervention or another MI; 'O' represents any clinical outcomes directly or indirectly indicative of alterations in the incidence, intensity, or duration of delirium or its symptoms, as well as enhancements in overall well-being; and 'S' represents any relevant quantitative designs such as RCTs, controlled trials, quasi-experimental studies (non-randomised designs, before-and-after designs, interrupted

time series designs) and observational studies (cohort and case-control studies; Golubovic et al., 2022).

Systematic review protocols specify the plan for conducting the review, with detailed descriptions of the main health issue of interest and the eligible interventions, comparators and outcome designs. They also provide details of the main procedures for searching, selecting and summarising the data. It is common for systematic review protocols to be published in relevant registries and databases to enable replicability and avoid duplications and research waste. Some of the relevant registries are the Cochrane Database and the International Prospective Register of Systematic Reviews (PROSPERO; Cumpston et al., 2019; Higgins & Deeks, 2008; Khan et al., 2003; Russell et al., 2010; Tawfik et al., 2019). Systematic review protocols usually follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist (Moher et al., 2010). Our systematic review protocol was formulated according to the PRISMA checklist, first submitted to PROSPERO on 10 October 2020 and registered/last edited on 3 November 2020, with the ID CRD42020212260.

4.1.1 Steps and procedures

Our systematic review was conducted following five methodological steps.

Step one mainly focused on formulating unambiguous key questions for the review (presented in Subchapter 1.3.). This step involved simple preliminary searches of the Google Scholar or PubMed databases that were intended to validate the originality of the idea and the questions, avoid duplication and ensure sufficient articles were available to conduct the review and analysis. This step also involved formulating eligibility criteria for study inclusion and exclusion based on the previously described PICOS principles (Table 4.1). Pre-defined and clear eligibility criteria were also part of the strategy to avoid inclusion bias (Tawfik et al., 2019).

	Inclusion	Exclusion
Participants	Adults (aged ≥18 years) with or at risk of delirium across clinical settings and care levels.	Children (aged <18 years)
Interventions	All music-based interventions delivered by music or non-music therapists.	Music is part of multi-component interventions, but its effect is not reported separately; studies where the effect on delirium cannot clearly be attributed to MIs.
Comparators	Usual care or another intervention	
Outcomes	Incidence, severity, and duration of delirium (directly or indirectly reported); changes/ improvement in general well-being attributable to delirium; delirium data is reported, regardless of whether the study aimed to investigate its prevention or treatment or delirium was its main focus; studies with mixed diagnoses where outcomes were reported separately for delirium.	Delirium or acute confusion is not explicitly mentioned or reported separately.
Design/ Methodology	RCTs; non-randomised, quasi-experimental studies; observational studies; case-control studies.	Qualitative studies, program descriptions, surveys, systematic reviews, or editorials.
Publication format	Full articles and reports published in peer-reviewed journals and higher degree theses and dissertations.	Ongoing studies, partially published research, informally reported and/or published studies, book chapters and books where the data was not reported.
Language	English, Scandinavian, Balkan, Spanish or Italian.	Other.

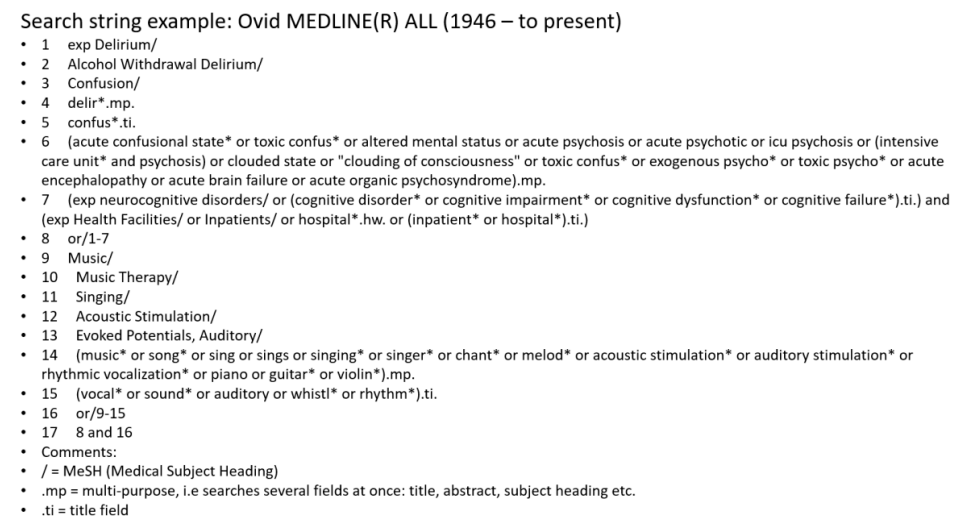
Table 4.1: The study eligibility criteria.

Note. Reprinted from the Article 1 (Golubovic et al., 2022).

Step two focused on identifying relevant studies for inclusion. This process involved developing a search strategy and a precise search string in collaboration with an experienced librarian, searching the relevant databases, and selecting eligible studies for inclusion. The choice of databases depends on the research topic and the review questions. Besides Google Scholar, which is a convenient general database for preliminary searches, reviews similar to ours usually include a combination of one database covering the most important journal articles in life sciences and medicine (e.g. PubMed, MEDLINE), one database covering articles from the behavioural and social sciences (including psychology; e.g. PsychINFO), one interdisciplinary database (e.g. Scopus, Web of Science) and databases where ongoing and unreported trials may be retrieved (ClinicalTrials.gov, Cochrane Central Register of Controlled Trials [CENTRAL]; Tawfik et al., 2019).

We searched the MEDLINE, PsychINFO, Scopus, ClinicalTrials.gov and CENTRAL databases and manually searched existing systematic reviews for relevant quantitative studies published from 1946 to 2022. A precise and comprehensive search string, combining the most relevant

search terms and synonyms, was developed for each database in collaboration with an experienced librarian. The main search terms were music and delirium, but synonyms were also searched. The search string(s) included both free terms and controlled vocabulary from the medical subject headings (MeSH) thesaurus or the database's own vocabulary/thesaurus. Figure 4.1. shows an example of a search string used for the MEDLINE database.


Search string example: Ovid MEDLINE(R) ALL (1946 – to present)

- 1 exp Delirium/
- 2 Alcohol Withdrawal Delirium/
- 3 Confusion/
- 4 delir*.mp.
- 5 confus*.ti.
- 6 (acute confusional state* or toxic confus* or altered mental status or acute psychosis or acute psychotic or icu psychosis or (intensive care unit* and psychosis) or clouded state or "clouding of consciousness" or toxic confus* or exogenous psycho* or toxic psycho* or acute encephalopathy or acute brain failure or acute organic psychosyndrome).mp.
- 7 (exp neurocognitive disorders/ or (cognitive disorder* or cognitive impairment* or cognitive dysfunction* or cognitive failure*).ti.) and (exp Health Facilities/ or Inpatients/ or hospital*.hw. or (inpatient* or hospital*).ti.)
- 8 or/1-7
- 9 Music/
- 10 Music Therapy/
- 11 Singing/
- 12 Acoustic Stimulation/
- 13 Evoked Potentials, Auditory/
- 14 (music* or song* or sing or sings or singing* or singer* or chant* or melod* or acoustic stimulation* or auditory stimulation* or rhythmic vocalization* or piano or guitar* or violin*).mp.
- 15 (vocal* or sound* or auditory or whistl* or rhythm*).ti.
- 16 or/9-15
- 17 8 and 16
- Comments:
- / = MeSH (Medical Subject Heading)
- .mp = multi-purpose, i.e searches several fields at once: title, abstract, subject heading etc.
- .ti = title field

Figure 4.1: An example search string used for the Ovid MEDLINE database.

Note. This figure was previously published as Appendix in the Article 1 (Golubovic et al., 2022) and is reprinted with permission.

Once the searches had been performed, all the references were imported into the bibliographic library software Endnote (version X9; Thomson Reuters), and duplicates were removed. The file was then uploaded to the online software Rayyan for further selection of the studies (https://rayyan.ai/cite; Ouzzani et al., 2016). The records were first screened based on their titles and abstracts, and then the final selected articles underwent full-text review.

The third step involved extracting data according to the previously determined data categories (Table 4.2.). One of the reviewers extracted data relevant to the key questions, which was checked for accuracy by the other two reviewers, and recorded in Microsoft Excel sheets for further analysis and synthesis. The methodological quality and risk of bias in the included studies were critically appraised using the standardised assessment scale PEDro (Maher et

al., 2003).[8] This scale consists of 11 items from the Delphi list of criteria for quality assessment of RCTs and was developed by expert consensus (Verhagen et al., 1998). It evaluates whether the included study(s) demonstrate internal validity (items 2–9), report sufficient details on the statistical analysis methods for their results to be interpretable (items 10 and 1), and maintain external validity/generalisability (item 1; de Morton, 2009). The scores also inform about the heterogeneity among the studies and help determine whether an overall or subgroup meta-analysis is possible (Khan et al., 2003). The general interrater reliability of PEDro scale scores for non-pharmacological trials has shown to be fair to excellent (intraclass correlation coefficient = 0.53–0.92), with the inter-rater reliability of each item ranging from fair to almost perfect (Cohen's Kappa = 0.36–1.00; Cashin & McAuley, 2019). The PEDro scale does not assess study conclusions, and high scores do not guarantee the treatment's clinical utility, effectiveness over potential side effects or cost-effectiveness. The PEDro scale is also not recommended for comparing the quality of trials across different therapy areas since it might not be possible to fulfil some of the scale criteria (Maher et al., 2003). The suitability of the PEDro scale for assessing MI studies will be further discussed in Chapter 6. Two blinded reviewers conducted the quality assessments, and disagreements between them were resolved by a third reviewer.

8 The PEDro scale was obtained from: https://www.pedro.org.au/wp-content/uploads/PEDro_scale.pdf (Accessed: 15/02/2024).

General	Date of extraction Author Title Publication type Country of origin Source of finding Language
Study characteristics	Aims and objectives Study design Eligibility criteria Recruitment strategy Unit of allocation Clinical context/level of care Theoretical framework
Participants (demographics)	Age Gender Ethnicity Disease Comorbidities
Interventions	Intervention(s) Dose/delivery Administrator Comparators
Outcomes	Primary outcomes Secondary outcomes Assessment tools Assessment protocols
Enrolment	Participants enrolled Participants included in the analyses Withdrawals/drop-outs
Findings	Results of the analyses Demographic data Costs Resources needed Adverse events Suitability of the measuring tools Strengths and limitations
Other	

Table 4.2: Categories for data extraction.

The fourth step involved summarising the collected data and conducting a narrative synthesis and meta-analysis. Our narrative synthesis was based on the adapted Economic and Social Research Council Methods Program (Popay et al., 2006). We applied only steps two and three of the frameworks: a preliminary synthesis with descriptions, systematising and tabulating the findings, and exploring the relationships between and within the studies. The included studies were first assessed for heterogeneity regarding interventions, outcomes, and population/clinical settings. The data from the sufficiently homogenous studies were statistically pooled to calculate summary effect estimates.

Only one subgroup meta-analysis was possible due to the generally high heterogeneity among the included studies. The meta-analysis compared the effect of exposure to music (both nurse-delivered music listening and music therapy) to no music on delirium incidence, including data from six included studies. The primary analysis used a statistical random effects model, which allows for a certain amount of heterogeneity among the studies by incorporating the heterogeneity into the statistical analysis (Kirkwood & Sterne, 2010). The consistency of the results was assessed using a sensitivity analysis with a fixed effects model. The Q and I^2 statistics (Higgins & Thompson, 2002) were used to assess heterogeneity between studies. Egger's test (Egger et al., 1997) and funnel plot inspection were used to evaluate publication bias. We conducted another sensitivity analysis to assess the robustness of the summary estimate, excluding one study at a time and assessing the impact on the summary estimate. We used Stata software (version 13.1) to conduct all the analyses (StataCorp, 2023).

The final fifth step involved interpreting the findings. The risk of bias in the included studies was carefully considered and explored during this step, and findings/effect estimates and reliability of the inferences and recommendations were evaluated and graded according to the methodological quality of the included studies (Khan et al., 2003).

4.1.2 Ethical considerations

To avoid duplicates and enable replicability, our systematic review protocol was registered at PROSPERO (ID: CRD42020212260), and the systematic review was reported according to the PRISMA checklist (Moher et al., 2010). To mitigate the risk of bias, three reviewers were always involved in screening and selecting the relevant articles, where the role of the third reviewer was mainly to resolve disagreements between the first two reviewers. To ensure the reliability of the results and robust effect estimates, we evaluated the methodological quality of the included trials using the standardised and reliable PEDro scale (de Morton, 2009) and calculated interrater agreements.

4.2 Pilot and feasibility trial

4.2.1 Pilot and feasibility testing

The clinical trial conducted within this PhD project belongs to the preparatory research category, aiming to explore the conditions and prepare the design of a large conclusive trial. It included both exploring feasibility and testing a pilot. It was designed according to the

Consolidated Standards of Reporting Trials (CONSORT) statement's extended checklist for pilot and feasibility trials (Eldridge et al., 2016). The terms feasibility and pilot are closely related and often used interchangeably (Lancaster & Thabane, 2019). However, no consensus currently exists in the research community on whether pilot studies are a subtype of feasibility studies or vice versa. While pilots have traditionally been used to estimate effect sizes and calculate sample sizes for subsequent larger trials, this approach has faced scrutiny because their typically small and unrepresentative samples might cause inaccuracies in parameter estimates and their standard errors, thereby producing misleading conclusions and power calculations (Kleinbaum et al., 2013). Evaluating the safety and tolerability of the interventions and aiming to obtain preliminary conclusions about their efficacy in pilot trials has also been criticised for potentially generating misinformed decisions about the proceeding to the conclusive trials (Kistin & Silverstein, 2015). Kistin and Silverstein (2015) also provided recommendations for what pilot trials should focus on:

> (…) pilot intervention studies are most effective when they focus on testing study logistics under the circumstances mimicking the eventual definitive study (i.e., field testing), optimising intervention delivery, understanding the barriers to and facilitators of eventual dissemination and implementation of an intervention, and obtaining empirical evidence of study parameters to help design the definitive clinical trial (p. 1561).

Teresi et al. (2022) further underlined that the questions that may and should be addressed in pilot trials concern the feasibility of data collection protocols, maintenance of intervention fidelity, participants' retention and adherence to the interventions and follow-up procedures. While pilot studies may still be used for power calculation for larger definitive trials, their main focus must be on confidence intervals (CIs) rather than determining point estimates (Teresi et al., 2022).

Our trial design was largely aligned with these recommendations. Our primary feasibility outcomes, assessed upon the completion of the intervention period, were: (1) recruitment rate: the average number of patients recruited per month; (2) retention rate: the proportion of participants completing the study per the protocol; (3) the proportion of sessions where the MIs and pre-post assessments were completed as planned, and the proportion of sessions with protocol deviations; (4) the success of treatment fidelity (Golubovic et al., 2023).

4.2.1.1 Efficacy and effectiveness research

An important distinction in our study design was the one between the explanatory (efficacy) research, conducted in ideal, experimental settings, with interventions delivered by the researchers or the hired interventionists, often specially designed and described in strict protocols to be consistent with their hypothesised mechanisms of action; and the more pragmatic effectiveness research, where the interventions are part of the routine clinical practice and delivered by existing staff in as authentic a format as possible, allowing for more flexibility in delivery, and where the success of delivery is measured by the balance between fidelity to the intervention protocol and adaptation to the context (Holtrop et al., 2022; Macpherson, 2004; Patsopoulos, 2011). The interventions in explanatory (efficacy) research will always differ to a certain extent from the real-world interventions and be more rigid in delivery to allow their potential effects to be better controlled and captured (Macpherson, 2004; Patsopoulos, 2011). While predominantly feasibility-focused regarding intervention delivery and assessment procedures, our trial design leaned more towards explanatory (efficacy) research due to (1) the fact that MIs were not routinely used in the acute geriatric ward, (2) the MIs were described and delivered according to a strict protocol, (3) we developed detailed procedures to evaluate treatment fidelity, and (4) the follow-up procedures for pre-post assessments were not part of the ward's normal routines.

4.2.2 Before-and-after design

Our pilot and feasibility trial used a repeated measure, within-subject, before-and-after design, often called a pre-post design. This type of design involves multiple measures on the same subjects before and after exposure to a treatment to assess its effect on the measured outcomes (Robson, 2001). While often characterised as uncontrolled due to the lack of a control group, the before-the-exposure measures serve as the control and a starting point for comparison (Robson, 2001). However, while it may prove certain indications of effect tendencies and correlations, the before-and-after design is generally less able than an RCT to generate proper causal inferences and to rule out that factors other than the treatment exposure might have caused the effect. Nevertheless, since conducting a comprehensive RCT is not always possible or appropriate, this design might be a good starting point for exploration, requiring significantly fewer resources and being more flexible. The before-and-after design is also recommended for exploring new treatment alternatives for a certain participant group and when there are practical limitations such as recruitment and randomisation uncertainties, potentially small available samples, or limited budget and time (Robson, 2001). Given the exploratory nature of this research project and the fact that generating strong efficacy claims

was not our primary objective, this design was evaluated as suitable for testing the potential of MIs as a novel treatment for delirium in patients receiving acute geriatric care.

4.2.3 Clinical setting and participants

This trial was conducted within the context of acute medicine, also known as acute internal medicine, and within the acute geriatric ward at Oslo University Hospital (OUH) Ullevål. The ward admits older patients with acute functional decline who exhibit new or worsening symptoms in cognitive function, walking/balance or fluid/nutrition intake within the two weeks preceding admission. The ward also prioritises individuals with acute somatic illnesses, complicating comorbidities, or requiring interdisciplinary geriatric assessment, treatment, or clarification of the care level (Akuttgeriatrisk sengepost, n.d.). Participants in this trial were hospitalised patients aged ≥65 years admitted to the acute geriatric ward, still experiencing delirium or subsyndromal delirium diagnosed within the last 72 hours, and with or without underlying dementia.

4.2.4 Interventions and delivery

The PLM and PRM interventions were delivered individually to each patient in their private or shared rooms once daily for 30 minutes over three consecutive days, and the minimum length for the intervention to be considered delivered per the protocol was 10 minutes. Both interventions were designed and delivered by a certified music therapist, who had previously assessed participants' musical preferences from them directly and their legal representatives in an interactive session. The preference assessment sessions were adapted to the participants' condition, lasted up to 30 minutes and included both musical and verbal interactions as well as observations of responses to musical examples introduced by the music therapist. A detailed description of the interventions and theoretical rationale for comparison was previously presented in Subchapter 3.2.

4.2.5 Randomisation and masking

The participants were allocated to two active treatment arms, one receiving PLM and the other receiving PRM, using permuted block randomisation (1:1), calculated using the True Random Numbers online randomisation software (https://www.random.org/) and randomisation blocks of 10 participants to maintain an even number of the participants in both arms. Masking of the participants and the interventionist was not feasible, but masking of the assessors was attempted. Several steps were undertaken to ensure the success of masking, such as

instructing the nursing staff not to reveal the allocation to the intervention groups and the music therapist always walking into the patients' room with both a guitar and a loudspeaker.

4.2.6 Clinical outcomes, tools and procedures

The clinical outcomes included: (1) The trajectories of delirium symptoms as defined by the diagnostic criteria outlined in DSM-5 and evaluated using a previously delineated diagnostic algorithm and validated tests (Appendix 3; Golubovic et al., 2023) – the Observational Scale of Level of Arousal (OSLA; Hall et al., 2020) and modified Richmond Agitation Sedation Scale (mRASS; Chester et al., 2012) for LoA, backwards and digit span tests for attention, and recall tasks and orientation questions from the Memorial Delirium Assessment Scale (MDAS; Breitbart et al., 1997) for orientation and short term memory; (2) delirium duration; (3) hospital stay length; and (4) use of *pro re nata* (PRN), non-prescribed psychopharmacological medication (benzodiazepines and antipsychotics).

The primary clinical outcomes (trajectory of delirium symptoms) were assessed within one hours before and after intervention exposure. The other clinical outcomes (delirium duration, hospital stay length and intake of psychopharmacological medication) were assessed at discharge.

4.2.7 Treatment fidelity evaluation

As described in Subchapter 4.2.1, one feasibility objective of this trial was evaluating treatment fidelity, which refers to the process used to ascertain whether the interventions and the broader study implementation conform to the intended design and plan. Evaluating and documenting the degree of intervention fidelity essentially explores whether an observed effect (or lack thereof) can be attributed to intentional or unintentional modifications to the intervention protocol (Baker, 2022).

A detailed procedure for evaluating treatment fidelity was developed for our trial based on the National Institute of Health Behavioural Change Consortium recommendations (Bellg et al., 2004; Borrelli, 2011; Borrelli et al., 2005). The evaluation focused on only two of the recommended features: (1) determining whether the trial's design had been clearly articulated before implementation, enabling it to address the research question and be reproducible, and (2) verifying that the treatments were administered according to the intended protocol, aiming for standardised delivery and strict adherence to protocol guidelines (Bellg et al., 2004; Borrelli et al., 2005). All music sessions were video recorded, with only the music therapist visible to protect the patients' identities and anonymity. Videos for 20% of the participants

in each intervention group who completed the interventions per the protocol were randomly selected for evaluation by an independent rater. Two versions of the checklists were developed for the PLM and PRM interventions (Appendix 4a-b), consisting of six items, of which the last three were categorised as compulsory (items 4–6). Each item was evaluated and scored (no = 0, yes = 1), with the predetermined threshold for satisfied treatment fidelity being ≥80% on average across the intervention days, including satisfied compulsory items.

4.2.8 Statistical methods

While primarily focused on a within-subject approach, our two-arm trial also compared the two active intervention groups to ascertain which intervention might be better suited for further testing in a future conclusive trial. Since we did not have a control group, this comparison was mainly exploratory and intended to supplement the primary feasibility evaluations. A pragmatic, intention-to-treat principle was applied to include all available data in the analysis, regardless of whether the participants received all interventions per the protocol. A per-protocol analysis was also planned but was not feasible since only a few participants completed the study per the protocol.

The collected pre-post intervention data were analysed using linear mixed models. We estimated marginal effects for each comparison (within subjects and between groups), adjusted for the participants' baseline scores and with participants' ID included as a random effect. Mixed linear regression models were unsuitable for analysing the delayed recall scores due to their very skewed residuals. Instead, we calculated the proportion of participants who could successfully recall at least one word. The non-parametric Mann–Whitney test U for skewed data was used to compare hospital stay lengths between groups. Fisher's exact test for small samples was used to compare the number of patients receiving PRN medication between groups.

4.2.9 Ethical considerations

Our pilot and feasibility trial was registered at ClinicalTrials.gov with the ID NCT05398211. This registration aimed to reduce publication and reporting bias, facilitate the realisation of ethical obligations towards participants and enhance the broader contribution of research findings to medical knowledge (Aslam et al., 2013). This trial was reported according to the CONSORT extended guidelines for reporting pilot and feasibility trials, and its results were disseminated in relevant scientific journals and at international conferences (Eldridge et al., 2016).

4.2.9.1 Ethical approvals, consent and data management

The clinical trial was ethically approved by the Regional Ethics Committee in Norway (REK; approval number: 457017; Appendix 1). Since most eligible participants were expected to have diminished capacity to provide consent, their ability to consent was assessed individually. Consent was obtained directly from the participants and, when necessary, supplemented or replaced by consent from their legal guardians. The consent forms were available in both Norwegian and English, although all participants included in this trial spoke Norwegian. It was imperative to underscore that participation in this trial was voluntary and, by doing so, uphold ethical standards and maintain the participant' autonomy over their involvement in the research process. The experienced physicians from the acute geriatric ward obtained consent using three distinct consent forms previously approved by the REK. While written consent was prioritised, the REK also approved verbal consent for cases where the legally authorized representative could not be physically present. Verbal consent was mainly obtained through a phone call, and written confirmation was then obtained at the earliest opportunity.

Permission to store the participants' personal data was obtained from the Data Protection Authorities at OUH and accompanied by a comprehensive data management plan. The data in this trial was collected through paper forms and from electronic journals, exclusively at the participating site. The data recorded during this trial was made indirectly personally identifiable through de-identification and coding procedures and stored on secure research servers at OUH and in secured cabinets with keys only available to two research team members (JG and BEN). Through the informed consent forms, the participants were provided with comprehensive information about the personal data collected about them and assured that the data would remain only indirectly identifiable (Appendix 2).

4.2.9.2 Patient safety

The risks posed to patients in this trial were deemed minimal and justifiable compared to the potential benefits. While patients could perceive the MIs as mildly intrusive or exhausting, we did not anticipate any severe adverse events. The engagement of a music therapist to administer both the PLM and PRM MIs was intended to contribute to fostering a safe environment for the patients during the sessions by securing the presence of a proficient professional capable of promptly addressing their needs and responses. The safety of the vulnerable patients with delirium was systematically monitored for the entire duration of the trial, and the potential adverse events were documented. The research team was highly committed to ensuring ethical considerations and participants' well-being and was always attuned and responsive to any indications of their desire to end the music sessions or withdraw from the study.

5 Results Summary

5.1 Article 1

The first article was titled: 'Music Interventions and Delirium in Adults: A Systematic Literature Review and Meta-Analysis'. A systematic search was conducted across multiple databases, including MEDLINE, PsychINFO, SCOPUS, ClinicalTrials.gov, and CENTRAL, to identify quantitative studies comparing any form of MI to standard care or alternative interventions. Out of 1150 studies initially identified, only 12 met the predefined inclusion criteria, of which six were included in the subsequent meta-analysis. The reasons for inclusion/exclusion were recorded and presented in a PRISMA flowchart (Figure 5.1.).

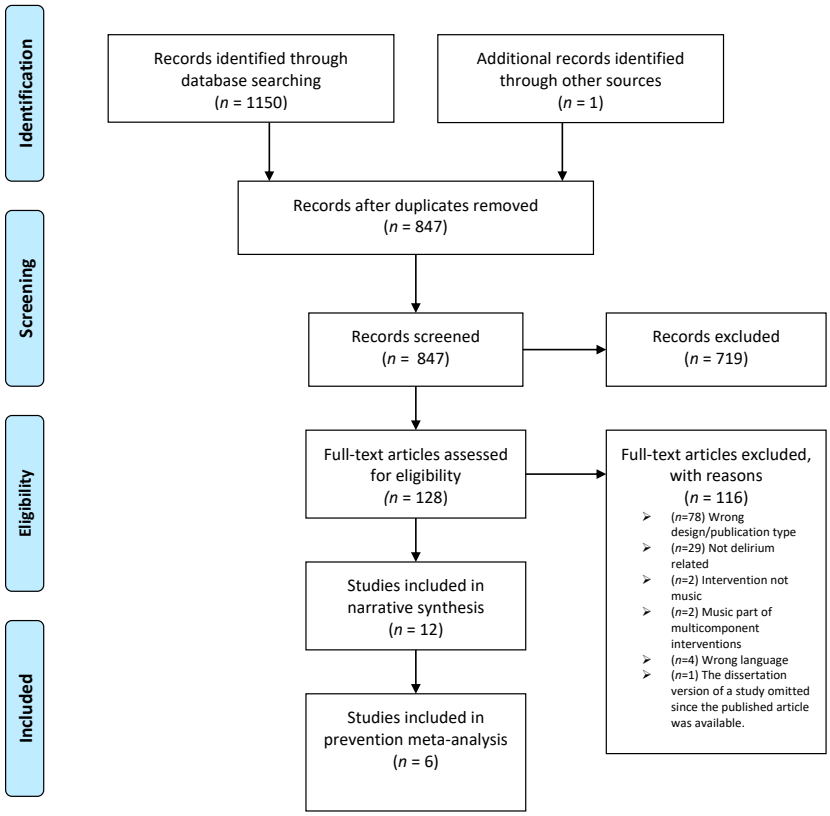


Figure 5.1: The PRISMA flowchart for Article 1.

Note. Reprinted from the Article 1 (Golubovic, et al., 2022).

The calculated Cohen's kappa coefficient (κ = 0.75) indicated substantial agreement between the primary reviewers during the evaluation of the risk of bias among the included studies. Based on the PEDro scores, the methodological quality of the included studies ranged from excellent (n = 1) to good (n = 4) to fair (n = 3) to poor (n = 4; mean = 4.9 ± 2.5; median = 4.5). The risks of bias primarily stem from a lack of masking (participant, interventionist, and assessor) and the lack of allocation concealment and randomisation.

The narrative synthesis revealed the following results:

- The average age of the participants across the studies was 76 years. The participants were mainly recruited from postoperative ICUs and recovery rooms (n = 572), with very few recruited from acute geriatric wards (n = 34) and long-term care (n = 78).
- Most of the included studies were pilot trials, with 10 including a group comparison and only two using a within-subject design, of which neither had explicitly formulated feasibility outcomes.
- There was a predominant focus on delirium prevention, with only a limited number of studies addressing treating and managing delirium severity.
- The methods used to assess delirium varied, encompassing standardised tools and systematic observations, mainly focusing on assessing delirium as a dichotomous variable (yes/no). A few studies assessed changes in delirium by examining indirect outcomes, such as physiological measures, anxiety, mood, engagement or sleep.
- Music listening interventions were more commonly used than music therapy administered by trained music therapists, and non-personalised, researcher-selected music was more common than preference-based music. MIs were mainly compared to usual care or another intervention, and treatment fidelity and adherence were not evaluated. Intervention protocols were mostly non-standardised, with variable dosage and delivery.
- Most of the included trials reported beneficial effects of MIs on delirium prevention and management.

Meta-analysis showed that the summary relative risk for incident delirium when comparing music exposure to no music among post-surgical and critically ill older patients in ICUs was 0.52 (95% CI = 0.20–1.35; I^2 = 79.1%, heterogeneity $p < 0.0001$) using a random-effects model and 0.47 (95% CI = 0.34–0.66) using a fixed-effects model (Figures 5.2. and 5.3.).

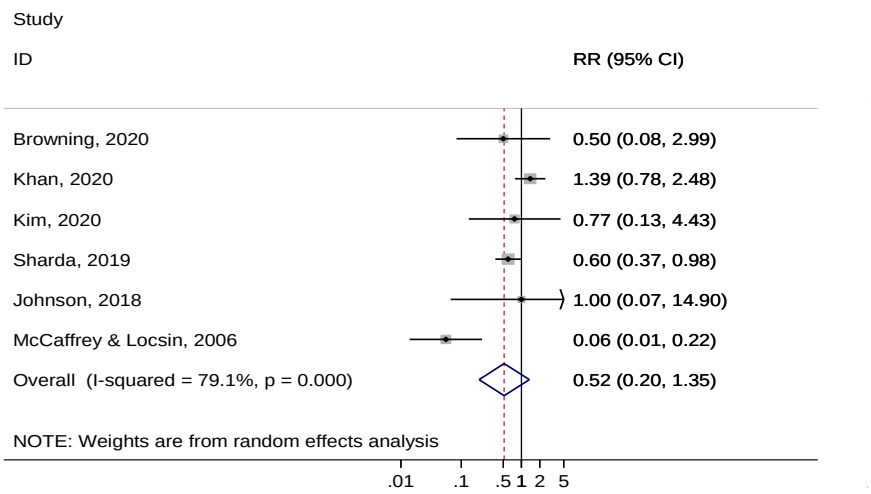


Figure 5.2: The effects of music exposure on delirium incidence (random effects meta-analysis).

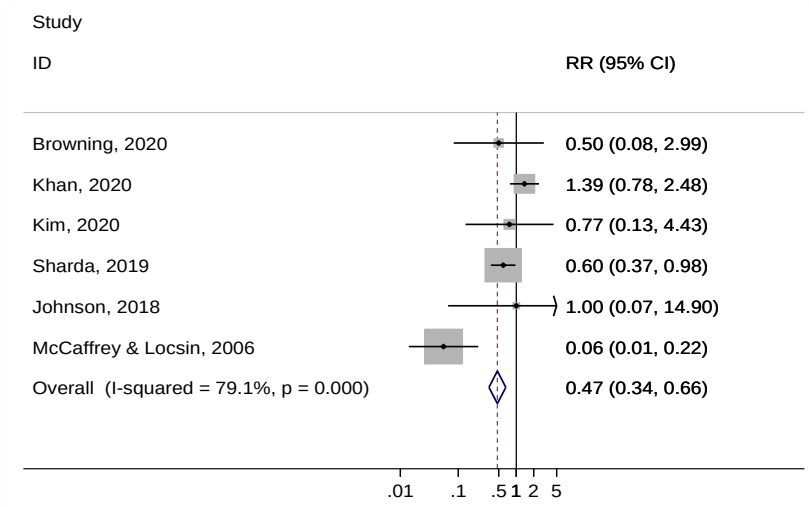


Figure 5.3: The effects of music exposure on delirium incidence (fixed-effects meta-analysis).

Note. RR stands for relative risk. Reprinted from Article 1 (Golubovic et al., 2022).

5.2 Article 2

The second article was titled: 'Live and Recorded Music Interventions for Management of Delirium Symptoms in Acute Geriatric Patients: Protocol for a Randomised Feasibility Trial'. This protocol article outlined the design of the pilot and feasibility trial and described the implemented MIs, their theoretical framework, and the theoretical rationale for their comparison.

The theoretical rationale was presented in Subchapter 3.2 and illustrated in Figures 3.1 and 3.2. The study design was described in Subchapter 4.2. Table 5.1. shows the schedule of the planned clinical activities, which was published in this protocol article.

Procedure	Screening (Day 0)	Baseline, enrolment, randomisation (Day 0)	Intervention period		End of treatment (registered during hospital stay)
			Before the intervention (Days 1, 2, 3)	After the intervention (Days 1, 2, 3)	
Assessment of eligibility (inclusion and exclusion criteria)	X				
4AT	X				
Informed consent	X				
Enrolment/randomisation	X				
DSM-5 delirium diagnosing	X	X	X	X	
DMSS-4 delirium subtyping		X	X	X	
Sociodemographic data		X			
Past and current medical conditions		X			X
Prescribed medications		X			X
IQCODE		X			
NEWS II		X	X	X	X
Assessment of personal music preference (family version)		X			
MAT (participant version)		X			
OSLA		X	X	X	
mRASS		X	X	X	
Attention tests		X	X	X	
Cognitive tests		X	X	X	
CFS		X			
MMSE-NR					X
Hospital stay length					X
Discharge information (home, nursing home)					X
Adverse events			X	X	X

Table 5.1: The schedule of clinical activities.

Note: 4AT, Alertness; Abbreviated Mental Test-4; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DMSS-4, Delirium Motor Subtyping Scale 4; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; NEWS II, National Early Warning Score II; MAT, Music Assessment Tool; OSLA, Observational Scale of Level of Arousal; mRASS, Modified Richmond Agitation and Sedation Scale; CFS, Clinical Frailty Scale; MMSE-NR, Norwegian Revised Mini-Mental Status Evaluation. Reprinted from the Article 2 (Golubovic et al., 2023).

5.3 Article 3

The third article was titled: 'A Randomized Pilot and Feasibility Trial of Live and Recorded Music Interventions for Management of Delirium Symptoms in Acute Geriatric Patients'. It enrolled 26 participants with a median age of 87 and predominantly experiencing hypoactive delirium at a rate of three per month into the PLM group (n = 14) and the PRM group (n = 12). The retention rates were 64% for the PLM group and 33% for the PRM group, with adherence to intervention protocols of 83% and 58%, respectively. Overall adherence to the assessment protocols was 44%. The PLM intervention was implemented as intended, with a treatment fidelity of 93%. In contrast, the PRM intervention did not meet the treatment fidelity criteria (83%) due to unmet compulsory items related to the patient-therapist interaction on the treatment fidelity assessment checklists. Quantitative measurements revealed improvement in pre-intervention scores for all delirium symptoms except arousal on day three compared to baseline, with the improvement in attention scores statistically significant (Table 5.2.).

Measure[b]	Day	Mean (95 % CI)[a]	Mean difference (95 % CI)[a]	p-value
OSLA	Baseline	4.2 (3.1 to 5.3)	Ref.	
	Day 1	4.4 (3.3 to 5.5)	0.1 (-1.3 to 1.4)	0.930
	Day 2	4.9 (3.7 to 6.1)	0.3 (-1.1 to 1.7)	0.659
	Day 3	3.4 (2.0 to 4.8)	-0.6 (-2.3 to 1.1)	0.502
mRASS	Baseline	-0.6 (-0.9 to -0.3)	Ref.	0
	Day 1	-0.8 (-1.2 to -0.5)	-0.2 (-0.7 to 0.3)	0.379
	Day 2	-1.0 (-1.4 to -0.6)	-0.3 (-0.8 to 0.2)	0.189
	Day 3	-0.4 (-0.9 to 0.0)	0.2 (-0.4 to 0.7)	0.546
Count 20 to 1	Baseline	8.7 (5.8 to 11.6)	Ref.	0
	Day 1	9.5 (6.4 to 12.6)	0.7 (-2.7 to 4.2)	0.687
	Day 2	9.3 (6.1 to 12.6)	0.5 (-3.1 to 4.1)	0.776
	Day 3	13.9 (10.2 to 17.6)	4.8 (0.5 to 9.0)	0.027
Days of the week	Baseline	3.2 (2.2 to 4.3)	Ref.	
	Day 1	4.0 (2.9 to 5.1)	0.7 (-0.6 to 1.9)	0.287
	Day 2	3.5 (2.3 to 4.6)	0.2 (-1.1 to 1.5)	0.779
	Day 3	5.4 (4.1 to 6.8)	2.1 (0.6 to 3.6)	0.006
Months of the year	Baseline	3.1 (1.8 to 4.5)	Ref.	
	Day 1	2.7 (1.2 to 4.1)	-0.6 (-2.1 to 1.0)	0.493
	Day 2	3.3 (1.8 to 4.9)	0.2 (-1.5 to 1.8)	0.825
	Day 3	3.3 (1.6 to 5.1)	-0.1 (-2.1 to 1.8)	0.882
Digit span	Baseline	2.8 (2.1 to 3.5)	Ref.	
	Day 1	4.0 (3.3 to 4.7)	1.2 (0.4 to 2.0)	0.003
	Day 2	3.2 (2.5 to 4.0)	0.5 (-0.3 to 1.4)	0.205
	Day 3	4.4 (3.6 to 5.3)	1.7 (0.8 to 2.7)	0.001

Measure[b]	Day	Mean (95 % CI)[a]	Mean difference (95 % CI)[a]	p-value
SAVEAHAART	Baseline	4.1 (2.9 to 5.4)	Ref.	
	Day 1	3.6 (2.3 to 5.0)	-0.5 (-1.9 to 1.0)	0.523
	Day 2	3.6 (2.2 to 5.0)	-0.7 (-2.2 to 0.9)	0.398
	Day 3	1.8 (0.2 to 3.3)	-2.3 (-4.1 to -0.6)	0.010
Orientation	Baseline	3.4 (2.5 to 4.3)	Ref.	
	Day 1	3.8 (2.9 to 4.7)	0.5 (-0.6 to 1.6)	0.355
	Day 2	3.6 (2.6 to 4.6)	0.2 (-0.9 to 1.3)	0.699
	Day 3	4.8 (3.6 to 5.9)	1.2 (-0.1 to 2.5)	0.073

Table 5.2: Daily mean score for clinical delirium outcomes and change from baseline.

Note. OSLA Observational Scale of Level of Arousal, mRASS Modified Richmond Agitation Sedation Scale SAVEAHAART/KATAMARAN Vigilance test.

a Marginal means and mean differences estimated using mixed linear model.

b Recall is not presented in this table because linear regression was not suitable. Reprinted from the Article 3 with adaptations (Submitted for publication).

No statistically significant pre-post or between-group changes were observed for any clinical outcomes (delirium symptoms, hospital stay length or use of PRN medication), and the CIs were wide due to the small sample size. It was not feasible to assess delirium duration due to the methodological challenges in accurately detecting its presence and recovery.

6 Discussion

6.1 Systematic review

This subchapter critically discusses the systematic review process and results, emphasising its strengths, limitations and implications for future research and practice. A systematic review was conducted within this PhD project for two reasons. First, we aimed to summarise published evidence on the effectiveness of MIs in preventing and treating delirium across age groups, clinical settings and care levels, as well as to systematise knowledge about the factors contributing to these effects. In this process, we attempted to address the methodological limitations in previous systematic reviews and designed our protocol and search string(s) to be both comprehensive and focused, setting a standard for future systematic reviews that will hopefully build up on ours.

Second, a systematic review was conducted before designing the clinical trial to generate findings that could inform the design and planning of both our and future clinical trials. Specifically, the goal was to generate relevant findings regarding tested interventions and the commonly used prevention/treatment focus, outcomes and assessment tools. One important goal was also to highlight the methodological limitations of previous trials and indicate potential contributors to the effectiveness or missing effectiveness of their interventions. Overall, the systematic review was conducted to provide guidelines for designing future clinical trials.

6.1.1 Critical discussion on the methodological process

The main strengths of our systematic review were its clear and focused primary research question and specific, detailed secondary questions, which helped develop a comprehensive search string and structured the data collection process. While the systematic review primarily aimed to generate summary estimates regarding the effectiveness of the MIs on delirium in adults, our secondary questions made it possible to summarise useful findings even if it was not feasible to calculate summary estimates, which was anticipated beforehand.

Additionally, our review was among the first in the music and delirium research field to include a comprehensive but specific search strategy and the first to conduct a meta-analysis. Our search included the most commonly used terms for delirium, such as acute confusion, encephalopathy, and ICU psychosis. These terms were identified in our preliminary searches and incorporated into our comprehensive search strategy. Our inclusion criteria were stringent

regarding delirium trials, and we only included those with a clearly stated delirium focus and separately reporting delirium-related outcomes. One risk of this decision was potentially identifying no or very few relevant trials since delirium is most often researched together with dementia or in the context of other critical care-related conditions, such as disorders of consciousness, pain, or postoperative anxiety. However, our preliminary searches yielded encouraging results and indicated that including a sufficient number of relevant trials in our systematic review might be feasible.

While our preliminary searches suggested that most published delirium and music studies have been conducted with older populations and within hospital settings, where delirium is most prevalent, we chose a broader search across age groups, clinical settings and care levels, albeit excluding studies on children and infants. This search focus was intended to address some of the challenges previous reviews faced[9] and generate findings potentially relevant or applicable across age groups and clinical settings. By adopting a broader scope, we aimed to simultaneously (1) mitigate the potential risk of identifying too few relevant trials for inclusion and (2) capture a more comprehensive understanding of the efficacy and implications of MIs in managing delirium, thereby facilitating the potential transferability of our findings across diverse patient demographics and healthcare settings. However, such an approach was also a limitation since it resulted in greater heterogeneity among the included studies.

We also searched broadly for trials encompassing all MIs, regardless of whether they were implemented within a music therapy or music medicine framework. Since our preliminary searches identified only a few published trials specifically addressing delirium and music, narrowing our search focus could have resulted in insufficient data. This limitation was demonstrated in the systematic review by Sherriff et al. (2017), which aimed to include only music therapy studies but ultimately failed to identify any. Additionally, unlike some previously criticised systematic reviews summarising the effectiveness of music listening and autism (Brandes et al., 2010), our review explicitly distinguished the music therapy approach from other music-based approaches, such as music medicine, even when music listening was used as a component of the music therapy approach (Kim et al., 2022). This differentiation was previously recommended to enable more precise and accurate inferences (Gold et al., 2011).

However, our eligibility criteria precluded the inclusion of trials assessing MNIs that incorporated music listening. This methodological decision stemmed from the observation that such trials typically do not report the effects of individual components but rather evaluate the collective impact of MNIs. Therefore, isolating the potential effects of listening to music alone would have been difficult. In hindsight, we consider not including MNI trials to be a

9 The strengths and limitations of prior systematic reviews are summarised in Subchapter 1.4.1.

limitation. These trials could have provided valuable insights into the possibilities for integrating MIs into the recommended interdisciplinary approaches for delirium management, some of which are presented in Subchapter 1.4.2. This limitation may have been resolved by including MNI trials and synthesising their findings as a subgroup.

6.1.2 Critical discussion on the narrative results

Our systematic review showed that the included experimental trials most often examined music-listening interventions and rarely examined music therapy interventions. Additionally, the review showed that the listening sessions primarily included non-personalised music and were implemented within a music-medicine framework. In contrast, the music therapy interventions involved participants' active engagement, non-verbal music-based interactions and improvisation with a trained music therapist, with personalised and non-personalised content. The reasons for the greater frequency of music listening interventions in published delirium trials may be that they are generally easier than music therapy to experimentally control and confine to strict intervention protocols, which enhances the internal validity of the trials and minimises methodological errors. In contrast, the inherently adaptable and personalised nature of music therapy interventions (Bruscia, 2014) poses challenges to their protocolising and experimental testing, which may be why they were omitted in previous studies. Additionally, since they do not need to be administered by trained music therapists, music listening interventions may be considered a lower-cost approach in research projects, which often have limited funding. However, the promising results of the trials examining music therapy interventions for delirium, and particularly their potential effects on indirectly related outcomes such as engagement, mood, anxiety, depression, and sleep quality, warrant their further exploration (Golubovic et al., 2022).

Furthermore, the dosage and delivery of MIs were generally not standardised and varied widely within and between the included trials. Such variability poses challenges to revealing the dose-response relationship and identifying the optimal dosage for achieving the desired effects (Shao et al., 2022). It also undermines the robustness of the findings and reliability of claims regarding the intervention's effectiveness. Moreover, it raises concerns about potential overexposure (when the interventions stop being beneficial and potentially become counterproductive) or underexposure (where the threshold for the minimum dosage needed to achieve an effect has not been reached; Shao et al., 2022). Our systematic review's conclusions regarding the previous trials' intervention delivery, dosage, and interpretation of their preliminary effects (or lack thereof) directly informed the design and planning of our pilot and feasibility trial. Several limitations and recommendations were addressed, such as the

need to standardise interventions within strict protocols and further explore and compare music listening and interactive music therapy approaches.

Our systematic review also highlighted the scarcity of studies on MIs and delirium in acute care settings, with only two published trials identified. The reasons for this may relate to the complex clinical picture of patients in acute hospital wards, which poses challenges to recognising and isolating delirium from other comorbidities and introduces potential issues with recruitment, inclusion and adherence to intervention and follow-up protocols. Other reasons for the lack of studies in acute care settings might be related to the ethical issues regarding the general appropriateness of conducting research with such vulnerable patient groups and the difficulties with obtaining written consent.

Furthermore, our systematic review identified a higher prevalence of prevention than treatment studies and a tendency towards examining prevention and treatment in the same study. This trend may again be associated with the challenges concerning delirium diagnostics, which complicate the formulation of stricter eligibility criteria and a more specific focus solely on treatment. Therefore, one of the most significant implications of our findings is the need for future trials to adopt more comprehensive delirium assessments based on recommended standards, which suggest a greater focus on symptom domains rather than dichotomous evaluations (yes/no; Abraha et al., 2016). Additionally, our results align with previous research regarding recommendations for subtyping delirium in future clinical trials and the need to explore treatment effects separately for different delirium subtypes (Ghezzi et al., 2022; Wilson et al., 2020). Moreover, our systematic review emphasised the importance of combining direct delirium outcomes, such as specific symptoms, severity and duration, with indirect but strongly correlated outcomes, such as circadian rhythm, physical activity, engagement, anxiety, mood, pain or physiological variables (Golubovic et al., 2022; Twiss et al., 2006; Weinhouse et al., 2009; Wilson et al., 2020).

The risk of bias in our included trials was assessed using the PEDro scale, which was developed explicitly to evaluate the methodological quality of RCTs (de Morton, 2009). While generally reliable for evaluating the methodological quality of RCTs, the PEDro scale may have been too strict to evaluate the risk of bias in the five included non-RCT trials, given that their methodology and design choice mandated non-randomisation. Maher et al. (2003) generally recommended caution when interpreting lower PEDro scores for trials testing complex behavioural interventions such as MIs, for which score eight out of 10, the highest limit, is suggested as optimal (Maher et al., 2003). In that regard, five of our included trials showed optimal methodological quality, with PEDro scores ranging between good and excellent (6–10), while seven had a higher risk of bias, primarily related to the lack of masking (participants,

interventionists and assessors), allocation concealment and randomisation. However, the lack of randomisation was a part of the study design in the five non-RCT trials (prospective cohort, quasi-experimental, and within-subject designs); masking of the interventionists and participants is generally infeasible when testing music-based interventions due to their specific nature and form of delivery. While these methodological limitations prevented generating robust effect estimates in the trials in question, their choice of non-randomised designs must also be considered pragmatic and directly related to the (1) early phase of research, where many factors regarding the feasibility of conducting an RCT are still unknown, and (2) the uncertainties related to diagnosing and recruiting patients with delirium.

Nonetheless, an important implication of our systematic review was the recommendation for future studies assessing feasibility and testing effectiveness to ensure a more comprehensive understanding of the acceptability, appropriateness and potential impacts of MIs in delirium management and to prevent misguiding inferences on the intervention's effectiveness (or lack thereof; Teresi et al., 2022). Our systematic review highlighted the lack of feasibility assessments and an undue and untimely emphasis on estimating effectiveness based on small samples and using insufficient study designs among the included trials. We attempted to address this particular limitation in previous trials in our pilot and feasibility trial design.

6.1.3 Critical discussion on the meta-analysis process and results

Due to the high heterogeneity among the included RCTs, only one subgroup meta-analysis of the effects of music exposure on delirium incidence was possible. Additionally, the PEDro scale scores indicated an average medium to high risk of bias among the RCTs, usually related to the lack of masking and allocation concealment.

Due to the small sample sizes in the included RCTs and limited available data, music-listening and music therapy trials were combined into a new variable called music exposure. Similarly, RCTs involving participants from different clinical settings, such as postoperative ICUs and critical care, needed to be combined to increase power. Such variations in cohort attributes and treatment choices, along with additional factors, suggest that RCTs might be unlikely to exhibit a uniform effect size but will instead exhibit diverse underlying effects (Barili et al., 2018). The level of assessed heterogeneity – the genuine variation in effect sizes attributable to inherent factors (Barili et al., 2018) – within the trials included in our meta-analysis was substantial (I^2 =79%). The best-suited statistical approach for such a high level of variability is the random effects model, which assumes there is no single underlying true effect but a range of true effects that can vary from study to study due to heterogeneity. Therefore, this statistically pooled estimate is an average effect (Barili et al., 2018). Random-effects models

are generally considered more generalisable than fixed-effect models since they account for entity-specific effects across different groups, capturing a broader range of population variation and enhancing the external validity of the results for broader contexts (Barili et al., 2018; Dettori et al., 2022). However, our random effects model analysis did not show a statistically significant result, most likely due to the few included RCTs and their small sample sizes. For the same reason, we chose to conduct a sensitivity analysis using a fixed-effect model to compare the two effect estimates.

The fixed-effect model assumes one underlying true effect exists in all the included studies. It may be suitable when the number of included studies is too small to accurately estimate the variance between them (Dettori et al., 2022). Incorporating a fixed effect model effectively eliminates the impact of the factors causing variance, leading to a more precise estimation of the potential effects (Borenstein et al., 2010). Our fixed effect model analysis showed a statistically significant summary effect of music exposure on delirium prevention in post-surgical geriatric patients, indicating a 50% reduction in delirium risk. Moreover, while the fixed effect model yielded a higher effect estimate than the random effects model, both effect estimates were similar, indicating that the true effect of music exposure in reducing delirium risk could be around 50%.

Since the power of a meta-analysis relies on various factors, including the number of included studies, heterogeneity, variance, and sample and effect sizes within the included studies, our meta-analysis could be considered sufficiently powered to detect a summary effect size. However, the main limitation of our meta-analysis is that it generated a summary effect estimate that was not sufficiently robust or specific and should be considered mainly exploratory. Nevertheless, our meta-analysis may still indicate that MIs warrant further exploration for preventing and managing delirium.

6.1.4 Critical overview of the clinical trials published after our systematic review

We performed a simple search in the PubMed database to gain an overview of the clinical research studies on music and delirium in adults aged ≥18, published after the last search for our systematic review (between October 6th and March 22nd, 2024). This search yielded six RCTs (Heiderscheit et al., 2022; Kaufmann et al., 2023; Esfahanian et al., 2022; Kappen et al., 2023; Keene et al., 2023; Dalli et al., 2023), and one study protocol (Seyffert et al., 2022).

Except for Dalli et al. (2023), most trials had large samples (n ≥ 100). Most trials were conducted within critical care settings, ICU, or postsurgical departments, including adult

patients undergoing mechanical ventilation, neurosurgery (craniotomy), coronary artery bypass grafting, or transcatheter aortic valve replacement. Keene et al. (2023) included older patients from emergency departments. Delirium was assessed using CAM-ICU and CAM-ICU-7 scales (for severity), which are best suited for patients in postsurgical and critical care settings. Prevention trials are still more common, and only Dalli et al. (2023) tested music intervention for regulating delirium severity. Music listening was mainly based on researcher-selected music, such as slow-tempo or new-age music with natural sounds (birds, waves, wind). In contrast, Kappen et al. (2022) tailored the interventions according to the participants' music preferences.

Most trials involved relatively long music listening sessions of at least one hour, and the delivery and dosage were also variable among the patients in music groups; further, music was mainly administered via noise-cancelling headphones. Aside from including music preference assessment, Kappen et al. (2023) also involved more comprehensive delirium evaluations using the Delirium Observation Screening Scale (DOSS) and DSM-5 criteria. However, the authors did not specify how these criteria were assessed.

The results show a positive and often significant decrease in delirium incidence and more delirium-free days in music-listening groups in the evaluated RCTs. Keene et al. (2023) explored the effects of listening to music alone and in combination with bright light therapy for patients at risk for delirium in emergency departments. The trial demonstrated the feasibility of both interventions and a tendency toward positive effects of music (with or without light) on delirium incidence. The one trial testing the effectiveness of music listening on delirium severity in critically ill, mechanically ventilated patients (Dalli et al., 2023) also showed statistically significant improvement in delirium symptoms, although the samples were small.

Head et al. (2022) also developed and published an intervention protocol for regulating delirium symptoms in sedated patients called Positive Stimulation for Medically Sedated Patients (PSMSP). PSMSP combines evidence-based and family-narrated, sensory-rich storytelling with personalised music. It was tested in a case study with a patient treated for COVID-19 pneumonia. Although the case-study results indicate the potential of PSMST to reduce agitation and stabilise arousal levels, rigorous feasibility trials and randomised controlled studies are needed to explore the acceptability and feasibility of this intervention and to determine its potential effectiveness (Head et al., 2022).

6.2 Pilot and feasibility trial

This subchapter discusses the strengths and limitations of our clinical trial and the implications for future research and practice.

6.2.1 Appropriateness of the design

A framework providing guidelines for assessing feasibility and addressing statistical and design issues in pilot studies has recently been developed (Teresi et al., 2022) as an elaboration of the framework previously formulated by the US National Centre for Complementary and Integrative Health (NCCIH; (*Pilot Studies: Common Uses and Misuses*, n.d.). In its framework and blog, the NCCIH is particularly critical of using pilot studies to preliminarily test the efficacy of interventions and estimate effect sizes for power calculations for future conclusive trials. One argument against this relates to the fact that knowledge of the optimal methods for implementing the intervention at the time of conducting the pilot trial is too limited for any accurate inferences about its potential effects to be possible; another argument is that small sample sizes cannot provide any interpretable effect size estimates or useful power calculation.

Teresi et al., (2022) argued that both large and small effect sizes in pilot trials could be misleading. Large effects could overestimate the true effect and provide incorrect power estimates with too small a sample size for a future RCT. Conversely, small effects may underestimate the true effect and provide incorrect power estimates with too large a sample size for a future RCT, reducing its chances for funding or leading to it not being pursued. Alternatively, the framework recommends that the power calculations for the large conclusive trials be based on clinically meaningful change, determined by considering the observed effect size with standard treatment, intensity of the interventions and risk of harm, and interviewing the stakeholders (Teresi et al., 2022). Crosby et al. (2003) had previously also emphasised the importance of considering clinically meaningful change for power calculations. They highlighted that while large effect sizes and statistical significance are important, they might not necessarily indicate clinical significance or that the change is meaningful for patients' well-being or is perceived as significant by them.

Since this comprehensive framework was published after our trial had commenced, its guidelines and recommendations could not be considered during our planning and design process. However, these critical perspectives are helpful to incorporate into the discussion of our design and to evaluate our process and implementation.

Our clinical trial was characterised as a pilot and feasibility trial to emphasise its dual aims of assessing feasibility and exploring the preliminary efficacy and sensitivity of the outcomes. Our intended sample of 60 participants, with 30 in each arm, would have been sufficient to evaluate feasibility and make some inferences on the effect tendencies and sensitivity of the outcomes. However, since the possible recruitment rate for patients with delirium in the acute-geriatric ward and the circumstances around diagnosis and inclusion were generally unknown, we expected to potentially be unable to reach this sample size and, therefore, prioritised the feasibility objectives.

While our primary aim in the trial was to assess feasibility, we also included preliminary efficacy testing and exploring the sensitivity of outcome effects. Given the aforementioned criticism, this inclusion may be considered a limitation. However, our pre-post measures design lacked a control group and, therefore, was not intended to investigate causative relationships. Furthermore, while preliminary efficacy was one of our clinical objectives, our intention, as clearly stated in the protocol article (Article 2), was primarily to examine correlations between delirium features and two different MIs. This exploration aimed to identify tendencies regarding which delirium symptoms might be more responsive to live or recorded music and to seek indications of which intervention might be more suitable for further exploration. We did not intend to draw conclusive interpretations or recommendations based on the small effect sizes, nor did we use these effect sizes to conduct any power calculation for future trials. Therefore, the primary focus of our trial remained on feasibility.

Despite our efforts to achieve an even sample size in the two intervention groups, the small size of the total sample, attrition and discontinuations resulted in the samples being slightly uneven for the PLM (n = 14) and PRM (n = 12) interventions. While the assessors were successfully masked, the participants and the interventionist could not be masked to group allocation due to the nature of the interventions. The lack of masking is a common limitation of trials testing behavioural and psychological interventions such as ours and poses additional interpretative limitations to the findings.

The symptom-based delirium assessments using the comprehensive DSM-5 diagnostic algorithm proved feasible, ensuring accurate and detailed evaluations and reliable recruitment and follow-up. Recognising and diagnosing delirium with certainty is generally challenging, a weakness in some prior trials, making this aspect one of our design's most crucial strengths. Furthermore, this assessment procedure was non-invasive and well-received by participants, as evidenced by the minimal refusals and deviations from the DSM-5 assessment manual. However, adherence to the extensive four-day, multiple-measurement protocol was low, primarily due to unavailable assessors or patients transitioning to palliative care or discharge.

The assessors' limited availability was generally the primary cause of slow recruitment, missed assessments and deviations from the study protocol, and the most significant limitation of our study design. However, engaging physicians from the acute geriatric ward to conduct delirium assessments was a deliberate decision. This choice was driven by this PhD project's constrained budget, which precluded involving a larger research team and external assessors or interventionists. However, using internal assessors was also considered advantageous since they possessed superior knowledge of the ward compared to external assessors and had high expertise in evaluating delirium within the patient population. Additionally, each internal assessor underwent specialised training in using the diagnostic algorithm for delirium assessments, potentially enhancing their proficiency in evaluating delirium throughout this trial. Nonetheless, to mitigate slow recruitment and missing data issues, it is recommended that future trials engage external assessors for delirium evaluations.

6.2.2 Music therapy interventions, strict protocols and medical context

Confining music therapy interventions to the strict intervention protocols, as exemplified in our trial, may initially appear to constrain their most distinctive and potentially effective features within a rigid, experimental, objectivist framework, thereby risking a reduction in their efficacy. However, it is crucial to emphasise that this pilot trial can be categorised as explanatory research, for which the specially tailored intervention protocols were developed. While our MIs were grounded in real-world practices and designed to be as authentic as possible, interventions used in experimental trials will inevitably exhibit a degree of rigidity and deviate somewhat from real-world contexts. Therefore, our trial does not intend to give exact recommendations for implementing these MIs based on our protocol. Instead, we intended to distil the MIs into specific components to effectively control their delivery and assess the potential impact of their underlying mechanisms. We also aimed to identify and articulate the most relevant components of the MIs and their potential correlation with delirium symptoms, focusing particularly on comparing live (human-delivered) and recorded (loudspeaker-delivered) components.

When implementing MIs in a research project within a medical context, they become influenced by the principles and postulates of the medical field. An ongoing debate revolves around whether music therapy should adhere to the medical model, considering the potential benefits or harms. Dileo (1999, p.6) contends that the experiences from music therapy research and practice affirm the interconnectedness of 'mind, body, the social environment, and spirit', suggesting that rigid divisions would be unnatural and inconsistent with reality. On the contrary, given the predictable impact of music on physiological parameters, Taylor (1997) and Thaut (Thaut & Clair, 2000) argued that music therapy should and must align with

the causal medical model, both in practice and research, for its most accurate application in treatment (Aigen, 2013).

Rolvsjord (2010) strongly criticised what she described as the pathologising tendencies and excessive emphasis on illness within the medical model, particularly in the mental health field, labelling it the 'illness ideology' (p. 20). She argued that the medical model imposes rigid thinking on music therapists, excluding any psychological explanations beyond physiological and biological terms. Furthermore, she proposed a shift to a new 'contextual model' through her resource-oriented approach to mental health (Rolvsjord, 2010). In her approach, Rolvsjord (2010) aligns with Antonovsky's salutogenesis, which conceptualises health beyond the mere absence of illness, linking it to concepts such as quality of life, meaningfulness, and overall well-being (Bruscia, 1998; Rolvsjord, 2010; Ruud, 1998).

Nonetheless, the medical model has undergone significant transformation in modern times, adapting to new insights, knowledge and requirements and gradually integrating both biopsychosocial philosophy and narrative evidence. Ruud (2020) also recognised that medical research and practice are constantly evolving, as is music therapy. He emphasised that music therapy is now more often integrated into biopsychosocial models in hospitals and features prominently in MNIs for various somatic and psychological conditions; its role is complementary, supportive and collaborative, and its function is preventive and health-promoting. Ruud (2020) underscored that there may no longer be a need to position music therapy in opposition to the medical model or the quantitative research tradition.

However, this paradigmatic shift appears not to be explicitly recognised by some music therapists and authors with a humanistic orientation since they continue to criticise the outdated, radical modernist medical model. While this model may still be sporadically present at institutional or individual levels, within some hospital departments or in the attitudes of some physicians, it may have become obsolete for some time. Furthermore, engaging in polarised discussions about the appropriateness of specific models and paradigms in music therapy may be seen as adopting a rigid understanding of these frameworks as fixed lenses through which we view our practice and research. Such an approach may also not align with music therapy's interdisciplinary, pluralistic nature. It may also be unsuitable to address the current needs and demands in the music therapy field, which is increasingly required to substantiate its importance and efficacy by presenting 'evidence' derived from research discoveries (Edwards, 2002).

6.2.3 Defining PLM and PRM as music therapy interventions

In this project, both PLM and PRM interventions were broadly categorised as music therapy despite differences in therapist engagement, patient-therapist interaction, and the nature and intensity of the therapeutic relationship. The PLM intervention distinctly met the criteria for being defined as music therapy, encompassing the active participation of a trained music therapist in tailoring and delivering the intervention alongside the establishment of a distinct therapeutic relationship through musical interaction with the participants (Gold et al., 2011; Raglio & Oasi, 2015). In contrast, classifying the PRM intervention as music therapy posed more significant challenges due to the lack of direct musical interaction and engagement between the therapist and the participants, as explicitly proscribed by our intervention protocol. However, despite differences in nature and intensity, it may be argued that the therapeutic relationship existed to some extent in the PLM and PRM interventions. This argument will be elaborated in the following paragraphs.

First, the music therapist assessed the music preferences of all participants before randomisation to PLM and PRM in a live, interactive session, potentially initiating and establishing the therapeutic relationship before the interventions began. Despite their diagnosis and vulnerability, most participants (n=25) could participate in the interactive preference assessments and were generally responsive and engaged in exploring their musical preferences with the music therapist, which was evident from the music therapist's session notes; only one participant with hypoactive delirium was too confused to participate. These sessions laid the groundwork for the therapeutic relationship to be established. Given that both PLM and PRM intervention participants had previously experienced these interactive, live preference assessment sessions, they may even be considered part of the interventions and potentially crucial for defining them as music therapy.

Second, the music therapist also consistently engaged with the participants at the beginning and end of the PRM sessions. This engagement involved introducing the intervention and ensuring participants could receive it. Additionally, the therapist verbally rounded up the music listening sessions, ensuring participants were safe and cared for before leaving the room. Such an approach potentially contributed to fostering safety, building trust, and enhancing the previously initiated relationship. Furthermore, although interaction was prohibited by the PRM intervention protocol to control interventionist variable and better compare live and recorded music, the music therapist occasionally engaged in verbal, non-verbal, and musical interactions with participants during PRM sessions. Despite breaching intervention protocol this way and contributing to PRM not meeting fidelity, these interactions may have

been essential for meeting the participants' immediate needs and fostering safety amid a vulnerable, distressing delirium episode.

While acknowledging that the therapeutic process during PRM interventions can resemble music-medicine, we argue that this intervention, due to the professional music therapist's involvement and interactions with the participants during music preference assessments, as well as her tailoring and facilitating receptive PRM, may also be defined as music therapy. However, music therapy literature is neither unambiguous nor specific regarding the optimal intensity and quality of the therapeutic relationship and interactions for the therapeutic process to be considered music therapy, which leaves the possibility for various interpretations. Moreover, since no specific definition outlines the "minimum" criteria for interventions to be classified as music therapy, our interpretation of the existing criteria must be regarded as highly subjective and open to discussion.

As previously emphasised by several authors (Gold et al., 2011; Raglio & Oasi, 2015), the therapeutic relationship established through music and musical interaction between the therapist and the client [10] differentiates the music therapy approach from other music-based approaches, thereby being essential for defining a process as music therapy. However, Pavlicevic (1997) underscored that the client-therapist relationship is not central concern for all music therapists. Particularly music therapists practising in the medical contexts, within the cognitive behavioural framework, and those addressing functional goals, put emphasis on the intervention itself and the nature of music as more central to the outcomes than the relationship (Aigen, 2013; Pavlicevic, 1997). Bruscia (2014) also emphasizes that the significance of the music experience, the therapist's engagement, and the quality and intensity of the therapeutic relationships usually vary in music therapy, as well as the relevance of these components to clients' primary health needs. Hence, he distinguishes between different levels of music therapy practice, which range from more supportive to intensive ones (Bruscia, 2014). A music therapy process with a less distinct relational component, such as the one embedded in our PRM intervention, might also be interpreted as an augmentative and supportive level of music therapy practice according to Bruscia's classification; during the PRM intervention, a music therapist in a supportive role facilitated and supervised the therapeutic process during which participants interacted more directly with music.

10 The term "client" is used when referring to the general music therapy definitions. Otherwise, the project utilised the term "patient" or "participant" to better align with the terminology common for the medical context within which it is conducted.

6.2.4 The implications of defining PLM and PRM interventions as music therapy

How the interventions in our clinical trial are defined is significant for the implications of our results for future practice and research. In this project, we aimed to investigate the effectiveness of live and recorded MIs for managing delirium, regardless of whether they were delivered within a music therapy or music medicine framework. Further, we also implicitly sought to explore whether the presence of a trained professional delivering music and engaging in responsive interaction and attunement with the participants influenced their outcomes, and if so, in which way. Since a professional music therapist administered both MIs, we categorize both PLM and PRM as music therapy interventions. However, engaging a music therapist to design and deliver both MIs was also partly a pragmatic choice since engaging other health professionals would not have been feasible due to this project's limited funding and time.

We recognise that the growing older population and the resulting increase in dementia and delirium cases require all potentially effective approaches, including music therapy and music medicine. Therefore, our findings have implications for both music therapy and music medicine research and practice. The need for human contact and reassurance clearly expressed by the participants in our clinical trial is particularly significant. Throughout our project, these needs were evident in initiating conversations and other interactions with the music therapist during the PLM and PRM interventions. These observations align with previous patient reports, such as one by a Norwegian physician who himself experienced a delirium episode: 'I'm not sure if it would have made any difference, but in hindsight, I think that someone should have tried to reassure me earlier, both verbally and by gently holding my hands' (Larsen, 2019, p. 1095).

While our trial did not indicate the effectiveness of either PRM or PLM, the results highlighted that PLM music was better accepted, more engaging, and demonstrated greater adherence. It also exhibited more stable delivery and dosage than PRM. In contrast, PRM appeared less engaging and accepted, with lower adherence and greater variability in dosage delivery. Patients' responses also indicated that it might have induced more restlessness, apathy and boredom. These adverse outcomes may be attributed to various factors, including the medium of delivery since previous studies have suggested that synthetic sound and complex, original song versions including more than one instrument and delivered through loudspeakers may induce habituation in listeners (Szpunar et al., 2004). Other contributing factors might be a non-interactive or minimally responsive therapist and music alone not sufficiently engaging the participants. The duration of music exposure and the amount of music contained in it

could have also contributed since 30 minutes of recorded music typically contains more songs than 30 minutes of live music, usually combined with verbalisation and improvisation.

These considerations are crucial for future testing of PRM intervention, although further testing of both PLM and PRM interventions is recommended. While trained music therapists should deliver PLM, PRM intervention may also benefit from being further tested within the music medicine framework and delivered by other health practitioners, such as nurses or physicians. While relational competence is not exclusive to music therapists, engaging a music therapist to deliver PRM interventions in future trials is still advisable due to their specific sensitivity to the effects of music on vulnerable patients with delirium and their ability to mitigate potential physiological and physiological harm that this intervention could inflict (Silverman et al., 2020; Taylor, 1997).

However, our live, interactive music preference assessments, conducted before the interventions were designed and delivered, allowed all the participants to experience live music and musical interaction with the music therapist before group allocation. Although beneficial for making the interventions more personalized, such a choice of design might have influenced the subsequent treatment and outcomes and introduced ethical and methodological issues, as the participants might have formed certain expectations about the coming interventions.

However, conducting live preference assessments with patients who were allocated to the PRM intervention and would continue receiving recorded music might also have been misleading and negatively impacted the acceptability of the PRM intervention, as well as their delirium symptoms. Potentially unmet expectations regarding the continuation of live interventions with the interactive therapeutic relationship might have impacted participants' motivation, acceptability and responsiveness to the PRM intervention, possibly decreasing its effectiveness. Due to the design, the patients randomised to the PLM intervention were also exposed to live music and musical interaction with the music therapist for a day longer than those in the PRM group, introducing heterogeneity in dosage delivery. In this context, the live, interactive preference assessment session may also be viewed as an intervention. Therefore, while live preference assessments provide more accurate information about patients' music preferences, they present challenges for the appropriate delivery of interventions per protocol and should thus be carefully considered in future studies.

6.2.5 Professional identity and intervention fidelity

My previously described dual role as both the interventionist and principal investigator in our clinical trial has given me a unique perspective on the challenges related to clinical professionals'

adherence to strict intervention protocols. While I aimed to follow the intervention protocols diligently, my inherent music therapeutic skills, sensitivity and impulses, achieved through my professional training and clinical practice, influenced my decisions and the progression of sessions. This influence was particularly evident when delivering the PRM intervention, where the protocol mandated the therapist to refrain from verbal and musical engagement with the participants during their listening sessions. However, due to the vulnerability of their condition, characterised by confusion, disorientation, emotional distress, and fearfulness, most participants repeatedly initiated communication and interaction with me during music listening and expressed the need for verbal and physical reassurance, medical assistance and emotional support. The participants' initiatives were impossible to overlook, resulting in my attending to their needs, thus violating the strict intervention protocol. In such instances, my identity as a clinical professional took precedence over my role as a researcher, prioritising the participants' well-being and safety over strict adherence to the protocol.

From a professional ethics perspective, this decision may be considered reasonable and necessary since it best served the participants' interests. However, from a research ethics perspective, it represents a deviation from the planned intervention protocol, potentially compromising the quality of the research data and outcomes since the PRM intervention did not satisfy treatment fidelity. Nonetheless, this issue was anticipated while planning the project, and different options were considered. One possibility was for the therapist to leave the room during the music-listening session, but this was quickly ruled out as inappropriate, considering the vulnerability of the participant's condition and the unpredictability of their responses to music. Another option was to have a non-music therapist administer the PRM interventions. However, this might still not have solved the issue since other health professionals, such as physicians and nurses, also have relational competence and are used to promptly responding to patients' needs in the moment. Furthermore, introducing another health professional as an interventionist, although worth exploring in future research, would introduce additional variables and factors that could complicate the analysis of the outcomes. The last option we considered was to exclude this particular criterion (refraining from interaction and engagement) from the intervention protocol. However, we opted not to pursue this alternative either since doing so would make it difficult to appropriately compare the effects of the PLM and PRM interventions live and recorded music components, which was our primary aim.

6.2.6 Feasibility, fidelity and factors influencing the clinical testing results

When pre-post differences in the measured outcomes are missing, as was the case in our trial, it might be challenging to interpret the results without supplementing them with qualitative evaluation to explore the reasons, which is what we attempted in our report article (Article

3) by discussing the results in the light of feasibility outcomes and other relevant factors, such as small sample size and absence of control group.

Given the lack of a control group, our trial aimed not to draw conclusive findings on effectiveness. Instead, it sought to identify interventions meriting further investigation in a properly powered RCT. Despite statistical analyses revealing no significant changes in delirium symptoms pre- to post-intervention in either group or any significant group differences, analysis of baseline and pre-intervention measurements on each intervention day showed symptom improvement, with significant improvement in attention. While this improvement could be attributed to various factors related to standard delirium care, the introduction of the MIs and patient interaction with the music therapist during this period may have contributed, underscoring the need for further exploration of MIs.

Of the two tested interventions, only PLM met fidelity criteria, while PRM did not due to a breached compulsory item on the treatment fidelity checklists (participant-therapist interaction). Since a trained music therapist administered the PRM intervention, it was anticipated that her implicit therapeutic skills, knowledge and sensitivity to patients' needs and the potential effects of music experience might hinder her adherence to the strict intervention protocol. The stringently formulated treatment fidelity checklists, which mandated that the therapist refrain from interacting with the patients, could, therefore, be perceived as setting her up for failure and PRM intervention for not meeting fidelity. However, this was a deliberate decision since the primary objective was to distil the most significant components of the two interventions to inform the designing of the most appropriate MI for a future conclusive trial. In this regard, we succeeded since the participants exhibited the highest levels of acceptance and engagement with intervention components such as personalised music preferences, live music performed by a human voice and an instrument, the presence of a person, and verbal and non-verbal interactions (both physical and musical) that fostered attunement and reassurance.

Since most of the included participants were diagnosed with hypoactive delirium, the PLM intervention's ability to foster engagement should be considered an important outcome and systematically assessed in future trials. Conversely, due to hypoactive delirium being most common among our participants, we cannot conclude whether PLM would also be the most appropriate approach for those with the hyperactive delirium subtype. Therefore, further exploration of this matter is warranted. Since hyperactive and hypoactive features might need to be approached differently, we recommend addressing delirium subtypes separately in future studies.

7 Conclusions

The results of our meta-analysis indicated an approximately 50% reduction in delirium risk in older, critically ill patients recovering from surgery, after exposure to music compared to non-exposure, with a medium risk of bias among the included RCTs. Therefore, our systematic review underscored the need for further treatment trials and generally better-designed studies to elucidate the effectiveness of MIs, delivered both within the music therapy and music medicine frameworks and to patients with specific delirium subtypes, and to explore potential correlations between intervention types, dosages, and the manifestation of delirium symptoms. Our pilot and feasibility trial conducted in an acute geriatric hospital ward indicated that recruitment procedures are feasible, MIs are deliverable, and assessment procedures are feasible, well-accepted and non-invasive for vulnerable patients with delirium. This trial recommended that future trials would benefit from using external assessors to perform delirium assessments to mitigate issues related to slow recruitment and low adherence to the study protocol. The PLM intervention demonstrated higher acceptability, safety and fidelity than the PRM intervention, although both are recommended for further exploration. Our clinical trial could not discern whether live or recorded MIs are effective in managing delirium symptoms, although such inferences were also beyond its objectives and design. However, our trial did aim to discern whether live or recorded music components shows better potential for further testing with older, acutely ill patients with delirium. We did not succeed in this regard, mainly due to the small sample size and challenges regarding engaging internal assessors and missing data. However, since our trial was the first in the music and delirium research field to use the comprehensive, symptom-focused delirium evaluations and the previously recommended diagnostic algorithm, the lack of observed effects might also be attributed to its strict design and delirium assessment procedures.

Therefore, the unanswered questions for future research to address are: (1) Whether live or recorded music is better suited to address delirium symptoms in older patients; (2) Whether different delirium subtypes respond differently to them; (3) Whether live and recorded interventions should be administered by trained health professionals and/or music therapists and if and to which degree this influences their effectiveness; (4) Whether live and recorded features should be considered crucial for addressing the clinical needs of patients with delirium, or if the relationship and interaction with trained health professionals and/or music therapists should be considered crucial.

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Articles

Article 1
Golubovic, J., Neerland, B. E., Aune, D., & Baker, F. A. (2022). Music interventions and delirium in adults: A systematic literature review and meta-analysis. *Brain Sciences*, *12*(5), 568. https://doi.org/10.3390/brainsci12050568

Article 2
Golubovic, J., Baker, F. A., Simpson, M. R., & Neerland, B. E. (2023). Live and recorded music interventions for management of delirium symptoms in acute geriatric patients: Protocol for a randomized feasibility trial. *Nordic Journal of Music Therapy, 33*(1), 62–83. https://doi.org/10.1080/08098131.2023.2192759

Article 3
Golubovic, J., Neerland, B. E., Simpson, M. R., Johansson, K., Baker, F. A. (submitted for publication to BMC Geriatrics). Randomized pilot and feasibility trial of live and recorded music interventions for management of delirium symptoms in acute geriatric patients.

Article 1

Golubovic, J., Neerland, B. E., Aune, D., & Baker, F. A. (2022).

Music interventions and delirium in adults: A systematic literature review and meta-analysis. *Brain Sciences, 12*(5), 568. https://doi.org/10.3390/brainsci12050568

brain sciences

MDPI

Systematic Review

Music Interventions and Delirium in Adults: A Systematic Literature Review and Meta-Analysis

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Abstract: Delirium is a neuropsychiatric syndrome represented by an acute disturbance in attention, awareness and cognition, highly prevalent in older, and critically ill patients, and associated with poor outcomes. This review synthesized existing evidence on the effectiveness of music interventions on delirium in adults, and music interventions (MIs), psychometric assessments and outcome measures used. We searched MEDLINE, PsychINFO, SCOPUS, Clinical Trials and CENTRAL for quantitative designs comparing any MIs to standard care or another intervention. From 1150 studies 12 met the inclusion criteria, and 6 were included in the meta-analysis. Narrative synthesis showed that most studies focused on prevention, few assessed delirium severity, with the majority of studies reporting beneficial effects. The summary relative risk for incident delirium comparing music vs. no music in postsurgical and critically ill older patients was 0.52 (95% confidential interval (CI): 0.20–1.35, I^2 = 79.1%, heterogeneity <0.0001) for the random effects model and 0.47 (95% CI: 0.34–0.66) using the fixed effects model. Music listening interventions were more commonly applied than music therapy delivered by credentialed music therapists, and delirium assessments methods were heterogeneous, including both standardized tools and systematic observations. Better designed studies are needed addressing effectiveness of MIs in specific patient subgroups, exploring the correlations between intervention-types/dosages and delirium symptoms.

Keywords: music interventions; music therapy; delirium; acute confusion; treatment; prevention; systematic review; meta-analysis

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1. Introduction

Delirium is a complex, neuropsychiatric syndrome represented by an acutely altered mental status, and disturbed cognition, attention and arousal [1], most prevalent in acutely hospitalized older patients and in those with pre-existing dementia. Delirium also affects younger age groups, particularly critically ill patients in the intensive care units (ICUs) [2]. Delirium may precipitate dementia, or exacerbate existing cognitive impairments, and is associated with prolonged hospital stay, increased need for long term care [3–5] and mortality [6].

Pharmacological agents show poor effect in managing symptoms of delirium, but there is evidence in favor of supportive non-pharmacological, multifactorial approaches [7,8]. As

multicomponent interventions are most effective in preventing delirium [9,10], literature highlights the need for further research on novel non-pharmacological prevention and treatment alternatives [11]. Music interventions are low-risk non-pharmacological approaches, with many known health benefits, already used in a variety of healthcare settings [12–17]. To date, a few reviews have synthesized the evidence on the effectiveness of music interventions for delirium [18–21]; however, they were not comprehensive, combined studies containing participants with other diagnosis, findings were not directly relevant for delirium and none included meta-analyses. The reviews suggest that music interventions could be effective [18] and warrant further exploration.

This study assessed the effectiveness of music interventions on prevention and/or treatment of delirium in adults (≥18 years) across clinical settings and levels of care. Our primary research question was: Are music interventions effective in preventing and treating delirium in adults? Secondary questions were: (1) What music interventions have been used with adults with delirium? (2) What standardized psychometric assessments have been used to measure the effect? and (3) What health outcomes did the music interventions aim to effect, and what were the sizes of these effects?

2. Materials and Methods

This review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [22], was submitted to PROSPERO on 10 October 2020, and registered/last edited on 3 November 2020 (ID: CRD42020212260).

2.1. Data Sources and Eligibility Criteria

We searched MEDLINE, PsychINFO, SCOPUS, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials. Primary search terms were music and delirium in combination. Other terms commonly used to describe delirium symptoms and to describe music were also searched. We included free terms and MeSH terms, or the database's own controlled vocabulary/thesaurus. Truncations and expanded functions were used where available (Supplementary Method S1).

No filters or limitations in the search engines of the databases were used. Search dates were for available quantitative studies from 1946 to present. The studies were uploaded to the online software Rayyan (https://rayyan.ai/cite) [23] for screening and selection and duplicates were identified and removed. Supplementary Method S2 illustrates our eligibility criteria.

2.2. Study Selection

Titles and abstracts were assessed for inclusion by at least two masked reviewers. Where the abstract and the title did not provide sufficient information to confirm inclusion/exclusion, the studies were included in the full text review. The decisions were made by at least two reviewers, with a third reviewer recruited to resolve disagreements. All decisions regarding the study selection and the reasons for exclusion were recorded in Rayyan software.

2.3. Data Extraction

One reviewer extracted the data using a tailored data extraction form which was informed by our review questions (Supplementary Method S3). Two reviewers independently checked the data for accuracy, and any discrepancies and disagreements were discussed and resolved between the reviewers.

2.4. Quality Assessment (Risk of Bias)

Each article meeting the inclusion criteria was subjected to a quality appraisal using the 11-item PEDro scale [24,25]. Points were awarded for items 2–11 if the criteria were clearly and undoubtedly satisfied, and no points were awarded to item 1 (Supplementary Table S1).

2.5. Data Analysis

2.5.1. Narrative Synthesis

Heterogeneity was observed in study designs, settings, interventions and outcome measures. A narrative synthesis was undertaken using the adapted Economic and Social Research Council (ESRC) Methods Program [26]. Only steps 2 and 3 of its four-pronged framework were undertaken iteratively. Step 2, a preliminary synthesis, included an initial description of the findings as well as identifying, listing, tabulating and counting the results. Exploring the relationships within and between the studies (step 3) helped identify factors that can explain the impact of the interventions, differences in effect sizes and direction of the effects across the studies, relationship between the methodology and the findings within the studies and the variability of findings between different studies [26].

2.5.2. Meta-Analysis and Statistical Methods

For homogenous studies, we performed a meta-analysis. Due to the few available studies and small sample sizes, we calculated the estimated effect of music exposure (of any kind), compared to no-exposure, on delirium incidence/prevention. No other meta-analyses were considered given the high heterogeneity for all other outcomes.

Since evidence of heterogeneity between the studies was detected, we used the random effects model to calculate summary relative risks (RR) and 95% confidence intervals (CI) [27]. The fixed effects model was also used as a sensitivity analysis to see whether the two models showed consistent results. Heterogeneity between the studies was evaluated using Q and I^2 statistics [28], and publication bias was assessed using Egger's test [29], as well as by inspection of the funnel plot. To assess the robustness of the summary estimate, a sensitivity analysis was conducted by excluding one study at a time and assessing its impact on the summary estimates. The statistical analysis was conducted using the Stata software (version 13.1) [30].

3. Results

3.1. Study Selection

Searches performed on the 16 October 2020, and updated on the 5 October 2021, yielded a total of 1150 studies. One additional study was identified during manual reference checking and citation tracking. After the duplicates were removed, 847 studies remained and after the first screening of the titles and abstracts, 128 studies were selected for the full-text review. After the full text review by 2 reviewers, a further 14 studies required a third reviewer. Our final selection consisted of 12 studies [31–42], with the publication years ranging from 2004 to 2020, and six of the studies were included in the meta-analysis [31,33,34,36,38,42] (Figure 1).

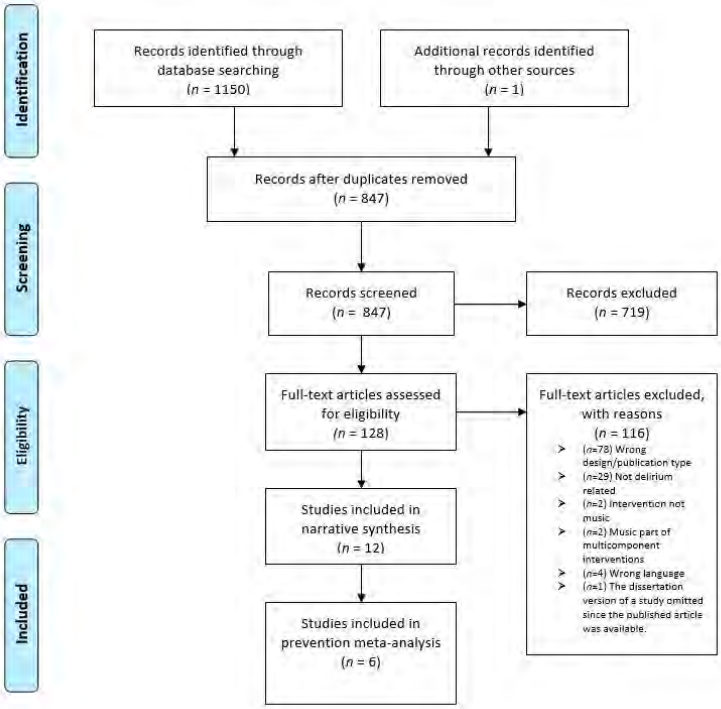

Figure 1. PRISMA flow diagram.

3.2. Study Characteristics

3.2.1. Research Designs

Two studies in our selection had a within-subject design [40,41], whereas 10 involved between-group comparisons. Seven studies were randomized controlled trials (RCTs), one an observational, prospective cohort study [42] and two non-randomized studies comparing an experimental group with a historical control group [38,39]. Five RCTs had a two-arm design involving one experimental condition [32,34–37] and two were three-armed trials comparing two experimental interventions with a control group [31,33]. All the included trials were feasibility studies (Table 1).

Table 1. Characteristics of the included trials.

Study [1] and Design	Setting and Participants	Mean Age (±SD) [2,3]	Enrolment Criteria (Delirium-Related)	Number of Participants
Khan et al., 2020 [31] RCT (3 gr.)	Medical and surgical ICU (mechanically ventilated patients)	Total: 57.4 (±14.2)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 56 Data analyzed: 52
Giovagnoli et al., 2018 [32] RCT (2 gr.)	LTC facilities or outpatient hospitals (moderate Alzheimer's patients)	M-AMT: 74.3 (±5.7) M:72.0 (±7.3)	Probable dementia, (delirium symptom of advancing dementia)	Enrolled: *n* = 45 Data analyzed: 43
McCaffrey and Locsin, 2006 [36] RCT (2 gr.)	Postoperative orthopedic unit (hip/knee patients)	Total: 75.7 (±6.1) EG:76.8 (±5.1) CG:77.3 (±5.4)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 126 Data analyzed: 124

Table 1. *Cont.*

Study [1] and Design	Setting and Participants	Mean Age (±SD) [2,3]	Enrolment Criteria (Delirium-Related)	Number of Participants
McCaffrey 2009 [35] RCT (2 gr.)	Postoperative orthopedic unit (hip/knee patients)	EG:74.5 (±4.8) CG:75.9 (±1.2)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 22 Data analyzed: 22
Kim et al., 2020 [33] RCT (3 gr.)	Postoperative ICU (postsurgical patients)	IMT:74.6 (±5.2) PML:72.3 (±4.7) CG:74.1 (±6.7)	Delirium risk (not diagnosed at enrolment)	Enrolled: 147 Data analyzed: 133
Johnson et al., 2018 [34] RCT (2 gr.)	TICU and TOU (postsurgical patients)	Total: 71.8 (±9.2)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 40 Data analyzed: 40
Browning et al., 2020 [42] Prospective cohort study (2 gr.)	Medical ICU (mechanically ventilated patients)	MLG: 64 (±12.96) CG:71 (±4.51)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 6 Data analyzed: 6
Correa et al., 2020 [39] Quasi-experimental study (2 gr.)	LTC institutions (patients with dementia/probable dementia)	IGPM: 85.1 (±8.7) CGCM: 85.3 (±7.6)	Probable dementia; (delirium symptom of advancing dementia)	Enrolled: *n* = 33 Data analyzed: 33
McCaffrey and Locsin, 2004 [37] RCT (2 gr.)	Postoperative orthopedic unit (hip/knee patients)	Total: 73.3 (±4.8)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 66 Data analyzed: 66
Cheong et al., 2016 [40] One-sample, within-subject	ACU (patients with delirium and dementia)	Total: 86.5 (±5.7)	Dementia with or without delirium	Enrolled: *n* = 25 Data analyzed: 25 (8 had delirium)
Sharda et al., 2019 [38] Pre-experimental (2 static gr.)	POSH clinic (postsurgical inpatients)	POSH: 75.0 CALM:74.6 (SD not reported)	Delirium risk (not diagnosed at enrolment)	Enrolled: *n* = 109 Data analyzed: 45
Helmes and Wiancko, 2006 [41] One-sample, within-subject (multiple case study)	ACU (geriatric assessment ward and family medicine ward patients)	Total: 82.7 (±7.4)	Diagnosis of dementia and delirium	Enrolled: *n* = 9, (2 had delirium) Data analyzed: 7 (including 2 with delirium)

Abbreviations: RCT: Randomized Controlled Trial; ICU: Intensive Care Unit; LTC: Long-Term Care; TICU: Trauma Intensive Care Unit; TOU: Trauma Orthopedic Unit; ACU: Acute Care Units; M-AMT: Memantine and Active Music Therapy group; M: Memantine group EG: experimental group; CG: control group; IMT: Interactive Music Therapy; PML: passive music listening; MLG: music listening group; IGMP: Intervention Group Popular Music; CGCM: Control Group Classical Music; POSH: Perioperative Optimization of Senior Heath group; CALM: Confusion Avoidance Led by Music group; *n*: number of participants; **Notes:** [1] The studies in this and all the other tables are listed according to their PEDro score—from the highest to the lowest quality. [2] Mean age and standard deviation (SD) values are reported according to the values available in the original included studies. Some studies reported the mean age/SD of the participants in each group, whereas others only reported the mean/SD age of all the participants. [3] The abbreviated names of the groups are presented in their original form, as identified in the articles.

3.2.2. Samples

The majority of the participants were mechanically ventilated patients from the post-surgical ICU units (*n* = 249) [31,33,34,42], and recovery-room patients from the surgical units (*n* = 323) [35–38]. Others were sampled from acute care units (*n* = 34) [40,41] and long-term care facilities (*n* = 78) [32,39]. The mean age of the participants across the included studies was 75.7 years. Only two trials reported a lower mean age (57.4 and 67.5) [31,42]. Eight studies included patients at risk of developing delirium, two studies involved patients with dementia/probable dementia with possible delirium as one of the symptoms of advancing dementia and two studies included patients with a delirium diagnosis at enrolment (Table 1).

3.2.3. Interventions

Nine studies involved music listening (ML) interventions, two studies included music therapy (MT) interventions delivered by credentialed music therapists [32,40] and one included MT and ML [33] (Table 2).

Table 2. Interventions and delivery.

Study [1]	Intervention [2,3] and Control	Primary Aims (Delirium-Related)	Dose and Delivery
Khan et al., 2020 [31]	EC: Personalized music listening (n = 17) EC: Pre-selected slow tempo music listening (n = 17) CC: Audiobook/attention control (n = 18)	Prevention and treatment (To impact the incidence and severity of delirium in ICU patients)	2 × 60 min p/day; 7 days (the same dose for all interventions)
Giovagnoli et al., 2018 [32]	EC: Active music therapy and Memantine (AMT) (n = 23) CC: Memantine (M) added to AchEI (n = 22)	Treatment (To affect language, global cognitive functioning, psycho-behavioral and social aspects, and daily activities of LTC patients)	AMT: 2 × 40 min p/week; 24 weeks. M: 20 mg per day
McCaffrey and Locsin, 2006 [36]	EC: Pre-selected music listening (n = 62) CC: Usual care (n = 62)	Prevention and treatment (To affect pain, cognition/acute confusion, the ability to ambulate and general satisfaction in postsurgical hip/knee patients)	Min. 1–4 × p/day, unreported duration; from awakening from anesthesia until discharge
McCaffrey 2009 [35]	EC: Pre-selected music listening (n = 11) CC: Usual care (n = 11)	Prevention and treatment (To affect cognitive function and acute confusion in postsurgical hip/knee patients)	Min. 4 × 60 min p/day; from awakening from anesthesia until discharge
Kim et al., 2020 [33]	EC: Interactive music therapy (IMT) (n = 44) EC: Passive, pre-selected, music listening (PML) (n = 44) CC: Usual care (n = 45)	Prevention (To prevent delirium through affecting sleep quality, melatonin/cortisol levels and pain in postsurgical ICU patients)	IMT: daytime (15–20 min), night-time (30 min). PML: night-time (30 min); from awakening until discharge
Johnson et al., 2018 [34]	EC: Pre-selected music listening (n = 20) CC: Usual care (n = 20)	Prevention and treatment (To affect delirium through decreasing physiologic variables in postsurgical patients)	2 × 60 min, p/day; 3 days (at 2 p.m. and 8 p.m.)
Browning et al., 2020 [42]	EC: Personalized music listening (n = 3) CC: Usual care (n = 3)	Prevention and treatment (To impact incidence and severity of delirium in ICU patients)	2 × 60 min p/day; 2 weeks
Correa et al., 2020 [39]	CC: Pre-selected Classical Music listening (n = 14) EC: Popular, Brazilian, personalized music listening (n = 19)	Treatment (To affect physiological, behavioral, and expressive outcomes in LTC patients with dementia/delirium)	4 × 20 min p/week (same dose for both interventions)
McCaffrey and Locsin, 2004 [37]	EC: Pre-selected music listening (n = 33) CC: Usual care (n = 33)	Prevention and treatment (To reduce delirium episodes in postsurgical hip/knee patients)	Max. 3 × 60 min p/day, (or at any time desired); from awakening until discharge
Cheong et al., 2016 [40]	EC: Creative Music Therapy (CMT) CC: The usual care (n = 25; 8 had delirium)	Treatment (To impact mood and engagement in AC patients with delirium/dementia)	CMT: 1 × 30 min p/day; 2 days
Sharda et al., 2019 [38]	EC: Confusion Avoidance Led by personalized Music (CALM) (n = 45) CC: Usual care (157)	Prevention and treatment (By affecting pain and anxiety to prevent/treat delirium in postsurgical inpatients)	CALM: Min. 2 × 20 min p/day, or at any time desired
Helmes and Wiancko, 2006 [41]	EC: Pre-selected music listening (Baroque music) CC: No music (2 trials of each condition compared in n = 9 participants; 2 had delirium)	Treatment (To reduce the frequency of disruptive behaviors in AC patients)	Minimum 4 × 30 min per day—minimum 3 days

Abbreviations: EC: experimental condition; CC: control condition; NR: not reported; ICU: Intensive Care Unit; LTC: Long-Term Care; TICU: Trauma Intensive Care Unit; TOU: trauma orthopedic; AC: acute care; M: Memantine; AchEI: acetylcholinesterase inhibitors/the usual pharmacological treatment; ATM: Active Music Therapy; ML: Music Listening; ITM: Interactive Music Therapy; PML: passive music listening; CMT: Creative Music Therapy; CALM: Confusion Avoidance Lead by Music; **Notes**: [1] The studies in this and all other tables are listed according to their PEDro score—from the highest to the lowest quality. [2] A more detailed description of the music interventions and the delivery procedures is given in the Supplementary Table S2. [3] The groups are defined and presented as experimental and control conditions (EC, and CC) with their particular content.

Music Listening

The ML is a receptive intervention, and was usually provided by the investigators, hospital carers, family members or patients themselves. ML consisted of pre-recorded music, delivered through various musical devices (e.g., MP3 player) using loud speakers or headsets. Music was played automatically, at pre-determined hours, or at patients' request, at any time of the day except overnight. ML protocols detailing the duration and the frequency of the music delivery were mostly not standardized and varied within and between the participants, with the reported duration of listening sessions ranging from 15–20 min to one hour, and the number of listening sessions per day varying between one and four. The total duration of the exposure to music varied widely—from 2 to 3 days, 1 to 3 weeks, and 24 weeks. The exact number of music sessions and total duration of music exposure were not always clearly reported.

ML involved either personalized, preferred music, or researcher-selected non-personalized music chosen because of its objective characteristics and known health benefits. Two studies reported using slow-tempo relaxing music (60–80 bpm) because of its simple repetitive rhythms and sedative-sparing and anxiolytic effects [31,34]. One study included baroque music because of its rhythmic nature and absence of sharp transitions in volume, which were viewed as calming and appropriate for the busy acute care hospital environment [41]. Some studies reported including lullaby music for its "soothing" properties [35,36], or classical music for being "relaxing" [42], whereas others included a broad musical selection including classical, popular, meditation music, musicals and jazz to appeal to patients' preferences [37]. Musical preferences were assessed on admission in only three studies [31,38,39] (Table 2).

Music Therapy

Three studies in our selection included music therapy interventions (MTI) delivered by the credentialed music therapists [32,33,40]. MTIs consisted of shared musical interactions where the patients actively participated in the music-making process. Giovagnoli et al. [32] included a non-verbal MTI based on the free sound–music interactions and the use of rhythmical and melodic instruments. Cheong et al. [40] MTI comprised a patient-centered, improvisational approach, involving playing and improvising on familiar, patient-selected music. Kim et al. [33] incorporated music listening into the individual MTI and delivered interactive MTI during the day and personalized music listening, following a music therapist's assessment of preferences, at night.

3.2.4. Comparators

Music interventions were compared either to usual care or to another intervention (non-pharmacological or pharmacological). Where two ML interventions were compared, one was usually based on personalized and the other on non-personalized music [31,39]. One study compared listening to two different musical genres [39], and one compared ML to MTI [33] (Table 2 and Supplementary Table S2).

3.2.5. Outcomes, Tools and Procedures

The incidence of delirium was mostly formulated as a binary, "yes/no" variable, and studies mainly focused on the preventive potential of music interventions. Delirium was either diagnosed by the use of standardized delirium diagnostic tools (e.g., Confusion Assessment Method for the Intensive Care Unit—CAM-ICU; Neelon, Champagne, Carlson and Funk, acute con-fusion scale—NEECHAM), or identified by reading the medical records. None of the studies described delirium subtypes.

Changes in delirium severity, and treatment effects of music interventions, were less commonly reported. Severity was assessed either directly, utilizing existing delirium-severity tools (e.g., Richmond Agitation and Sedation Scale-RASS, CAM-ICU-7), or indirectly by observing changes in other outcomes, such as physiological variables, mobility, changes in engagement, mood and emotional state, pain, anxiety, episodes of disruptive

behaviors and cognitive changes, changes in sleep quality and the duration of hospital stay. In two studies [32,39], delirium was considered a symptom of advancing dementia and assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q) (Table 3).

Table 3. Outcomes and assessment tools.

Study [1]	Delirium Outcomes and Tools	Other Outcomes and Tools [2]
Khan et al., 2020 [31]	OUTCOMES: Number of delirium-free/coma-free days and severity TOOLS: RASS; CAM-ICU; CAM-ICU-7	Anxiety (Face Anxiety Scale—VAS) Pain (CPOT) Physiological stress (HR, BP, RR) Sleep (STOP-BANG-RCS-Q) Mobility (physical/occupational therapy notes)
Giovagnoli et al., 2018 [32]	OUTCOMES: NR but delirium measured as one of the neuropsychiatric symptoms of advancing dementia TOOLS: NPI-Q	Language (SIB-L) Social interactions, memory, orientation, attention, praxis, visual–spatial ability and orientation (SIB) Independence in daily activities, instrumental activities (ADL and IADL) Psychic and behavioral symptoms of dementia (NPI-Q) Neurocognitive functions (MMSE) Perceived social support (LSNS)
McCaffrey and Locsin, 2006 [36]	OUTCOMES: Number of episodes of delirium/acute confusion TOOLS: Nurses' narrative notes in medical records	Pain (numeric rating scale; number of pain medications) Ambulation (medical records and notes from nurses and physical therapists) Patient satisfaction (self-rating-post-discharge phone call.)
McCaffrey 2009 [35]	OUTCOMES: Presence and severity of delirium/acute confusion TOOLS: NEECHAM	Cognitive function (MMSE) Physiological measurements (oxygen saturation, BP, RR)
Kim et al., 2020 [33]	OUTCOMES: Incidence of delirium TOOLS: CAM-ICU	Quality and the duration of sleep (RCS-Q) Pain (NRS) Recovery after anesthesia (QoR-40) Cortisol and melatonin levels (Salivette tube)
Johnson et al., 2018 [34]	OUTCOMES: Presence of delirium/acute confusion TOOLS: CAM-ICU	Physiological measurements (SBP, HR, RR)
Browning et al., 2020 [42]	OUTCOMES: Incidence and severity of delirium TOOLS: CAM-ICU; RASS	NR
Correa et al., 2020 [39]	OUTCOMES: NR, but delirium measured as one of the neuropsychiatric symptoms of advancing dementia TOOLS: NPI-Q	Severity of neuropsychiatric manifestation (NPI-Q). Cardiovascular biofeedback (Cardio emotion) Facial expressions (FACS) Body movements (reactions grouped into body parts)
McCaffrey and Locsin, 2004 [37]	OUTCOMES: Number of delirium episodes TOOLS: Nurses' notes and checklists	Ambulation (physiotherapists' notes)
Cheong et al., 2016 [40]	OUTCOMES: NR, but delirium is assessed at baseline TOOLS: CAM	Engagement regulation (MPES) Mood regulation (OERS)
Sharda et al., 2019 [38]	OUTCOME: Incidence of delirium TOOL: ICD codes	Length of hospital stay (hospital records) Pain and mood (patient survey)
Helmes and Wiancko, 2006 [41]	OUTCOMES: NR, but delirium is assessed at baseline TOOLS: NR	Frequency and incidence of repetitive vocalizations/shouting and banging objects (systematic observations)

Abbreviations: NR: not reported; LAR: legally authorized representatives; NEECHAM: Neelon, Champagne, Carlson and Funk, (1996) acute confusion scale; RASS: Richmond Agitation and Sedation Scale; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method for Intensive Care Units; CAM-ICU-7: Delirium Severity Scale; ICD: international classification of diseases; VAS: Face Anxiety Scale—Visual Analogue Scale; CPOT: Critical Care Pain Observation Tool; NPI-Q: Neuropsychiatric Inventory Questionnaire; SIB-L: Severe Impairment Battery Language; SIB: Severe Impairment Battery; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; MMSE: Mini-Mental State Evaluation scale; LSNS: Lubben Social Network Scale; RCS-Q: Richard-Campbell Sleep Questionnaire; QoR-40: self-rating—The Quality of Recovery—40 questionnaire; Cardio emotion: Cardiovascular biofeedback; SBP: systolic blood pressure; HR: heart rate; RR: respiratory rate; FACS: Facial Action Coding System; MPES: Menorah Park Engagement Scale; OERS: Observed Emotion Rating Scale; NRS: numeric rating scale. **Notes**: [1] The studies in this and all other tables are listed according to their PEDro score—from the highest to the lowest quality. [2] Details of the assessment procedures for each outcome are given in the Supplementary Table S3.

Only two of the included studies had delirium diagnosis as the enrolment criteria [40,41], although all the studies assessed delirium pre-intervention. Delirium was usually assessed daily or several times per day, within a specific timeframe, for as long as the intervention was administered (from 2–3 days to 24 weeks). The majority of studies focused on assessing

effects immediately after the interventions, and only two looked at the changes in delirium symptoms over time for sustained effects [31,32] (Table 3 and Supplementary Table S3).

3.3. Risk of Bias

The calculated Cohen's Kappa coefficient (k = 0.75) indicated a substantial level of agreement between the two principal reviewers [43]. The PEDro scores of the included studies ranged from "excellent" (n = 1), "good" (n = 4), "fair" (n = 3) to "poor" (n = 4) (mean 4.9 ± 2.5; median 4.5). The risk of bias was usually related to the absence of participant, intervention-administrators, and assessor masking, as well as the absence of allocation concealment and randomization (Supplementary Table S1).

3.4. Synthesis of Results

3.4.1. Direct Outcomes

Nine studies compared music-interventions (MIs) to usual care, and three compared music to another intervention. Five studies focused on prevention [33,34,36–38], three focused on prevention and treatment [31,35,42] and four examined treatment only [32,39–41]. Heterogeneity was present in study design, type of MIs and comparators, as well as assessment measures of delirium incidence and severity.

Music—No Music (Prevention)

Four RCTs examined delirium incidence in postsurgical orthopedic patients by comparing ML to the usual care. Two RCTs [36,37] assessed the number of delirium episodes using systematic observations and reported significant differences between the intervention and control groups (F = 29.56, p = 0.001; F = 19.56, p = 0.001). The methodological quality of these studies was "fair" [36] and "poor" [37] (Supplementary Table S1). While Johnson et al. [34] reported no delirium episodes in the two groups, McCaffrey [35] reported lower incidence of ICU delirium in the experimental group, on all 3 data-collecting days (df = 1.22, F = 7.28, p = 0.014). The methodological quality of these trials was assessed as "good" [35] and "fair" [34].

The prospective cohort study by Browning et al. [42] reported less proportion of time with ICU delirium in the ML groups (33%), compared to the usual care groups (67%). The non-randomized trial by Sharda et al. [38] assessed delirium in postsurgical patients using ICD codes and found lower incident delirium in the ML group (17.8% of the participants) compared to the usual care (28.7%). The outcomes of the two trials were not statistically significant, had small samples, and "poor" to "fair" methodological quality.

Music—No Music (Prevention Meta-Analysis)

Six studies were included in the meta-analysis of music vs. no music and delirium incidence. The summary RR for incident delirium was 0.52 (95% CI: 0.20–1.35, I^2 = 79.1%, heterogeneity <0.0001) for the random effects model (Figure 2). The studies showed some variation in interventions and comparators, with four of them comparing ML to usual care and two including interactive MT and another intervention as a comparator. There were also variations in the musical content of the interventions, and type of participants. When studies reported results for multiple MI groups vs. a control group [31,33] we combined the results for the two intervention groups and used the combined result in the analysis for consistency with the remaining studies, which only had one intervention group [34,36,38,42].

The summary RR ranged from 0.38 (95% CI: 0.13–1.08) when excluding the study by Khan et al. [31] to 0.84 (95% CI: 0.53–1.34) (Supplementary Figure S3). In a sensitivity analysis using a fixed effects model the summary RR was 0.47 (95% CI: 0.34–0.66) (Supplementary Figure S1). Methodological qualities ranged from "poor" to "excellent" (PEDro score median 5.5; mean 5.5; SD 2.42), with the risk of bias usually related to the lacking allocation concealment and masking. There was no indication of publication bias with Egger's test (p = 0.51) or by inspection of the funnel plot (Supplementary Figure S2).

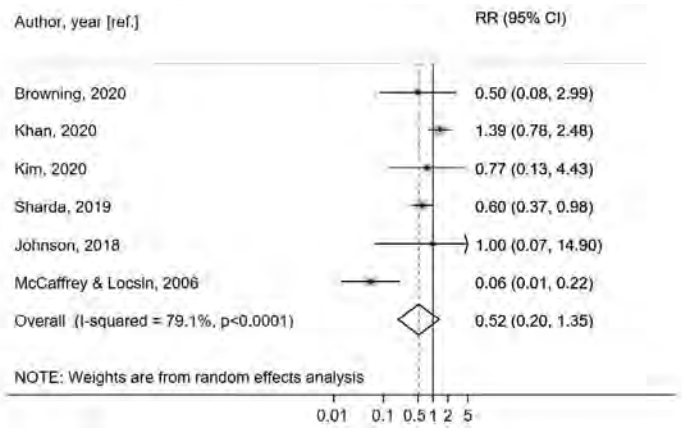

Figure 2. Music exposure and delirium incidence (random effects meta-analysis) [31,33,34,36,38,42].

Music—Another Intervention (Treatment)

Three treatment studies reported changes in delirium symptoms post-intervention in mechanically ventilated ICU patients [31], and LTC patients with dementia/probable dementia [32,39]. The "excellent" methodological quality RCT of Khan et al. [31] compared two MIs and one attention-control intervention and assessed delirium severity using RASS and CAM-ICU-7. Although not statistically significant, their results showed a trend towards improvement in delirium symptoms and suggested that researcher-selected slow tempo music is more effective than personalized music.

Two studies compared two ML interventions [39], or a MT intervention with a pharmacological agent [32] and assessed changes in delirium, using NPI-Q, in patients with advanced dementia. Giovagnoli et al. [32] reported no significant changes in delirium symptoms between the groups, but also no worsening of overall cognitive performance. Conversely, Correa et al. [39] found decreases in delirium symptom severity post-intervention in the group receiving personalized, popular music ($t = 2.3$; $p = 0.02$).

Music—No Music (Treatment)

Browning et al. [42] trial of a "fair" methodological quality and with a small sample, reported mean RASS score for delirium severity in mechanically ventilated ICU patients, suggesting that ML group spent more time alert and calm to agitated ($1.3 \pm 1.2(5)$), while the control group fluctuated between sedated and agitated.

Cheong et al. [40] examined the effectiveness of MT, and Helmes and Wiancko [41] of ML in treatment of delirium in acute geriatric hospital patients. Neither of these studies reported assessment of delirium severity, nor the use of any standardized instruments. Despite their high risk of bias, these studies reported some significant changes in outcomes indirectly relevant for delirium severity (e.g., mood, engagement, and frequency of disruptive behaviors).

3.4.2. Indirect Outcomes

Physiological Measures

Physiological variables can be biomarkers signaling physiological stress associated with the presence of delirium, and changes in these variables might thus be indicative of changes in delirium severity. Khan et al. [31] reported a significant increase in HR ($p = 0.02$) and DBP ($p = 0.02$) in the ML group, receiving researcher-selected slow tempo music compared to the personalized music group. However, Johnson et al. [34] showed that the ML group had a decrease in HR post-intervention ($p \leq 0.01$), as well as an increase

in SBP post-intervention comparing to pre-intervention ($p \leq 0.01$), for the postoperative orthopedic ICU patients. This study also showed significant differences in SBP between the ML group and the control group.

Anxiety, Mood, and Engagement

Khan et al. [31] detected non-significant changes in anxiety between the groups in critically ill patients. Cheong et al. [40] reported statistically significant pre-post intervention changes in engagement and mood in patients with delirium. Notably, there was a higher frequency of positive Menorah Park Engagement Scale (MPES)—constructive and passive engagement ($p = 0.01$), and positive Observed Emotion Rating Scale (OERS)—pleasure and general alertness ($p = 0.01$), as well as lower frequency of negative MPES—self-engagement and non-engagement ($p = 0.02$), and negative OERS—anger, anxiety and sadness ($p = 0.045$). Correa et al. [39] reported more expressions of joy ($p = 0.039$) and surprise ($p = 0.041$) in the group receiving personalized, popular music compared to the non-personalized, classical music groups.

Sleep

Kim et al.'s [33] "excellent" quality study, reported that music was effective in promoting sleep in the critically ill patients, and thus may also prevent delirium. Results suggested that patient-directed interactive MT intervention might be more effective than ML ($p < 0.01$).

4. Discussion

Our meta-analysis indicated an approximately 50% reduction in risk of delirium after exposure to music compared to non-exposure in postsurgical and critically ill ICU patients. Although the results were statistically significant only in the secondary, sensitivity analysis using a fixed effects model, and not in the primary random effects analysis, the summary estimate was similar for the two models. Our narrative synthesis showed that most studies reported some beneficial effects of MIs on direct or indirect delirium outcomes, although the results were not always statistically significant. The majority of the studies involved receptive, ML interventions, while few examined the effects of expressive, improvisational MT.

Due to the few available homogenous studies, we were not able to make strong claims as to which type of MIs are the most effective for specific delirium symptoms. However, there are indications that ML might be more effective than usual care, pharmacological treatment, and other attention-control interventions in management of delirium. More studies with larger sample sizes are, therefore, necessary to confirm these hypotheses.

There is strong evidence on the correlation between anxiety [44], sleep disturbances [45] and delirium incidence [44]. Furthermore, changes in engagement and mood might be considered indicators of the improvement in delirium severity [46]. Improvisational MT showed promising effects on improving engagement, mood, anxiety, depression symptoms and sleep quality in three studies from our selection. The reported effects could indicate the potential role of MT interventions in treatment of these delirium symptoms, and in facilitating otherwise regular treatment (e.g., medication, procedural support, physiotherapy, etc.). More evidence is needed to substantiate these claims.

Compared to other studies involving pharmacological and non-pharmacological agents, studies on MIs showed heterogeneity concerning delirium outcomes and assessments, as several different diagnostic tools and procedures were used. Due to the complexity of delirium, and the multifaceted nature of MIs, it might be necessary to combine different direct and indirect measures in future research.

Delivery and dosage of MIs were not standardized in the majority of studies, which might influence the reliability of our claims. This can be attributed to the complex nature of the MIs themselves, the fluctuating nature of delirium, the challenges concerning the availability of a researcher to provide the intervention at the exact time needed, as well as the culture of acute medicine and the busy hospital environment. Music preferences

were not always systematically assessed, despite the majority of studies emphasizing the importance of patients' involvement in choosing the music.

Most studies in this review reported a high adherence in the music groups, and cost-efficient interventions. Patient-survey data revealed high participant enjoyment of the MIs [31], which might also serve as additional argument for further exploration of their utility in management of delirium.

Strengths and Limitations

While our review asked focused questions, and we implemented a sensitive and comprehensive search strategy, our broad inclusion criteria led to high heterogeneity of participant samples and therefore limited the generalizability of the findings. Some relevant data may have been omitted due to the exclusion of the studies where music was applied as a part of the multicomponent interventions. Nevertheless, including such studies would have made it difficult to isolate the specific effects of music on delirium from the effects of other components.

This study included a narrative synthesis and meta-analysis. The narrative synthesis highlighted the possibility for applying statistical methods, and the results of our meta-analysis allowed for more specific claims about the effectiveness of music interventions on prevention of postoperative delirium in older patients. We could not make claims related to whether ML is more efficient in prevention than MT, nor which type of MIs were more efficient for prevention and which for treatment. As none of the studies involved systematic subtyping of delirium or standardized interventions, we could also not make any conclusions as to which interventions related better to which subtypes or symptoms, nor which dosage/delivery was optimal.

Only six studies were included in our meta-analysis, with allocation concealment and masking lacking in the majority of them, and with one study also lacking randomization; thus, indicating relatively high risk of bias. Given that the power in a meta-analysis depends both on the effect size, variance, heterogeneity, number of studies and sample size in the studies, our meta-analysis may be considered powered to detect a summary effect size. Conducting both the Chi-squared test and the I-squared test to detect heterogeneity and inconsistencies across the studies is a strength, given that the Chi^2 is less powered when few studies with small samples are included, whereas the I^2 test gives an estimate that is less dependent on the number of included studies and more focused on the impact of the heterogeneity on the meta-analysis. The I^2 result of 79.1% shows that the variability in observed effects can be attributed to the substantial heterogeneity among the included studies, and that the result of our meta-analysis is thus not robust and should be considered as only explorative, warranting more and better designed research.

In conclusion, this review presents the evidence on MIs potentially being effective in prevention of postoperative delirium in older adults, based on the meta-analysis of the data from six clinical studies, with substantial heterogeneity, small samples and high risk of bias. More high-quality studies with larger homogenous samples are necessary to substantiate the inferences about the application and effectiveness of MIs in treatment/prevention of delirium in specific patient groups, as well as about correlations between different types and dosages of MIs, and particular delirium symptoms.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/brainsci12050568/s1, Supplementary Figure S1: Music exposure and delirium incidence (fixed effects meta-analysis); Supplementary Figure S2: Publication bias assessment; Supplementary Figure S3: Influence analysis; Supplementary Method S1: Full search strategy; Supplementary Method S2: Eligibility criteria; Supplementary Method S3: Data extraction categories; Supplementary Table S1: Risk of bias assessment and PEDro-scale criteria; Supplementary Table S2: Music intervention description and delivery procedures; Supplementary Table S3: Assessment procedures.

Author Contributions: All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, have read the last draft of the manuscript and agree with the findings presented. J.G. was responsible for the library of references and the uploading process. J.G., F.A.B. and B.E.N. selected the studies for inclusion, J.G. extracted the data from the included studies. All the decisions concerning screening, inclusion/exclusion and data-extraction were cross-checked with F.A.B. and B.E.N., J.G., F.A.B. and B.E.N. performed risk of bias assessment, and J.G. and D.A. calculated interrater reliability. J.G. extracted the data for meta-analysis and D.A. conducted the meta-analysis. J.G. wrote the first draft of the paper with contributions from F.A.B., B.E.N. and D.A. All authors have read and agreed to the published version of the manuscript.

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Supplemental material

Supplementary figure S1. Music exposure and delirium incidence (fixed effects meta-analysis)

Supplementary figure S2. Publication bias assessment

Supplementary figure S3. Influence analysis

Supplementary methods S1. Full search strategy

Supplementary methods S2. Eligibility criteria

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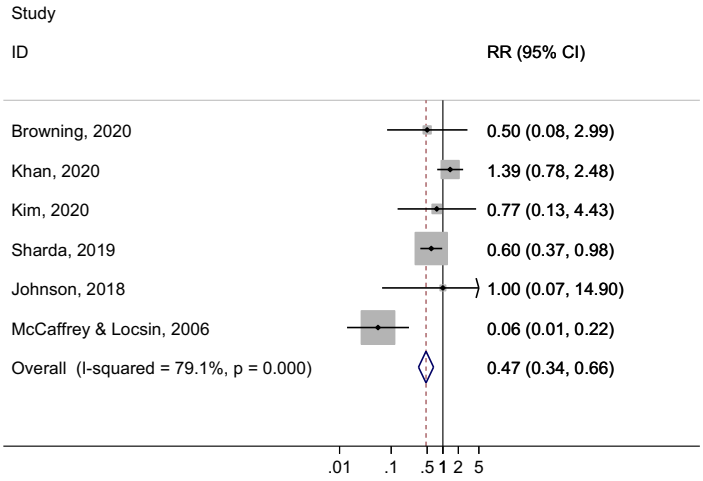
Supplementary table S1. Risk of bias assessment and PEDro-scale criteria

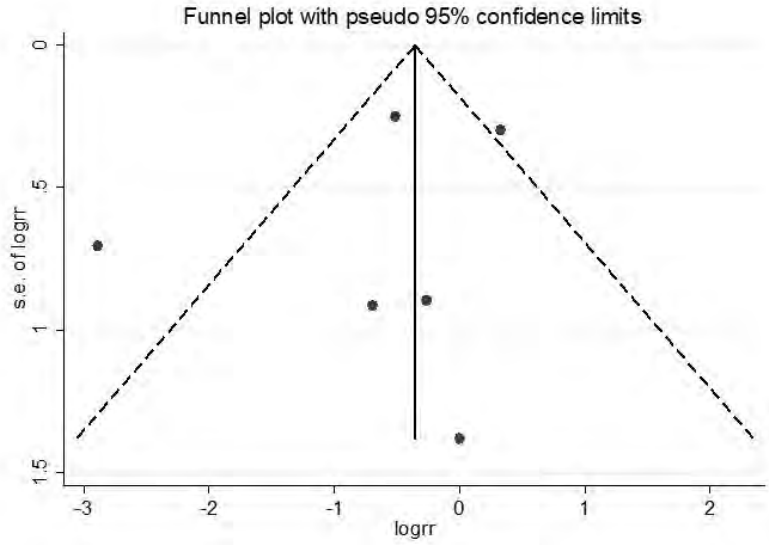
Supplementary table S2. Music intervention description and delivery procedures

Supplementary table S3. Assessment procedures

Supplementary figure S1. Music exposure and delirium incidence (fixed effects meta-analysis)

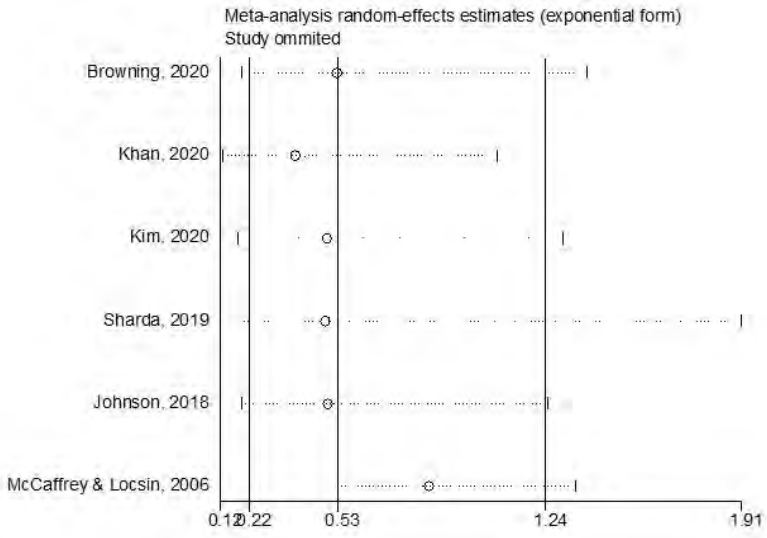


Supplementary figure S2. Publication bias assessment



Egger's test, p-value=0.51

Supplementary figure S3. Influence analysis



Study omitted	e^coef.	[95% Conf.	Interval]
Browning, 2020	0.52411324	0.19874562	1.3821422
Khan, 2020	0.38084498	0.13465166	1.0771713
Kim, 2020	0.4902105	0.18477046	1.3005668
Sharda, 2019	0.48443422	0.12256318	1.914739
Johnson, 2018	0.4943558	0.19554184	1.2497972
McCaffrey & Locsin, 2006	0.84168667	0.5271588	1.3438768
Combined	0.52544621	0.22232503	1.2418472

Supplementary methods S1. Full search strategy

Database: Ovid MEDLINE(R) ALL (1946 – to present)

1 exp Delirium/
2 Alcohol Withdrawal Delirium/
3 Confusion/
4 delir*.mp.
5 confus*.ti.
6 (acute confusional state* or toxic confus* or altered mental status or acute psychosis or acute psychotic or icu psychosis or (intensive care unit* and psychosis) or clouded state or "clouding of consciousness" or toxic confus* or exogenous psycho* or toxic psycho* or acute encephalopathy or acute brain failure or acute organic psychosyndrome).mp.
7 (exp neurocognitive disorders/ or (cognitive disorder* or cognitive impairment* or cognitive dysfunction* or cognitive failure*).ti.) **and** (exp Health Facilities/ or Inpatients/ or hospital*.hw. or (inpatient* or hospital*).ti.)
8 or/1-7
9 Music/
10 Music Therapy/
11 Singing/
12 Acoustic Stimulation/
13 Evoked Potentials, Auditory/
14 (music* or song* or sing or sings or singing* or singer* or chant* or melod* or acoustic stimulation* or auditory stimulation* or rhythmic vocalization* or piano or guitar* or violin*).mp.
15 (vocal* or sound* or auditory or whistl* or rhythm*).ti.
16 or/9-15
17 8 and 16

Comments:
/ = MeSH (Medical Subject Heading)
.mp = multi-purpose, i.e searches several fields at once: title, abstract, subject heading etc.
.ti = title field
.hw = subject heading word, allows you to retrieve every Ovid Descriptor that includes a particular word.
Exp = explode. The MeSH term “Delirium” are "exploded", i.e. it retrieves automatically citations that carry the specified MeSH heading as well as the more specific term indented beneath it in the MeSH hierarchy: Emergence Delirium

APA PsycInfo

1 Delirium/
2 Delirium Tremens/
3 Mental Confusion/
4 delir*.mp.
5 confus*.ti.

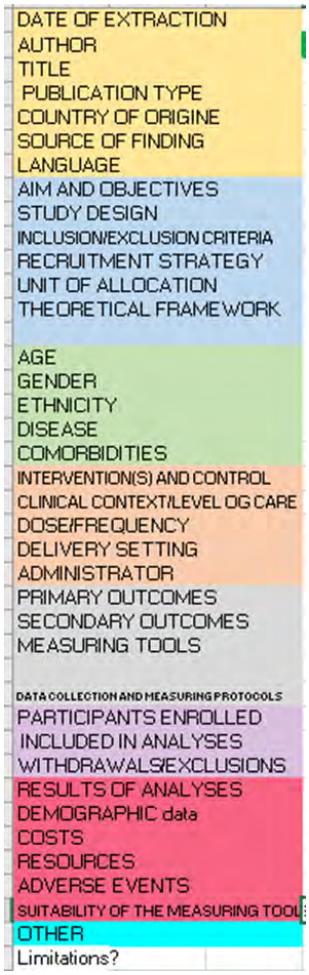
6 (acute confusional state or toxic confus* or altered mental status or acute psychosis or acute psychotic or icu psychosis or (intensive care unit* and psychosis) or clouded state or "clouding of consciousness" or toxic confus* or exogenous psycho* or toxic psycho* or acute encephalopathy or acute brain failure or acute organic psychosyndrome).mp.
7 or/1-6
8 exp Music/
9 Music Therapy/
10 Singing/
11 Auditory Stimulation/
12 exp Music Perception/ or Musical Ability/
13 (music* or song* or sing or sings or singing* or singer* or chant* or melod* or acoustic stimulation* or auditory stimulation* or rhythmic vocalization* or piano or guitar* or violin*).mp.
14 (vocal* or sound* or auditory or whistl* or rhythm*).ti.
15 or/8-14
16 7 and 15

Scopus
Advanced > Enter query string
(TITLE-ABS-KEY (delir*) OR TITLE (confus*) OR TITLE-ABS-KEY (“acute confusional state*” OR “toxic confus*” OR “altered mental status” OR “acute psychosis” OR “acute psychotic” OR “icu psychosis” OR (“intensive care unit*” AND psychosis) OR “clouded state” OR "clouding of consciousness" OR “toxic confus*” OR “exogenous psycho*” OR “toxic psycho*” OR “acute encephalopathy” OR “acute brain failure” OR “acute organic psychosyndrome”)) **AND** (TITLE-ABS-KEY (music* OR song* OR sing OR sings OR singing* OR singer* OR chant* OR melod* OR “acoustic stimulation*” OR “auditory stimulation*” OR “rhythmic vocalization*” OR piano OR guitar* OR violin*) OR TITLE (vocal* OR sound* OR auditory OR whistl* OR rhythm*))

Supplementary methods S2. Eligibility criteria

	INCLUSION	EXCLUSION
Participants	Adults (≥18) with or at risk of developing delirium, across medical settings and levels of care.	Younger adults (≤18)
Music intervention	Any type of music intervention (including listening to live or pre-recorded music, music making, singing, playing, improvising, music and movement, music and dance, relaxation to music, music therapy etc.). Music interventions delivered and administered by either the medical staff, trained music therapists, musicians, or others.	Music is a component of an intervention, and the impact of music is not reported separately . The effects on the outcome measures for delirium cannot be clearly attributed to the music interventions.
Comparator	We put no limitations on the type of comparators used in the studies, and expected to find the studies in which the comparator is mainly "the usual care" or another intervention.	
Outcome measures	Incidence, severity and/or duration of delirium, any changes and improvements in general well-being related to delirium. Delirium data is reported, regardless of whether the aim of the study was to investigate prevention or treating, and regardless of whether delirium was the main focus of the study. Studies with mixed diagnoses where outcomes were reported separately for delirium;	Delirium or acute confusion not explicitly mentioned;
Methodology	Randomized controlled trials, controlled trials, and quasi-experimental studies, as well as observational studies;	Qualitative studies, program descriptions, surveys, systematic reviews or editorials
Publications	Full papers in peer-reviewed journal, those published as reports, higher degree theses and dissertations;	Ongoing studies, partially published research, studies that were informally reported and/or unpublished, book chapters and books where data was not reported.
Language	Studies in English, Norwegian, Swedish, Danish, Serbian (Croatian, Bosnian), Spanish and Italian.	

Supplementary methods S3. Data extraction categories



Supplementary table S1. Risk of bias assessment and PEDro-scale criteria

	PEDro item number[a] ✓✗											
Reference	1	2	3	4	5	6	7	8	9	10	11	Total (/12)
Khan et al., 2020	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	9
Giovagnoli et al. 2018	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	✓	8
McCaffrey & Locsin 2006	✓	✓	✓	✓	✗	✗	✗	✓	✓	✓	✓	7
McCaffrey 2009	✗	✓	✓	✓	✗	✗	✗	✓	✓	✓	✓	7
Kim et al., 2020	✓	✓	✗	✓	✗	✗	✗	✓	✓	✓	✓	6
Johnson et al., 2018	✓	✓	✗	✓	✗	✗	✗	✗	✓	✓	✓	5
Browning et al., 2020	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	4
Correa et al., 2020	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	4
McCaffrey & Locsin, 2004	✓	✓	✓	✗	✗	✗	✗	✗	✗	✓	✗	3
Cheong et al., 2016	✓	✗	✗	✗	✗	✗	✗	✓	✓	✗	✓	3
Sharda et al. 2019	✓	✗	✗	✗	✗	✗	✗	✗	✓	✓	✗	2
Helmet & Wiancko 2006	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	1

Notes. [a]PEDro items: 1. eligibility criteria were specified. 2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received). 3. allocation was concealed: 4. the groups were similar at baseline regarding the most important prognostic indicators. 5. there was blinding of all subjects. 6. there was blinding of all therapists who administered the therapy. 7. there was blinding of all assessors who measured at least one key outcome. 8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups. 9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat". 10. the results of between-group statistical comparisons are reported for at least one key outcome. 11. the study provides both point measures and measures of variability for at. least one key outcome. NB. Item 1 not included in total score.

Supplementary table S2. Music intervention description and delivery procedures

STUDY[1]	MUSIC INTERVENTION DESCRIPTION AND DELIVERY PROCEDURES
Khan et al., 2020	• Personalized music (PM) was assessed from the legally authorized representatives (LAR), pre-intervention, using Music-preference Assessment Tool (MAT). • Non-personalized, relaxing slow tempo music (STM) (60-80bpm) consisted of guitar, piano, classical music, Native American flute sounds, pre-selected by a board-certified music therapist (MT). • Attention control (audiobook). All the interventions were delivered through noise-cancelling headphone and MP3 player devices.
Giovagnoli et.al., 2018	• Active music therapy (AMT) was given in addition to Memantine (M) drug, and involved a non-verbal approach and free sound-music interactions, using rhythmical and melodic instruments (xylophones, glockenspiels, triangles, wind-chimes, maracas, small woods, guiros, and ethnic percussions). Each session began with musical improvisation inviting patients to choose an instrument and to play using a free technique.
McCaffrey & Locsin, 2006	• The first music listening (ML) CD placed on the player was a lullaby musical selection while the patients were awakening from the anaesthesia. • After they were awake the patients could choose from any of the CDs from the preselection provided by the researchers. It isn't reported how the music selection was made. Interventions were delivered via CD player placed by the bedside.
McCaffrey, 2009	• A music listening (ML) CD containing "soothing lullaby music" was delivered immediately upon the arrival at the orthopaedic floor from the recovery area, and played continuously from a CD player. • As soon as they were awake the patients could choose from a variety of music provided by the researchers (a variety of genres, styles, artists, etc.). It isn't reported how the music selection was made. Interventions were delivered via CD player placed by the bedside.
Kim et al., 2020	IMT intervention consisted of individual music therapy during the day (15-20min) and personalized music-listening (PML) (30min), following a music therapist's assessment of willingness to listen and preferences, at night. • PML intervention was delivered only night-time. Music consisted of several pre-selected relaxing classical pieces previously utilized for their relaxing properties in other studies, that patients could choose from. All music listening was facilitated through earphones and MP3player.
Johnson et al., 2018	• Pre-recorded, researcher-selected music, with slow tempo, low pitch and simple repetitive rhythms was played for the participants through an IPod and headsets, over 3 days upon admission. The intervention was standardized.
Browning et al., 2020	• Therapeutic music listening (ML) delivered as a nursing intervention, involving patient-specific, passive listening to pre-recorded music. The music listening content was selected in collaboration between the patients, family, and PI.
Correa, et al., 2020	• The tracks for the popular/familiar music group (IGPM) were based on the assessed music preferences of the participants. The intervention was delivered in a silent room, previously prepared, and accompanied by the notebook of songs previously selected for each participant. • Classical piano music was selected for the other group (CGCM). Both interventions were delivered through a Sony Headphone of the over-ear type and the volume in the headphones had a frequency of 60-70 decibels (corresponding to the volume of normal conversation).
McCaffrey & Locsin, 2004	• Researcher-selected pre-recorded music for patients to choose from. The intervention was delivered through a bed-side CD player placed within patients' reach, that could be automatically turned on.
Cheong, et al., 2016	• The CMT intervention consisted of active, music improvisation such as spontaneous music making, and playing familiar songs of patient's choice.
Sharda, et al., 2019	• An iPod shuffle with personalized music lists was prepared and delivered along with the headphones as a part of CALM intervention. Intervention was delivered either through disposable earbuds, disposable over the ear headphones, or reusable over the ear headphones.
Helmes & Wiancko, 2006	• Baroque music was pre-selected by the researchers because of its rhythmic nature and absence of sharp transitions in volume. It consisted of orchestral pieces by Albinoni, Pachelbel, and Bach. • A minimum of 2 trials of each condition was delivered to each participant in randomized order. Music was played in the room from a portable compact disc player.

Abbreviations: PM: Personalized music; STM: Slow Tempo Music; MAT: Music Assessment Tool[49]; LAR: Legally authorized representatives; MT: Music Therapist; AMT: Active Music Therapy; M: Memantine drug added to AchEI – acetylcholinesterase inhibitors/the usual pharmacological treatment; ML: Music Listening; IMT: Interactive Music Therapy; PML: Passive music listening; PI: Primary Investigator; IGMP: Intervention Group Popular Music; CGCM: Control Group Classical Music; CMT: Creative Music Therapy; CALM: Confusion Avoidance Led by Music. **Notes**: [1] The studies in this and all other tables are listed according to their PEDro score – from the highest to the lowest quality.

Supplementary table S3. Assessment procedures

STUDY[1]	ASSESSMENTS PROCEDURES FOR EACH OUTCOME
Khan et al., 2020	• Delirium/delirium severity: assessed at enrolment; twice daily until discharge or day 28 - after audio interventions); and 72h after mechanical ventilation (RASS, CAM-ICU, CAM-ICU-7)). • Anxiety: assessed once daily (after morning intervention) using self-report Visual Analogue Scale, (VAS-Face Anxiety Scale). • Pain: assessed twice daily (after each intervention) using CPOT. • Vital signs: HR, BP, RR recorded before and after each session. • Sleep: patients screened for sleeping apnoea (STOP-BANG, Richards-Campbell Sleep Questionnaires) during intervention and 72h after mechanical ventilation. • Mobility: assessed from the inpatient occupational/physical therapy notes. • Critical care recovery centre follow-up: 90 days after discharge.
Giovagnoli et.al., 2018	• Delirium: measured as one of the dementia features in NPI-Q at baseline and at 12 and 24 weeks. • Other outcomes: also assessed at baseline, and at weeks 12 and 24 (the patients were evaluated blindly by a neuropsychologist).
McCaffrey & Locsin, 2006	• Acute confusion: assessed from the nurses' narrative postoperative notes. • Postoperative pain: numerical rating on a scale 1-10 by nurses every 8 hours; the number of pain medications received by each patient after the discontinuance of the patient-controlled analgesia pump on the first postoperative day. • Readiness to ambulate: assessed by the physical therapist (right after the surgery). The score was based on the patient's cognitive status, pain and willingness to participate in his/her own recovery. The distance ambulated on each postoperative day assessed from physical therapy notes. • Patient-satisfaction: assessed during a post-discharge phone-call (2weeks later); patients were asked to rate their hospital experience on a scale 1-10.
McCaffrey, 2009	• Acute confusion: assessed preoperatively as well as during the first 3 postoperative days. • Cognitive function: assessed with MMSE preoperatively, and on the 3 consecutive postoperative days. • Physiological measurements: obtained by measuring physiological factors (oxygen saturation, blood pressure, pulse, and respiration).
Kim et al., 2020	• Delirium: Subjects were screened for postoperative delirium three times a day during ICU stay. • Saliva melatonin and cortisone levels: measured 3 times, on preoperative, operation day, and postoperative day1 (POD1). • Sleep quality: RCSQ and QoR-40 assessments conducted on the preoperative day and POD1 and 2.
Johnson et al., 2018	• Delirium: screened on admission and every 12 hours at the beginning of each shift. • Physiological measurements: collected on admission and every four hours over a three-day period.
Browning et al., 2020	• Delirium: RASS and CAM-ICU assessments were performed by the PI during the prescribed dosing intervals, and recorded in the patients' charts every 8 to 12 hours (or as needed with any change in clinical status).
Correa, et al., 2020	• Neuropsychiatric manifestations: the NPI questionnaire administered to family members and/or care givers for pre/post-intervention evaluation. • Body movements/facial expressions: systematic observations/recordings during interventions, individually, weekly. • Cardiovascular biofeedback: recording the time intervals between heartbeats through an external sensor placed on the fingers or the auricular lobe, the heart rate and the frequency at which the participants maintained emotional balance (cardiac coherence) was also assessed (before and after intervention).
McCaffrey & Locsin, 2004	• Delirium: assessed from the containing the nurses' notes on episodes of confusion, disorganized thinking, altered level of consciousness or cognitive disturbances. • Readiness to ambulate: assessed from physiotherapists' notes (on the day of surgery). One of the measures for ambulation was also that the patient is alert and oriented to time, place and person.
Cheong, et al., 2016	• Mood & Engagement: patients assessed for 3 consecutive days (day 1=baseline, days 2&3 = intervention days). DAY 1- 90, during the usual care; DAYS 2 & 3 - 30 min before, 30 min during and 30 min after the intervention. • The MPES and OERS were rated for each patient with 5-min intervals (1 point accorded for the most frequently observed behaviour in each scale during 5 min interval). • Two raters coded affect and mood independently but simultaneously, so that both affect and mood data could be available for the same timeframe.
Sharda, et al., 2019	The two groups were compared at baseline and post-intervention. • Baseline: demographics, cognitive status, depression, hearing deficits, Laparoscopic procedure. • Post- intervention: delirium incidence, discharge disposition and length of stay, patient-survey.
Helmes & Wiancko, 2006	• Frequency and incidence of disruptive behaviours: the number of bangs, shouts, or uses of the call bell per minute observed/recorded during the intervention trials and non-intervention trials, at random hours (between 10 a.m. and 5 p.m.); • Each participants observed for a minimum of 4 trials a 30-min periods, on a minimum of 3 successive days.

Abbreviations: NEECHAM: Neelon, Champagne, Carlson & Funk, (1996) acute confusion scale; RASS: Richmond Agitation and Sedation Scale; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method for Intensive Care Units; CAM-ICU-7: Delirium Severity Scale; ICD: International classification of diseases; VAS: Face Anxiety Scale- Visual Analogue Scale; CPOT: Critical Care Pain Observation Tool; NPI-Q: Neuropsychiatric Inventory Questionnaire; SIB-L: Severe Impairment Battery Language; SIB: Severe Impairment Battery; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; MMSE: Mini-mental State Evaluation scale; LSNS: Lubben Social

Network Scale; RCS-Q: Richard-Campbell Sleep Questionnaire; QoR-40: self-rating-The Quality of Recovery - 40 questionnaire; Cardio emotion: Cardiovascular biofeedback; SBP: systolic blood pressure; HR: heart rate; RR: respiratory rate; FACS: Facial Action Coding System; MPES: Menorah Park Engagement Scale; OERS: Observed Emotion Rating Scale; NRS: numeric rating scale. **Notes**: [1] The studies in this and all other tables are listed according to their PEDro score – from the highest to the lowest quality.

Article 2

Golubovic, J., Baker, F. A., Simpson, M. R., & Neerland, B. E. (2023).

Live and recorded music interventions for management of delirium symptoms in acute geriatric patients: Protocol for a randomized feasibility trial. *Nordic Journal of Music Therapy, 33*(1), 62–83
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Live and recorded music interventions for management of delirium symptoms in acute geriatric patients: Protocol for a randomized feasibility trial

Jelena Golubovic, Felicity A. Baker, Melanie R. Simpson & Bjørn Erik Neerland

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Live and recorded music interventions for management of delirium symptoms in acute geriatric patients: Protocol for a randomized feasibility trial

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ABSTRACT

Introduction: Delirium is an acute alteration in attention, awareness, arousal, and cognition, precipitated by a sudden illness and highly prevalent in older, frail and acutely hospitalized patients. It is associated with poor outcomes, and few effective treatment alternatives. Non-pharmacological interventions and music show promising effects, warranting further research. This pilot randomized repeated measures trial aims to test feasibility of the trial methodology, acceptability, fidelity and safety of the music interventions, suitability of the effect-outcomes. and preliminary effectiveness.

Method: Acute geriatric patients with delirium or subsyndromal delirium will be randomized to Preferred Recorded Music ($n = 30$) or Preferred Live Music ($n = 30$), delivered for 30 minutes, over three consecutive days. Planned feasibility outcomes will comprise recruitment rate, retention and attrition rates, percentage of adherence, deviations rates, and success of treatment fidelity. Clinical outcomes will include: (a) trajectory of delirium symptoms: level of arousal as assessed by Observational Scale of Level of Arousal (OSLA) and modified Richmond Agitation Sedation Scale (mRASS); attention, assessed using backwards tests and digit span tests; orientation and short-term memory, assessed using recall tasks and orientation questions from Memorial Delirium Assessment Scale, (b) duration of delirium, (c) length of hospital stay, and (d) use of PRN medication (benzodiazepines and antipsychotics).

Discussion: The trial will provide results needed to design a subsequent sufficiently powered RCT, informing on the expected recruitment, feasibility and acceptability of the interventions and assessments and preliminary effectiveness

ARTICLE HISTORY Received 5 October 2022; Accepted 27 February 2023

KEYWORDS Feasibility; delirium; music; music therapy; severity; COVID-19

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/08098131.2023.2192759.

Introduction

Delirium is a neuropsychiatric syndrome characterized by an acute alteration in attention and consciousness, followed by cognitive dysfunction and psychomotor disturbances (5th ed.; DSM-5; American Psychiatric Association, 2013). The multifactorial aetiology of delirium involves an interplay between the predisposing factors and precipitating triggers such as acute illness or medical complications (Marcantonio, 2017; Ocagli et al., 2021; Wilson et al., 2020). In older individuals, delirium is a common and often early presenting symptom in COVID-19 (Shao et al., 2021; Tyson et al., 2022). Its psychomotor presentation is variable, involving hyperactive, hypoactive, or mixed features, and is usually fluctuating (Maldonado, 2017; Marcantonio, 2017). Delirium is undetected or misdiagnosed in 50–75% of the cases, often confused with other conditions with overlapping symptoms such as dementia, depression or psychosis (Kean & Ryan, 2008). Old age, dementia, acute illness, and hospitalization increase the risk, and the prevalence is thus highest in acutely hospitalized, older patients with dementia (50%) (Juliebø et al., 2009; Korevaar et al., 2005; Siddiqi et al., 2006), and in mechanically ventilated patients at intensive care units (ICUs) (80%) (Stollings et al., 2021). Delirium can last from a few days to weeks or even months (Maldonado, 2017; Wilson et al., 2020). The prognosis is often severe, with prolonged hospitalization (Gleason et al., 2015), increased need for long-term care (Krogseth et al., 2014; Witlox et al., 2010), onset of or accelerated progression of cognitive impairment (Gleason et al., 2015), and increased risk for mortality (Asghar et al., 2017; Wilson et al., 2020).

While early detection and treatment of underlying causes might reverse delirium (Bull et al., 2016), clinical management of its symptoms is necessary to prevent poor medical and functional outcomes and complications. Benzodiazepines and antipsychotic medication, commonly used for management of delirium, are not recommended because they are ineffective and can have serious side-effects (Agar et al., 2017; Evensen et al., 2019). Multicomponent approaches can prevent delirium (Asghar et al., 2017), decrease agitation (Marcantonio, 2017; Oh et al., 2017), and derive interest, pleasure and general well-being (O'Hanlon et al., 2014), however, more evidence for their effectiveness in delirium management is needed (Oh et al., 2017).

Music interventions (MIs), including both music therapy delivered by certified music therapists and music-based interventions facilitated by non-music therapists, have shown promise in regulating cognitive and behavioural symptoms in conditions like delirium (Brancatisano et al., 2020; O'Kelly et al., 2013; Sihvonen et al., 2017). Caregiver-facilitated music listening and music therapy interventions can: (a) improve disruptive behaviours, depressive symptoms, cognitive function and engagement in persons with dementia (Bian et al., 2021; Moreno-Morales et al., 2020; Ridder et al., 2013; van der Steen et al., 2018; Vink et al., 2014); (b) elicit favourable behavioural and physiological responses in patients with disorders of consciousness (Grimm & Kreutz, 2018; Li et al., 2020); and (c) reduce anxiety, respiratory rate and systolic blood pressure in ICU patients, highly predisposed to delirium (Bernatzky et al., 2011; Bradt & Dileo, 2014). In a recent systematic review (Golubovic et al., 2022), we found that despite high risk of bias and heterogeneity of studies, MIs delivered by certified music therapists and caregiver-facilitated music listening had positive effects on prevention and treatment of delirium. Further, adherence to the MIs was high. The meta-analysis showed 50% reduction in the risk of developing delirium after exposure to music in postsurgical, critically ill, and mechanically ventilated patients (Golubovic et al., 2022). Significant post-intervention improvements in delirium severity, mood, and engagement

were also found in acute geriatric and long-term care patients (Browning et al., 2020; Cheong et al., 2016; Correâ et al., 2020). Future MI studies should incorporate comprehensive delirium assessments, better defined intervention protocols, correlations between intervention types, dosage, and different delirium symptoms, and evaluate treatment fidelity (Golubovic et al., 2022). The transient nature of delirium makes designing research on potential treatment alternatives challenging, as accurate delirium assessments, diagnosing, as well as inclusion of the participants may be difficult. Evaluating feasibility of assessment procedures and protocols is therefore essential for designing robust trials in the future.

Aims and objectives

As there are only a few published studies with poor methodological quality and scarce available evidence of the effectiveness of MIs in management of delirium, there is a need to implement robust trials. This feasibility and pilot randomized repeated measures trial aims to test pilot and test the feasibility of a RCT design for acceptability, intervention fidelity and safety of the MIs for the patients with delirium. In addition, it will test the suitability of the outcome measures and assess preliminary efficacy of the interventions.

The feasibility objectives are to examine:

(1) Feasibility of recruitment procedures as determined by the proportion of eligible participants who gave informed consent from those screened as eligible, as well as the recruitment rate in a given period.
(2) Feasibility of assessments and follow-up procedures, as assessed by the proportion of fully completed pre-post-intervention assessments.
(3) Success of and fidelity adherence of interventions implementer by the therapist.
(4) Interventions acceptability as determined by the number of the music sessions attended, refused, or not attended for other reasons.
(5) Safety of the interventions determined by monitoring and registering minor and major adverse events potentially caused by the intervention, such as non-specific treatment effects, or other identifiable negative effects.
(6) Sensitivity and suitability of the effect-outcomes (attention, cognition, arousal) to test the efficacy of the music interventions.

Clinical objectives are to (a) estimate preliminary efficacy of live and recorded MIs on severity of delirium symptoms, and (b) determine which specific delirium symptom domains are possibly most responsive to the MIs.

Theoretical framework

Delirium pathophysiology and targeted features

Onset of delirium has been understood as a central neural integration failure, caused by dysregulation in neurotransmitters and disruption to brain network connectivity, necessary for processing and maintaining sensory, cognitive, and motor responses (Maldonado, 2017; Wilson et al., 2020). An altered level of arousal (LoA) affects inattention, disorientation, agitation, sleep disturbance, delusions, visual hallucinations, anxiety, irritability, and depression (American Psychiatric Association, 2013; Inouye et al., 2014; Maldonado, 2017;

Marcantonio, 2017; Neerland et al., 2018; Wilson et al., 2020). External manifestations of LoA inform diagnosis of hypoactive and the hyperactive delirium subtypes (Chester et al., 2012), and detecting delirium superimposed on dementia (Richardson, Davis, Bellelli, et al., 2017). The impact of suboptimal LoA impacts delirium patients' attention and orientation, which further impacts their capacity to participate in cognitive tests (Neerland et al., 2018).

Rationale for MIs for delirium

Our hypothesis is that Preferred Recorded Music (PRM) and Preferred Live Music (PLM) interventions, delivered by a certified music therapist (MT), may positively affect changes in arousal, attention, agitation, apathy, and cognitive performance. For PLM intervention, music attunement created through live music, and responsive non-musical interactions with the MT, may regulate LoA. Conversely, the synthetic sound delivered from the loud-speakers and original versions of the preferred music are the core component of the PRM intervention. There is currently no strong evidence supporting superiority of either MI type in treatment of delirium.

Shared therapeutic mechanisms of PRM and PLM

The multisensory nature of PRM and PLM simultaneously engage and modulate neurocognitive, perceptual, behavioural, physiological and psychosocial functions simultaneously (Hillecke et al., 2005; Schaefer, 2017). In doing so, they activate neuro-plastic and neurochemical processes, auditory-motor coupling, neural entrainment, arousal-mood pathways, autobiographical and implicit memory, and affect attunement (Brancatisano et al., 2020; Gold et al., 2019; Koelsch, 2014; O'Kelly et al., 2013; Park et al., 2016; Sihvonen et al., 2017; Vuilleumier & Trost, 2015). The interplay between the musical components regulates behavioural and psychological change (Ellsworth & Scherer, 2003; Koelsch, 2014; Sihvonen et al., 2017) (Figure 1). The

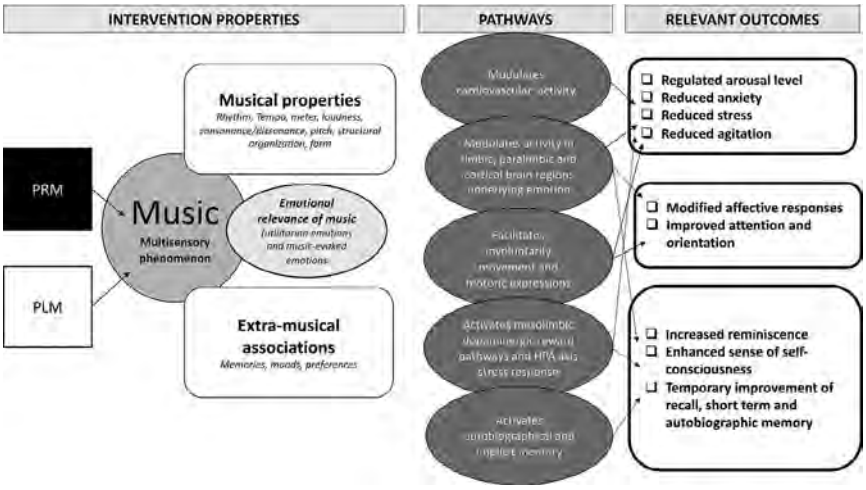

Figure 1. Shared therapeutic mechanisms of PRM and PLM

novelty, surprise, importance, anticipation, expectation, and predictability induce a process of tension, release and emotional contagion, and subsequently regulates attention and LoA (Schaefer, 2017; Thaut & Hoemberg, 2014) (Figure 1).

Music regulates (a) cardiovascular activity, (b) limbic, paralimbic and cortical brain activity responsible for emotion (Koelsch, 2014; Schaefer, 2017; Sihvonen et al., 2017), (c) mesolimbic dopaminergic reward pathways, the hypothalamus-pituitary-adrenal axis stress response (Blood & Zatorre, 2001; Schaefer, 2017; Sihvonen et al., 2017), and (d) involuntary movement and motoric expressions (Grahn & Brett, 2007; Koelsch, 2014). Collectively, the activation of these mechanisms results in improved memory, reduced anxiety, stress (Baker, 2001; Bradt & Dileo, 2014), agitation (Baker, 2001), and improved attention and orientation to space, time and person (Baker, 2001), in older adults with neurological conditions similar to delirium (Figure 1). Further, as music preferences can stimulate autobiographical recall, it holds promise in modifying affective responses (Baird & Samson, 2015), enhancing a sense of self-concept (Arroyo-Anlló et al., 2013), and temporarily improving cognitive functions (Thaut & Hoemberg, 2014) (Figure 1).

Rationale for comparison

Music itself and the therapeutic relationship in which the musical interactions are situated are the main agents for change in the PLM intervention, which may thus be considered a music therapy intervention (Sihvonen et al., 2017). As a music therapist (MT) can respond moment to moment and adapt the PLM to the changing needs of participants, it may be better suited than PRM in responding to the fluctuating nature of delirium. Additionally, the shared musical interactions with the MT may lead to emotional connectedness, safety and agitation regulation (McDermott et al., 2014). Live performance and improvisation elements are engaging for patients with delirium (Cheong et al., 2016); synchronize the patients' internal physiological rhythm, and thus reduce anxiety and stress (Bush et al., 2021). Sound vibrations, live performance and the presence of the musical instrument(s) might provide additional sensory input, introduce a visual and sound-localization component, and thus impact on attention, orientation, reminiscence, and recall (Lee et al., 2021) (Figure 2).

In the absence of a musical interaction, and fewer stimulating sensory element, the PRM may allow the participants to interact more directly with the music itself, and therefore be more calming and relaxing, for those with hyperactive delirium symptoms when compared with PLM. Recorded music has positive effects on cognition, orientation, recall, anxiety and aggression (Clare & Camic, 2020). Further, orientation and biographical recall may be stronger with the recognition of the unique "sound" of an original version of the song (Baker, 2001). However, habituation may result after prolonged exposure to the complexity of a music containing more than one instrument (Szpunar et al., 2004) (Figure 2).

Method

This study protocol follows the Consolidated Standards of Reporting Trials (CONSORT) statement's extended checklist for pilot and feasibility studies (Eldridge et al., 2016).

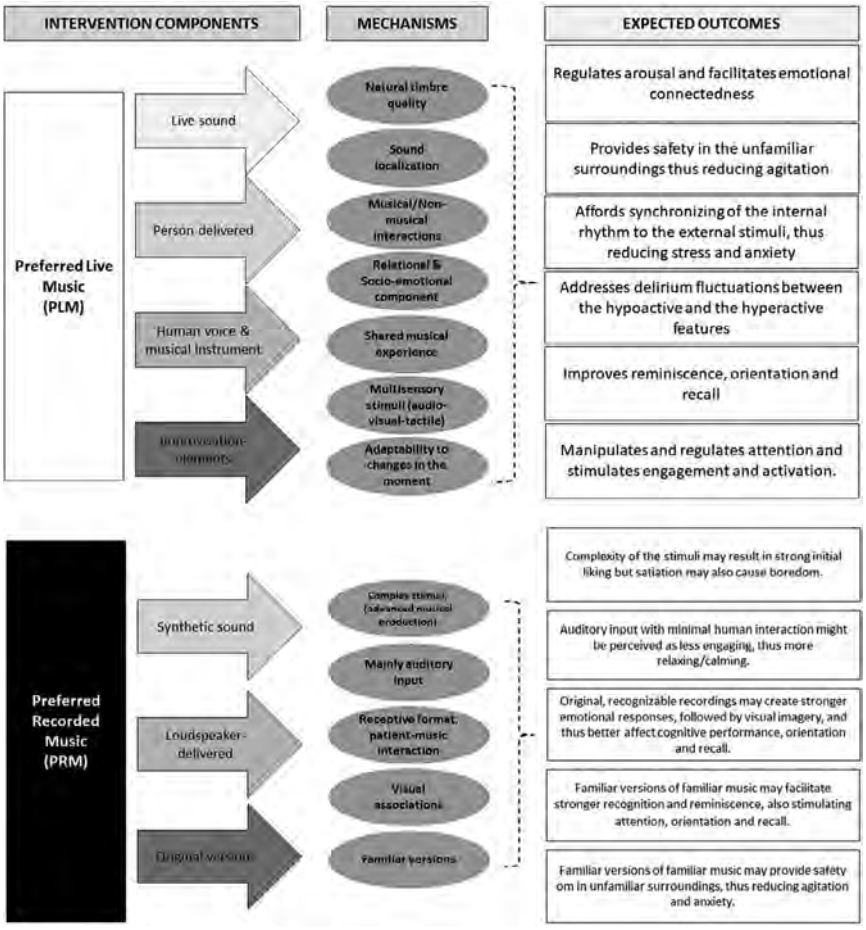

Figure 2. Rationale for comparison

Study design

To evaluate the feasibility and preliminary effectiveness of the PLM and PRM interventions, a two-arm randomized repeated measures design will be implemented. Participants will receive either PRM or PLM, once a day for three consecutive days. Delirium symptoms will be assessed in participants pre and post each daily exposure to the allocated intervention.

Participants and setting

Participants will be recruited from an acute geriatric (AG) hospital ward (Ahmed, 2017) where there is a high prevalence of delirium and dementia comorbidities. The

ward admits approximately 75 new patients per month with a patient average length of stay of 6.5 days (Ahmed, 2017).

Eligibility criteria

Patients admitted to the AG ward will be eligible if:

(1) Aged ≥ 65
(2) Diagnosed with delirium or subsyndromal delirium within the last 72 hours and is still present.
(3) Appropriate informed consent is obtained.

Patients will not be excluded if they are under long-term care, have co-morbidities such as dementia or mild cognitive impairment, or if they have COVID-19. Patients will be excluded if:

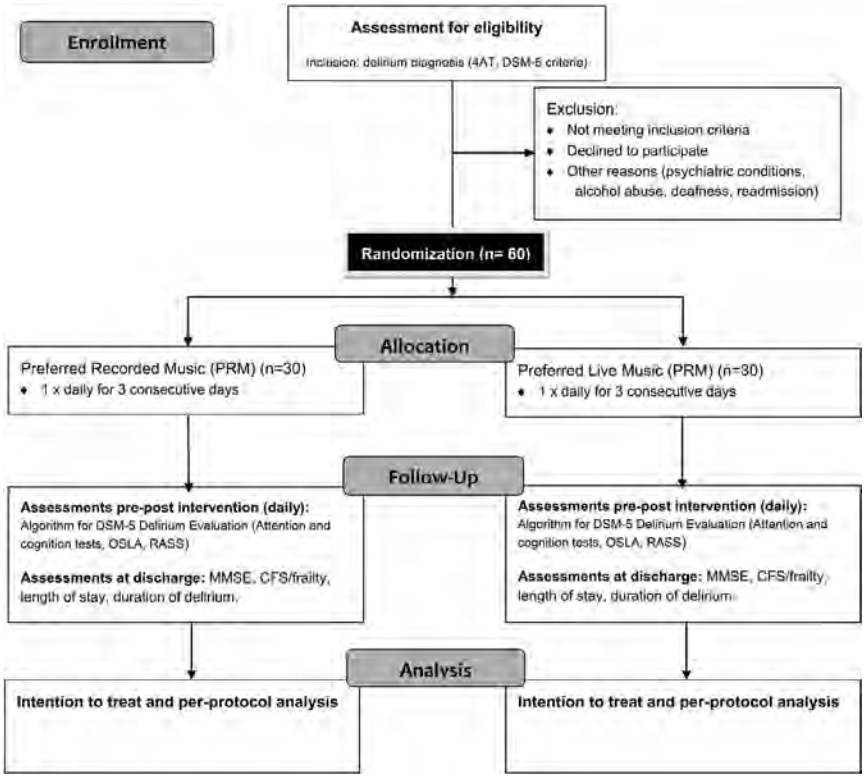

Figure 3. CONSORT study flow diagram

(1) Previously enrolled in the study and were readmitted during the study period,
(2) Present with severe hearing impairments,
(3) Present with severe psychiatric conditions other than delirium, or
(4) Admitted due to severe alcohol or substance addiction,
(5) Their musical preferences include orchestral or other kinds of music impossible to perform live by voice and the guitar (Figure 3).

Recruitment procedures

Screening and enrolment

All the patients admitted to the AG ward will be routinely screened for delirium by the hospital nurses, using the 4AT which is a validated rapid (<2 min) screening tool for delirium (Shenkin et al., 2019). Patients with a 4AT score of ≥4 will be assessed by geriatricians according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria (American Psychiatric Association, 2013) and using a diagnostic algorithm applied in several other trials (Table 1) (Neerland et al., 2015; Richardson, Davis, Stephan, et al., 2017; Tsui et al., 2022). Delirium subtypes will be determined using Delirium Motor Subtype Scale (DMSS-4) (Meagher et al., 2014). Geriatricians at the ward are responsible for obtaining informed consent from eligible patients or their legal representatives and will be masked to intervention allocation post randomization.

Randomization

Consenting eligible patients will be randomly assigned to two different MIs using permuted block randomization 1:1, and the online randomization software, True Random Numbers (https://www.random.org/). The random allocation sequence will be generated by an independent researcher, and the participants will be enrolled and assigned to interventions by the music therapist. Randomized blocks of 10 participants aim to maintain even numbers of participants per study-arm.

Masking

Masking the therapist and the participants will not be possible. Masking assessors will be attempted. In case where allocation is revealed, the assessor will be replaced with a new assessor masked to allocation wherever possible. Success of masking will be verified for each of the post-intervention delirium assessments. The success of masking will be reported.

Interventions

Participants' music preferences will be determined by legal guardians completing an adapted Norwegian version of the Assessment of Personal Music Preference (family version) tool (APMP) (Gerdner, 2021). A Music Assessment Tool (MAT), developed for the use with critically ill and mechanically ventilated patients (Chlan & Heiderscheit, 2009) will be used to assess music preferences directly from the participants. Assessment sessions will be performed by the certified MT prior to other baseline assessments, will not exceed 30 minutes, will be adapted to the participants' cognitive functions and responsiveness, and will include observation of responses to

Table 1. Diagnostic algorithm for DSM-5 delirium evaluation.

DSM-5 Criteria	Tests to be performed and information to be collected			Is DSM-criteria fulfilled? YES	NO
A. Disturbance in **attention** (i.e. reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced orientation to the environment	**Evaluation**	**Attention-tests**	**Cut off (definition of inattention)**		
	Daily	SAVEAHAART/ KATAMARAAN	2 or more errors		
		Days of the week in reversed order	Any error		
		Months of the year in reverse order	Unable to reach July		
		Count backwards from 20 to 1	Any error		
		Digit span forward	Less than 5 forward		
	Observation: Easily distracted? Collaborative? Has a tendency to "loose thread" in the conversation? Arousal: OSLA>3 and/or mRASS other than 0?				
B. The disturbance develops over a **short period of tim**e (usually hours to a few days), represents **a change** from baseline attention and awareness, and **tends to fluctuate** in severity during a day.	Informant history from patient's carers and nursing staff. Questions to carer/nursing staff or derived from clinical notes: • Has there been a sudden change in the patient's mental state? • Does the patient seem to be better at any period in the day compared to other times? • Has the level of consciousness been altered (drowsy/not responsive, or agitated)? • Sleep-wake cycle disturbances?				

(*Continued*)

Table 1. (Continued).

DSM-5 Criteria	Tests to be performed and information to be collected	Is DSM-criteria fulfilled? YES	NO
C. An additional **disturbance in cognition** (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).	Questions to the patients: Orientation-tests: Orientation to time, place, and person; Why are you in hospital? Will a stone float in water? Are there fish in the sea? (Any error = disorganized thinking) Recall (3 words) Questions to carers/nursing staff/clinical notes: Has there been any . . . Perceptual disturbances? Sleep-wake cycle disturbances? Memory disturbances? Psychotic episodes? Psychomotor disturbances?		
D. The disturbances in Criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.	Information from history/chart/clinical assessment.		
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.			
Delirium, based on the tests and information above?	All DSM-5 criteria are fulfilled		
Subsyndromal delirium, based on the tests and information above?	Defined as evidence of change, in addition to any of the following: (a) altered arousal, (b) attention deficits, (c) other cognitive change, (d) delusions or hallucinations. Criteria D and E must be fulfilled.		

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OSLA – Observational Scale of Level of Arousal; mRASS – Modified Richmond Agitation and Sedation Scale.

musical pieces played within the assessment session. The MT will design PRM and PLM interventions and select the songs to be included, using the information derived from the APMP, MAT and preference assessment session.

Participants will receive the PRM or PLM intervention, once per day, for 30 minutes, for three consecutive days. The same songs in the same order will be used in each of the three daily sessions, to ensure familiarity, foster safety and minimize confusion. PLM intervention will involve singing preferred songs live with or without the guitar/tone-chimes accompaniment. MT will actively engage with the participants while singing and playing the selected songs by encouraging them to sing along, move to the music, and, if appropriate, offer small percussion instruments for them to play on. Elements of musical improvisation, both vocal and instrumental will be present, including techniques such as repetition, variation, and extension of the themes from the selected songs, as well as musical matching, mirroring or imitating the participants' responses that occur. Eye-contact, and both verbal and physical interaction will be in focus. Music attunement created through such live musical interaction, and responsive non-musical interactions with the MT are, thus, the most important components of this intervention. During the PRM intervention, the MT will refrain from engaging with the participants during their listening session. However, the MT's implicit therapeutic skills might make it challenging to adhere to the protocol and refrain from interacting with the patient. Each interaction between the MT and the participants during the sessions will, thus, be considered a deviation from the protocol, and recorded post session.

In addition to the MIs, all the participants will receive usual care. The MIs will take place in the participants' private rooms containing a single-bed, night table, chairs, wardrobe and a TV. As the bedrooms do not usually contain radio devices, we expect the participants' music listening during the intervention days to be limited but will, nevertheless, attempt at recording it by talking to the caregivers and the nursing staff. Interventions will be discontinued or modified in response to participants' request or worsening of their health condition.

Outcomes

Primary outcomes (feasibility outcomes)

Primary outcomes of the feasibility trial comprise: (a) recruitment rate, (b) retention and attrition rates, (c) percentage of adherence and deviations rates, and (d) success of treatment fidelity, to determine the extent to which the study design is replicable and its results generalizable (external validity), and that no other factors/variables caused the observed effect (reliability and internal validity) (Borrelli, 2011).

Secondary outcomes (clinical outcomes)

Clinical outcomes comprise: (a) trajectory of delirium symptoms: level of arousal as assessed by Observational Scale of Level of Arousal (OSLA) (Hall et al., 2020) and modified Richmond Agitation Sedation Scale (mRASS) (Chester et al., 2012); attention, using backwards tests and digit span tests; orientation and short-term memory, using recall tasks and orientation questions from Memorial Delirium Assessment Scale (Breitbart et al., 1997), (b) duration of delirium, (c) length of hospital stay, and (d) use of PRN medication (benzodiazepines and antipsychotics).

Table 2. Schedule of clinical activities.

Procedure	Screening (Day 0)	Baseline, Enrolment, Randomization (Day 0)	Intervention period		End of treatment (Registration during hospital stay)
			Before intervention (Day 1, 2, 3)	After intervention (Day 1, 2, 3)	
Assessment of eligibility (inclusion and exclusion criteria)	X				
4AT	X				
Informed Consent	X				
Enrolment/Randomization	X				
DSM-5 delirium diagnosing	X	X	X	X	
DMSS-4 delirium subtyping		X	X	X	
Sociodemographic data		X			
Past and current medical conditions		X			X
Prescribed Medications		X			X
IQCODE		X			
NEWS II		X	X	X	X
Assessment of Personal Music Preference (family version)		X			
MAT (participant version)		X			
OSLA		X	X	X	
mRASS		X	X	X	
Attention tests		X	X	X	
Cognitive tests		X	X	X	
CFS		X			
MMSE-NR					X
Length of hospital stay					X
Discharge information (home, nursing home)					X
Adverse Events			X	X	X

4AT – Alertness, Abbreviated Mental Test-4; DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DMSS – Delirium Motor Subtype Scale; IQCODE – Informant Questionnaire on Cognitive Decline in the Elderly; NEWS II – National Early Warning Score II; MAT – Music Assessment Tool; OSLA – Observational Scale of Level of Arousal; mRASS – Modified Richmond Agitation and Sedation Scale; CFS - Clinical Frailty Scale; MMSE-NR – Norwegian Revised Mini-Mental Status Evaluation.

Data collection and study procedures

Background variables

Demographic data collected will include gender, age, marital status, education, accommodation, alcohol/tobacco use, etc. Clinical baseline data comprise height/weight, past diagnoses, comorbidities, and prescribed medication. Frailty status will be assessed using the Clinical Frailty Scale (CFS) (Rockwood et al., 2005) and cognitive status pre-admission will be assessed by asking the patients primary caregiver to complete the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm, 1994). Severity of acute illness will be assessed using New Early Warning Score 2 (NEWS2) (Royal College of Physicians [RCoP], 2012). The Mini Mental Status Evaluation Norwegian version (MMSE-NR) (Arevalo-Rodriguez et al., 2015) will be performed at discharge for the purpose of general cognitive screening (Table 2).

Delirium assessments

Pre-and post-intervention changes in delirium severity will be assessed after each music session, using the DSM-5 algorithm (described earlier). As DSM-5 only specifies

criteria to be evaluated and not the tests that should be used, our algorithm includes validated attention and cognition tests, as well as the Observational Scale of Level of Arousal (OSLA) and Richmond Agitation and Sedation Scale (RASS).

The validated Observational Scale of Level of Arousal (OSLA) involves assessing LoA through observation of eye opening, eye contact, posture and movement (Hall et al., 2020). The test is performed by trained geriatricians, takes under one minute to complete, and requires no verbal interaction with the patient. Total scores range from 0 to 15, with a cut-off of ≥ 2 or ≥ 3 already indicating abnormal arousal (Hall et al., 2020). For a cut-off ≥ 2 OSLA scale has sensitivity of 0.87 (95% CI [0.84, 0.93]), and specificity of 0.53 (95% CI [0.48, 0.58]). OSLA is sensitive to within-patient fluctuations in delirium status, and thus recommended for monitoring and assessing changes in LoA and delirium severity over time (Hall et al., 2020).

Richmond Agitation and Sedation Scale (RASS) is a validated observational scale that takes less than 20 seconds to administer, and measures sedation and agitation – the main components of consciousness, and strong indicators of the hypoactive and hyperactive delirium subtypes (Chester et al., 2012; Han et al., 2015). Changes in agitation/sedation are recorded by observing the duration of eye contact following verbal and physical stimulation, with level of agitation ranging from "combative" to "calm", and level of sedation ranging from "alert" to "comatose" (Ely et al., 2003). Scores range from −5 (comatose state) to +5 (combativeness) (Han et al., 2015). A modified version of RASS scale incorporating attention assessments (mRASS) is recommended for use with geriatric and critically ill patients (Chester et al., 2012). mRASS has a sensitivity of 0.64, and specificity of 0.93, using a cut-off ≥ 3 (Chester et al., 2012) (Table 2).

Cut-off scores for the attention tests, recall tasks and orientation and short-term memory questions from Memorial Delirium Assessment Scale (Breitbart et al., 1997) are described in Table 1.

Length of hospital stay, duration of delirium during hospital stays and the use of psychopharmacological medications per patient during the hospitalization will be assessed from electronic medical journals before discharge from the ward (Table 2).

Assessments of feasibility outcomes

(1) Recruitment procedures will be evaluated, and recruitment rate calculated by dividing the total number of the eligible patients randomized per month by the total number of months that the trial recruited for.
(2) Retention is defined as trial completion on study intervention and will be calculated by dividing the number of participants completing the study by the total number of participants recruited. Attrition rate is defined as the percentage of the participants that did not complete the study and will be calculated by dividing the number of the participants who withdrew by the total number recruited.
(3) Adherence to the study protocol relates to compliance with the described study protocol and procedures, and protocol deviations to any change or divergence from the protocol for each participant. Overall adherence rate will be estimated by calculating the percentage of the music sessions and assessments completed from those described in the protocol by dividing the number of completed sessions/assessments by the number that was planned. The percentage of participants who had received all three sessions as per protocol will also be

estimated. Deviation rates will be measured by counting the deviations per participant during their participation in the study.

(4) The level of treatment fidelity will be determined according to the National Institute of Health Behavioural Change Consortium (NIH BCC) recommendations (Bellg et al., 2004; Borrelli, 2011; Borrelli et al., 2005), directly, by observing the recorded sessions with randomly selected 10% of the participants, and indirectly by self-reporting via MT's logs and checklists (Supplementary material S1). Only two of the NIH BCC features will be assessed: (a) whether the design of the trial has been defined and described prior to implementation in such way that it can answer the proposed research question and be replicated and (b) whether the treatments are delivered as intended (Bellg et al., 2004), with the general goal of standardizing delivery, and ensuring adherence to the intervention protocols (Bellg et al., 2004; Borrelli et al., 2005). A full description of the fidelity strategy can be found in Supplementary material S2.

Participant retention and withdrawal

Participant retention and withdrawal and reasons for doing so will be tracked. These include early discharge, participant/guardian withdrawal of consent, safety concerns identified by the geriatrician, and an inability/low compliance with the study protocols and procedures. All participants who had received at least one session will be included in an intention-to-treat analysis.

Analytical methods

Statistical considerations

Changes in OSLA, mRASS, attention and cognitive status scores assessed pre and post session will be recorded for three consecutive days until the end of the intervention. Changes in response pre- and post-intervention within the participants and between the two participant samples will be compared each day and across the three consecutive days. The between groups effect will be estimated in mixed linear regression models for each outcome with adjustment for their respective pre-intervention score and participant ID included as a random-effect. For outcomes measured only at discharge (length of stay, duration of delirium, PRN medication), the Independent Samples t-test for the normally distributed, or Mann-Whitney test for the skewed data, will be used to compare intervention groups for continuous variables, and a Chi-squared test for binary variables. Any participants who are discharged prior to completion of three music sessions, or have not been able to receive the intervention as per protocol for other reasons, will be included in the analysis under the intention-to-treat principle. We will also attempt per-protocol analysis, for the participants that have received all the interventions as per protocol.

Sample size and test power

This feasibility study is not intended to be adequately powered to draw conclusive findings on the effects on delirium symptoms. We aim to recruit the sample of 60 participants in accordance with CONSORT recommendations. The sample size of $n = 60$ participants will enable us to examine the main objectives of the study, and also allow for dropouts, which may be expected in the context of acute-geriatric medicine,

considering the frailty and sensitivity of the patients, as well as the challenging and fluctuating nature of delirium. This sample size will allow for collecting sufficient data to inform a robust, more conclusive RCT in the future.

Ethical considerations

Research ethics approval and consent

Ethical approval has been obtained from the Regional Ethics Committee in Norway (REK 457017). The trial is registered at Clinical Trials (NCT05398211). Most eligible participants in this study are expected to have reduced ability to give consent, and each patient's ability to give consent will be individually evaluated. Experienced physicians will be obtaining consents from the patients directly and supplement or replace them by the consent from the legally assigned representatives (LAR) when necessary, using three different consent forms. Consents will be obtained primarily in written format. However, the use of verbal consent was also approved by REK in cases where the LAR is not present physically. The verbal consent will then be obtained via phone-call, and the written confirmation will be obtained at the first possible occasion.

Data management

Appropriate permission for personal-data storage has been obtained from Data Protection Authorities at Oslo University Hospital (OUS) and a data-management plan has been created. The data in this study will be collected both using paper forms, and electronically, and all the data collection will take place at the participating site, where the data originated. The data registered during the study will be indirectly personally identifiable (de-identified/coded) and will be stored safely on the research servers at OUH, and in locked cabinets. The participants will be thoroughly informed about the personal data collected about them, as well as that the data will be unidentifiable, through the informed consent forms.

Risk management

The potential risks associated with this study are slow recruitment, poor fidelity and acceptability of the interventions, low reliability of clinical outcomes, poor adherence to assessment procedures, and high percentage of dropouts and/or adverse events due to the challenging and fluctuating nature of delirium. As our primary aim is investigating feasibility, most risks will be viewed as relevant findings. We will not be able to influence recruitment rate, drop-outs or adverse events. To mitigate the risk of poor adherence to the interventions, we developed a detailed intervention manual with accompanying treatment fidelity protocol checklist for PRM and PLM interventions (Supplementary material S1 and S2).

To reduce the risk of low reliability of the clinical outcome measures we will report delirium by symptom domains rather than present/absent, using continuous variables rather than dichotomous (Tieges et al., 2021). We chose mRASS and OSLA scales as they are highly correlated, have high interrater reliability ($k = 0.91$), can reliably assess changes in delirium severity over time (Chester et al., 2012; Hall et al., 2020) and when used in combination, increase the accuracy of diagnosis.

Assessing LoA, combined with monitoring cognitive status and attention, is the most efficient approach to evaluating short-term post-intervention changes in delirium severity. Combined arousal-attention assessments (e.g. OSLA and

SAVEHAART attention test), are, thus, more efficient and diagnostically accurate, particularly for detecting delirium in patients with dementia, and diagnosing delirium superimposed on dementia (Quispel-Aggenbach et al., 2018; Richardson, Davis, Bellelli, et al., 2017). Adherence to assessment procedures is protected by training the assessors in using the specially developed assessment-algorithm. Potential adverse events and unintended effects of the interventions will also be monitored and documented using treatment fidelity checklists.

Dissemination

Findings of this trial will be published in relevant scientific journals, and presented at international conferences.

Discussion

Relevance, benefits, and implications

While music interventions (MIs) are moderately used in hospital settings and with various neurological conditions, their use in management of delirium is mainly unexplored, both in the Norwegian context and internationally. The existing research is scarce, with small samples, poor designs, and heterogeneous effects (Golubovic et al., 2022). The proposed randomized feasibility study is designed to provide necessary knowledge for improving the design of future research, particularly the standardization of intervention protocols, relevance of effect-outcomes, validity of delirium-assessments, as well as the power calculation and optimal recruitment strategies. Measuring intervention effects will enable us to identify and evaluate correlations between different MIs and changes in the targeted delirium symptoms and evaluate sensitivity and accuracy of delirium tools and assessment procedures for measuring post-intervention effects. The results are expected to contribute to developing generalizable knowledge on the appropriateness and preliminary effectiveness of MIs in delirium management in acutely ill older patients.

By involving a music therapist (MT) in delivery of both PLM and PRM interventions, rather than having PRM delivered by a non-music therapist, we wish to isolate live and recorded music as main variables without introducing an additional facilitator variable. While we view the involvement of the MT important for the music preference assessments and designing of both interventions, we do acknowledge that PRM intervention may also be delivered by a non-music therapist if the study should be replicated in the future. However, the PLM intervention should be facilitated by a certified music therapist, due to its complexity and the therapeutic techniques demanding music therapeutic expertise.

Strengths and limitations

A strength of this study are our comprehensive music preference assessments, which will allow us to individualize the interventions. As people with delirium

may not be able to voice their music preferences, MTs are specially trained and experienced in conducting interactive music preference assessments with people who have reduced cognitive abilities and physical functions. Our comprehensive, validated algorithm for assessing changes in delirium severity, which includes both continuous and categorical variables, is a strength because it offers a more nuanced picture of the changes in delirium after exposure to the MIs.

The main limitation of this feasibility study protocol is the lack of a control group, which would make it possible to compare the changes in severity of delirium symptoms between patients receiving usual care and the two MIs offered. However, as the recruitment-rate, feasibility of recruitment and assessment-procedures, as well as the feasibility, suitability and acceptability of the MIs is still widely unknown, we have considered it appropriate to omit the control group, and rather focus on exploring and determining feasibility using a pre-post measures design.

Conclusion

In conclusion, this study is expected to contribute to extending and strengthening the interdisciplinary collaboration between the fields of geriatric and acute medicine, neuroscience, nursing, music therapy and music medicine and drive changes in the care for older adults with delirium. The generated knowledge might indirectly contribute to an increased implementation of MIs in management of delirium across the clinical settings and levels of care, and thus open new research areas of high relevance for the public health.

Disclosure statement

The authors report no conflict of interest.

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Supplemental material

Supplementary material S1: Self-Reporting Checklists for Treatment Fidelity Evaluation (PRM, PLM)

Supplementary material S2: Treatment fidelity strategy

Supplementary material S1: Self-Reporting Checklists for Treatment Fidelity Evaluation (PLM, PRM)

Treatment fidelity checklist and intervention manual PLM

Study-ID: **Intervention day (1-3):** **Date:** **Time:**

1. Were music preferences assessed prior to randomization? YES NO
2. Were there enough songs for the intervention? YES NO.
3. Was music intervention session completed? YES NO
4. Was the intended dosage delivered? YES NO. If not, how long did the session last?
   - Shorter (how long?)……..
   - Longer (how long?)……..
   - Why did the session last shorter/longer?
     ……
5. Were the preference songs always played in the same order? YES NO. If not, which order of songs was delivered?
   A……
   B……
   C……
   D……
   E……
6. What was the reason for changing the order?……
7. Was the delivery of MI disrupted? YES NO. How/Why was the MI disrupted?
   - Patients' desire
   - Patients' health condition
   - Environmental factors
8. Describe the form of delivery:
   - Only MT singing/playing
   - Only voice
   - Voice and accompaniment (Which? Guitar? Tone-chimes? Other rhythmical instruments?)
   - Were there elements of Improvisation? YES NO
   - Did the patient engage? YES NO
   - How did the patient engage? (Playing percussion instruments? Singing? Movement/dance? Talking/reminiscing along the way? Crying? Clapping hands? Other?)
   - Which song(s) did the patient particularly respond to (A –E) and how?
     ……
     ……
9. Did the participant listen to music outside of the study this day? YES NO. If yes, what and for how long? (describe duration and content)

   ……
10. Were there any nonspecific treatment effects? YES NO.
    Which? (describe)……

Intervention manual:

In PLM intervention music therapist should chose the music for the sessions from patients' assessed preferences and make sure not to change their order of deliverance. MT should enter the room, say hi to the patient, introduce the intervention, and offer the participants small percussion instruments that they can play on during the session in appropriate. Thereafter MT should deliver the intervention live, by singing/playing the songs either A Capella, or accompanied by a guitar, tone-chimes, or percussion instruments. The intervention may involve interaction with the patients (e.g. physical, musical, verbal), the songs are not expected to be delivered in a way that is identical to their original versions, and elements of improvisation are both allowed and expected, as well as other forms of attunement to the patients. After max. 30 minutes, the MT should collect the instruments, say good bye to the patient, and leave the room.

Treatment fidelity checklist and intervention manual PRM

Study-ID: Intervention day (1-3): Date: Time:

1. Were music preferences assessed prior to randomization? YES NO
2. Were there enough songs for the intervention? YES NO.
3. Was music intervention session completed? YES NO
4. Was the intended dosage delivered? YES NO.
5. If not, how long did the session last?
   - Shorter (how long and why?)……..
   - Longer (how long and why?)……..
6. Were the preference songs always played in the same order? YES NO.
7. If not, which order of songs was delivered?
   A -
   B –
   C –
   D –
   E –
   What was the reason for changing the order of songs?.....
8. Was the delivery of MI disrupted? YES NO.
9. How/why was the MI disrupted?
   - Patients' desire
   - Patients' health condition and/or physiological need (e.g. bathroom visit).
   - Environmental factors (e.g. visitors)
   - Patient talking to the therapist
10. Was the intervention first introduced verbally?
11. Was the intervention delivered by the musical device and Bluetooth speaker? YES NO
12. Was the intervention ended/rounded up verbally? YES NO
13. Did the music therapist stay inactive during the session? YES NO
14. If not, why and how did the MT engage with the patient (disruption)?.....
    .....
15. Did the patient engage with the music during the session? YES NO
16. How did the patient engage?
    - Playing /singing
    - Movement/dance
    - Talking/reminiscing
    - Crying
    - Clapping hands
    - Other:……
17. Which song(s) did the patient particularly respond to (A –E) and how? (Describe important moment during the session)
18. Did the participant listen to music outside of the study this day? YES NO
19. If yes, for how long? (describe duration and if possible content)
    ……
    ……
20. Were there any nonspecific treatment effects? YES NO.

If yes, which ones were there?
(describe)……
……

Intervention manual:

In the PRM intervention, music therapist (MT) should chose the songs for the sessions from the patients' assessed preferences and deliver the songs in the same order each of the intervention days. MT should enter the participant's room, say hi and shortly introduce the intervention verbally, and subsequently start the music from a musical device and a Bluetooth speaker. MT should not engage with the patient neither verbally nor musically while the music is played. Any engagement should be registered as the disruption from the protocol. After 30 minutes the MT should stop the music, round up the session verbally, say good bye to the patient and leave the room.

Supplementary material S2: Treatment fidelity strategy

Treatment fidelity strategies				
Design of the study				
Recommendation	Measure	Reported?		
		YES	NO	Nr.?
Same treatment dose within PRM and PLM conditions	Number of sessions? Length of sessions? Frequency of sessions? Content of sessions?			
Equal treatment dose across the PRM and PLM conditions	Number of sessions? Length of sessions? Frequency of sessions? Content of sessions?			
Plan for implementation setbacks				
Mention of the provider credentials				
Mention of the theoretical model underpinning the interventions				
Treatment delivery				
Reduce differences within treatment *(Provider in the same condition always delivering the same intervention)* Ensure adherence to treatment protocol *(Treatments are being delivered as they were conceived regarding content and dose)* Minimize contamination between the conditions.	Included method to ensure the content of the intervention was being delivered as specified (manual/protocol)? Included method to ensure that the dose of the interventions was being delivered as specified (number of contact minutes)? Included mechanisms to assess if the provider actually adhered to the intervention plan (e.g. video, audio, self-report etc.)? Assessed nonspecific treatment effects? Used treatment manual?			

Article 3

Golubovic, J., Neerland, B. E., Simpson, M. R., Johansson, K., Baker, F. A. (submitted for publication to BMC Geriatrics).

Randomized pilot and feasibility trial of live and recorded music interventions for management of delirium symptoms in acute geriatric patients.

A Randomized Pilot and Feasibility Trial of Live and Recorded Music Interventions for Management of Delirium Symptoms in Acute Geriatric Patients

Abstract

Background: Delirium is an acute shift in attention and arousal, usually triggered by acute illness or surgery in older dementia patients. Prognosis is poor, and pharmacological options are limited; non-pharmacological interventions and music show promise.

Methods: This randomised pilot and feasibility trial tested feasibility, acceptability, fidelity, and safety of music interventions (MIs) for delirium patients and assessed preliminary effectiveness and suitability of the selected effect outcomes. Participants from an acute geriatric ward were randomised to Preferred Recorded Music (PRM) and Preferred Live Music (PLM), delivered for 30 minutes over three consecutive days. Feasibility outcomes included recruitment rate, retention, adherence, deviations, and treatment fidelity. Clinical outcomes were trajectory of delirium symptoms (arousal, attention, cognition), delirium duration, hospital stay length, and medication intake. Post-intervention and between groups changes in delirium symptoms were compared using mixed linear regression models for the repeated measurements. Mann-Whitney test and Fishers exact test were used for length of stay and medication use, respectively.

Results: 26 participants (PLM=14; PRM= 12), median age 87, most with hypoactive delirium were recruited at a rate of 3 participants per month. Retention rates for PLM and PRM were 64% and 33% respectively, and adherence to PLM and PRM intervention protocols were 83% and 58%, respectively. Total adherence to the assessment protocols was 44%. PLM was delivered as intended, (treatment fidelity 93%), and PRM did not satisfy treatment fidelity (83%). All delirium symptoms except arousal improved on day 3 compared to baseline, with statistically significant improvement in attention. No conclusive pre-post or between-group differences were detected for any outcomes; confidence intervals were wide.

Conclusions: Feasibility of recruitment, interventions and assessments was indicated, and greater acceptability, safety and fidelity of the PLM intervention compared with the PRM. Adoption of external assessors is warranted in future trials, to mitigate slow recruitment and low adherence. Wide confidence intervals for most measures and comparisons indicate

that the possible effect of the MIs on delirium cannot be excluded. The trial was registered at Clinical Trials, ID: NCT05398211, on May 31, 2022.

Keywords: feasibility, delirium, music, music therapy, severity, Covid-1

Background and objectives

Delirium is a clinical syndrome represented by an acute change in mental status (1) and inattention; cognitive dysfunction, disturbed level of arousal, psychotic episodes, emotional and behavioural changes may also be present (1, 2). Delirium is common in hospital settings, occurring in >50% of patients (3), with the highest prevalence in older, frail (4-6), acutely hospitalized, and mechanically ventilated patients in postsurgical intensive care units (ICUs) (7-9). Delirium develops suddenly, is transient with fluctuating symptoms (7). Pathophysiology is complex and not completely understood, involving an interplay between the predisposing factors such as advanced age, underlying illness like dementia, and precipitating factors such as acute illness, drugs, or surgery (7). Delirium is strongly correlated with Covid-19 (10, 11), and is likely to cause complications in older adults (12).

Delirium is often undetected, misdiagnosed, or confounded with other conditions, sharing symptoms with dementia, depression or psychosis (13). Prognoses is poor, including prolonged hospitalization (14), need for long term care (15, 16), onset or worsening of cognitive impairment (7, 14), and increased mortality risk (7, 17). Benzodiazepines and antipsychotic medication are ineffective in treating delirium and may have adverse side-effects (18, 19). Non-pharmacological, multicomponent approaches might address multifactorial delirium etiology, and are showing promising effects in preventing delirium (3, 17), decreasing agitation (8, 20), and deriving interest, pleasure and general well-being (21). The evidence of their effectiveness in clinical management of delirium symptoms is still scarce (20, 22).

Music interventions (MIs) have positive effects on behavioural and psychological symptoms of conditions similar to delirium, such as dementia (23-30) and disorders of consciousness (31, 32), and may also be effective in prevention and treatment of delirium in older individuals. Our systematic review (33) showed that research on MIs for delirium is scarce; existing trials show promising results, particularly for delirium prevention. High patient acceptability and enjoyment of MIs, cost-effectiveness, and absence of adverse effects were also commonly reported (33). Despite the moderate-high risk of bias among the included studies, our meta-analysis indicated that postsurgical, critically ill, and mechanically ventilated patients were 50%

less likely to develop delirium after being exposed to music postoperatively (33). Significant improvements in engagement, mood, and delirium severity were also found in acute geriatric and long-term care patients post-intervention (34-36). However, better designed trials, with standardized interventions, in specific clinical settings and utilizing outcome measures able to capture clinically meaningful changes, are still needed to substantiate existing effectiveness claims. The aim of the current trial was to pilot test and establish feasibility to determine the need for investing in a future randomised controlled trial (RCT) design. The objectives of this study were to establish: (1) the feasibility of recruitment procedures and establish the likely recruitment rate; (2) the feasibility of assessments and follow-up procedures; (3) the success of and fidelity adherence of interventions implemented by the therapist; (4) the interventions' acceptability; (5) the safety of the interventions; and (6) the sensitivity and suitability of the selected effect-outcomes to assess the efficacy of the music interventions. Clinical objectives were: (1) to estimate preliminary efficacy of live and recorded MIs on severity of delirium symptoms, and (2) to establish preliminary evidence of the specific delirium symptom domains most responsive to the MIs.

Methods

Trial design

We adopted a two-arm randomized repeated measures design to evaluate the feasibility and preliminary effectiveness of Preferred Recorded Music (PRM), and Preferred Live Music (PLM) interventions. Participants received the interventions once a day, for three consecutive days. The main clinical outcomes were assessed at baseline, one-hour pre-intervention, one-hour post intervention each day, and at discharge. Our study protocol detailing the intervention description, theoretical rationale, and statistical analysis plan, was published prior to the completion of data-collection (37). This trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement's extended checklist for pilot and feasibility trials (Additional file 8)(38). The trial was registered at Clinical Trials (NCT05398211) on May 31st 2022.

Participants

Participants were recruited from an acute geriatric ward within the Division of Geriatric Medicine at Oslo University Hospital (OUH), where the prevalence of dementia and delirium is high. The 20 bed ward admits 75-80 older patients per month (≥65 years) for acute medical care

(39). After delirium screening at admission, using 4AT(40) – a rapid validated tool for delirium detection – patients with the score ≥ 4 were assessed by geriatricians for eligibility. Delirium was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria (1) applying a recommended diagnostic test battery, previously described in our protocol (2, 37, 41-44) (Additional file 2). Subtypes were determined using the well validated Delirium Motor Subtyping Scale (DMSS-4)(45) .

Patients were eligible if:

(1) aged ≥ 65 years
(2) diagnosed with delirium or subsyndromal delirium within the last 72 hours and still present
(3) informed consent was obtained.

Patients with comorbidities such as dementia, mild cognitive impairment, or those under long-term care were also included, and we did not exclude patients with COVID-19. Patients were excluded if:

1. Previously enrolled in the study and were readmitted to the ward during the study period
2. Presenting with severe hearing impairments
3. Presenting with severe psychiatric conditions other than delirium
4. Admitted due to severe alcohol or substance addiction
5. Their assessed musical preferences included orchestral or other kinds of music impossible to perform live by voice and accompaniment

The 5th criteria was included after the trial commenced, registered at Clinical Trials on the 5th of December, 2022, and included in the published protocol (37).

Randomization and Masking

Eligible, consenting patients were randomized to study arms using permuted block randomization 1:1, and the online randomization software, True Random Numbers (https://www.random.org/). An independent researcher generated randomization blocks of 10 participants, to maintain even number in the two study-arms. The participants were assigned to their respective interventions by the music therapist, after baseline delirium assessments and before assessments of music preferences.

The therapist and the participants could not be masked to group allocation due to the nature of the interventions; assessors were masked. To increase the success of masking of assessors, staff at the ward were instructed not to reveal what treatment arm participants were assigned to, and the music therapist walked into the participants' rooms with her guitar and the loudspeaker, regardless of assigned intervention.

Interventions and comparators

Two interventions tested in this study, 1) Preferred Recorded Music (PRM) and 2) Preferred Live Music (PLM), were delivered by a certified music therapist (MT). PLM was delivered by voice and a guitar and included improvisation elements and active engagement of the MT. The PRM was delivered via a loudspeaker; the MT was instructed to refrain from engaging therapeutically with the patient. The potential therapeutic efficacy of preferred music, underlying both interventions, stems from its personal, social and cultural attributes, allowing it to alter emotional responses (46), boost self-awareness (47), and transiently enhance certain cognitive functions like autobiographical memory (48). The live music component and responsive musical and non-musical interactions with the MT in the PLM intervention were expected to regulate arousal levels and attention. Synthetic, loudspeaker sound and original versions of the preferred music in PRM intervention were expected to stimulate autobiographic memory and moderate attention and arousal. A more detailed description of the interventions and the theoretical rationale is provided in our published protocol (37).

After the baseline assessments, the MT assessed participants' music preferences from legal guardians, using an adapted Norwegian version of the Assessment of Personal Music Preference tool (APMP) (48), and after that, directly from the participants in an interactive, 30 minutes' session, using a Music Assessment Tool (MAT) (49). Music for the interventions was selected by the MT using the acquired information. The participants received their allocated interventions for 30 minutes (between 8 AM and 5 PM) over three consecutive days, in addition to usual care. Participants were considered to have adhered to the intervention protocol if they completed at least 10 minutes of the sessions. MIs were primarily delivered in the participants' private rooms, except when they shared a room with another patient.

Outcomes

Our published protocol previously described outcomes relevant to our feasibility and clinical objectives and the detailed assessment schedule (37). The main properties of the assessment tools are provided in Additional files 1-3.

Feasibility outcomes were assessed during and upon the completion of the intervention period and comprised:

(1) Recruitment rate: an average number of patients recruited per month.

(2) Retention rate: the proportion of participants completing the study as described in the protocol. Withdrawals were defined as withdrawing consent to participate in the study. Dropouts were defined as any discontinuations of the interventions and assessments due to the participants' health condition, discharge, or an unavailable assessor. Refusals were defined as the patient declining invitations to be involved in assessment or treatment.

(3) The proportion of sessions where the MIs and pre-post assessments were completed as planned (adherence to study protocol) and the proportion of sessions with protocol deviations. Deviations were categorized as patient or interventionist-related and further classified as minor, major, or fatal based on their impact on data quality and patient safety, with the fatal category indicating patients' death (49).

(4) The success of treatment fidelity (TF) was determined by observing the video recordings of 20% of randomly selected participants from both intervention groups who had completed the interventions as per protocol. Video recordings were evaluated by an independent rater using a bespoke checklist for each intervention. The six checklist items were scored and calculated (no = 0, yes = 1 point), and the threshold for satisfied treatment fidelity for each participant was ≥80 % averaged across the three intervention days, including satisfied compulsory items 4-6 for each session. The intervention was considered not to have met fidelity if the compulsory items were not satisfied even if the total score was ≥80 %.

Secondary clinical outcomes were assessed at baseline, pre- and post-session, and at discharge by the specially trained geriatricians at the ward and included:

(1) Trajectories of delirium symptoms, assessed using DSM-5 diagnostic test-battery (37) comprising: Observational Scale of Level of Arousal (OSLA)(42) and modified Richmond Agitation Sedation Scale (mRASS)(50-52) for level of arousal; backwards tests and digit span tests for attention (41, 44).; orientation and short-term memory, using delayed recall tasks and orientation questions from Memorial Delirium Assessment Scale (MDAS) (53) for orientation and short term memory.

(2) Duration of delirium: determined by an experienced delirium researcher (BEN) after the discharge from the ward, based on all the previously assessed data.

(3) Length of hospital stay (LOS)

(4) Use of Pro Re Nata (PRN), non-prescribed psychopharmacological medication (benzodiazepines and antipsychotics).

LOS and use of psychopharmacological medications during the hospitalization were retrieved from the electronic medical journals at discharge (Additional file 1).

Adverse events were recorded after music and assessment sessions and from daily reports by the medical staff at the ward. The events were categorized as critical and non-critical for the patients' health and well-being and related or unrelated to the interventions.

Statistical methods

The statistical analysis plan is described in our previously published protocol (37).

Linear mixed models were used to estimate the change in OSLA, mRASS, attention and cognitive status from pre- to post-intervention and from baseline for each assessment day, and for the comparison between the intervention groups. The marginal effects were calculated for each of these comparisons, with adjustments for the participants' baseline scores, and using participants' ID as a random effect, to incorporate the individual differences into the analysis. The Mann-Whitney test for skewed data was used to calculate the difference between the groups in length of hospital stay. We applied Fisher's Exact test for small samples to determine group differences in received PRN medication.

Results

Participants flow and recruitment

Potential participants were screened for eligibility between 15th June 2022 and 21st April 2023 (approximately 39 weeks). Of the 809 patients admitted to the acute geriatric ward during the recruitment period, 66 patients were assessed for eligibility (Figure 1). Of these, 40 were excluded due to uncertain delirium diagnosis, patient receiving end of life care, or being discharged before the sessions could begin, contagion (other than COVID-19), aphasia preventing completion of assessments of delirium, unavailable assessor for the rest of the

evaluations, or music therapist unavailability. In total n=26 patients met all the inclusion criteria and were randomized (PLM, n=14; PRM, n=12) (Figure1).

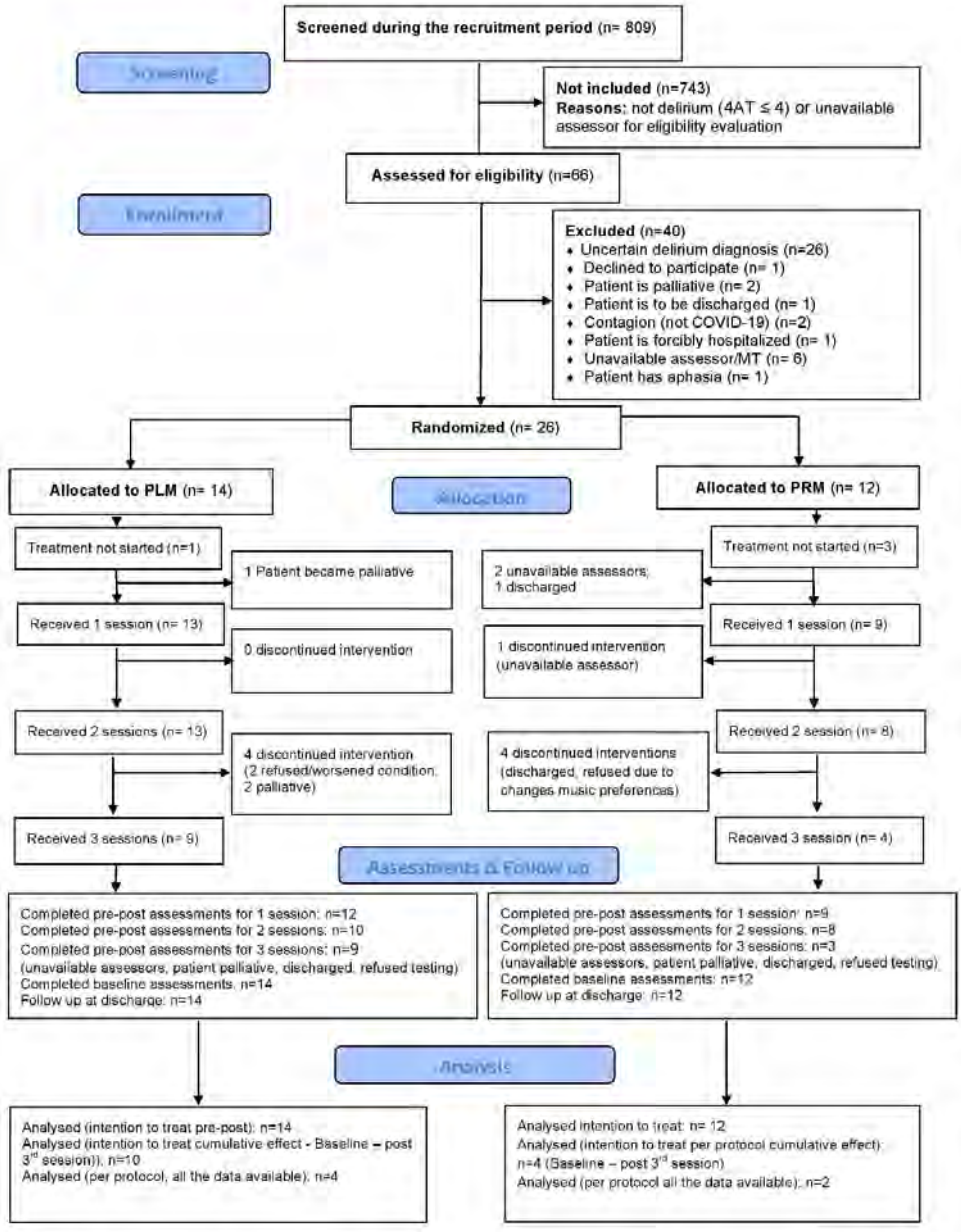

Figure 1: CONSORT Flow Chart

Baseline demographic and clinical characteristic were similar across the intervention groups (Table 1). Participants' median age was 87, half were female (n=13), and the majority lived alone (n=19, 73%,), or with others (n=4, 15%,) in the community. All had DSM-5 delirium at baseline, 68% hypoactive and 20% had no recognizable subtype. In 73% of cases (n=19), infection, fracture or a cardiovascular event precipitated delirium. For some participants the trigger was unknown, or hard to ascertain due to underlying dementia or depression. Clinical frailty scale scores were obtained for n=15 participants (58%), showing scores of ≥5 in 14 out of 15 tested patients, and a median score of 7. Along with the median frailty index of 0.40 in these participants, this score indicated severe frailty. The median NEWS2 score of 3 at admission to the AG ward indicated low to moderate acute illness severity (Table 1).

Characteristics	All participants n=26	PLM n=14	PRM n=12
Demographics			
Age, median (IQR)	87.0 (80.8 – 92.3)	87.0 (79.3-92.3)	89.5 (83.3-92.8)
Women, n (%)	13 (50)	7 (50)	6 (50)
Men, n (%)	13 (50)	7 (50)	6 (50)
Place of residence before hospitalization			
Private home, with others, n (%)	4 (15.4)	4 (28.6)	0
Private home, alone n (%)	19 (73.1)	10 (71.4)	9 (75.0)
Assisted Living facility, n (%)	2 (7.7)	0	2 (16.7)
Residential care home, n (%)	1 (3.8)	0	1 (8.3)
Level of care			
No public services, n (%)	5 (19.2)	2 (14.3)	3 (25.0)
House help/practical assistance, n (%)	1 (3.8)	1 (7.1)	0
Home nursing care, n (%)	16 (61.5)	8 (57.1)	8 (66.7)
Long term residential care, n (%)	2 (7.7)	1 (7.1)	1 (8.3)
Other, n (%)	2 (7.7)	2 (14.3)	0
Medical, at admission			
Reasons for hospitalization, n (%)			
Fall, fracture, injury, n (%)	12 (46)	3 (21)	9 (75)
Chest pain, shortness of breath, n (%)	4 (15)	1 (7)	3 (25)
Delirium, confusion, somnolence, n (%)	8 (30)	3 (25)	5 (42)
Other, n (%)	9 (35)	9 (64)	0
Clinical Frailty Scale, median (IQR)[a]	7.0 (6.0 - 7.0)	7.0 (5.0 - 7.0)	6.0 (6.0 - 7.0)
Frailty index (FI), median (IQR)[e]	0.4 (0.4 - 0.5)	0.4 (0.3 - 0.4)	0.4 (0.4 - 0.5)
Number of prescribed medications, median (IQR)	5.5 (3.0 - 7.0)	6.0 (3.5 - 8.3)	5.0 (3.0 - 6.0)
IQCODE[b]	3.6 (3.3 - 4.5)	3.4 (3.0 - 3.4)	3.7 (3.5 - 3.7)
NEWS II at admission to hospital, median (IQR)[c]	3.0 (1.0 - 6.0)	3.0 (1.0 - 5.8)	3.5 (0.3 - 6.8)
NEWS II at admission to the acute geriatric ward	3.0 (1.0 - 5.0)	2.0 (0.8 - 5.3)	3.0 (2.3 - 5.0)

Characteristics	All participants n=26	PLM n=14	PRM n=12
Delirium status at baseline			
DSM-5 delirium, n (%)	26 (100)	12 (100)	14 (100)
Digit Span forward, digits correct, median (IQR)	3.0 (0.0 - 4.3)	3.00 (0.8 - 4.3)	3.5 (0.0 - 4.8)
SAVEAHAART/KATAMARAAN, number of mistakes, median (IQR)	2.0 (0.0 - 10.0)	3.5 (0.8 - 10.0)	1.0 (0.0 - 8.0)
Days of the week backwards, numbers correct, median (IQR)	3.0 (0.0 - 7.0)	1.0 (0.0 - 6.3)	5.5 (0.0 - 7.0)
Months of the year backwards, numbers correct, median (IQR)	3.0 (0.0 - 5.5)	1.5 (0.0 - 4.3)	4.5 (0.0 - 7.0)
Count backwards from 20 to 1, numbers correct, median (IQR)	7.0 (0.0 - 20.0)	2.5 (0.0 - 15.5)	14.5 (3.5 - 20.0)
Orientation, number of correct items, median (IQR)	3.0 (0.8 - 7.0)	2.5 (0.0 - 4.8)	5.5 (2.3 - 7.0)
Delayed recall, numbers correct, median (IQR)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.8)
OSLA score, median (IQR)	2.5 (1.3 - 6.8)	2.0 (1.5 - 8.0)	3.0 (1.0 - 6.0)
mRASS score, median (IQR)	0.0 (-1.0 - 0.0)	0.0 (-1.0 - 0.5)	-0.5 (-1.7 - 0.0)
Delirium motor subtype, n (%) according to DMSS4[d]			
Hyperactive, n (%)	2 (8)	1 (8)	1 (8)
Hypoactive, n (%)	17 (68)	10 (77)	7 (58)
Mixed, n (%)	1 (4)	1 (8)	0
No subtype, n (%)	5 (20)	1 (8)	4 (33)

Table 1 Demographic and clinical characteristics at baseline

PLM Preferred Live Music, PRM Preferred Recorded Music, IQR Inter quartile range, IQCODE Informant Questionnaire on Cognitive Decline in the Elderly, CFS Clinical Frailty Scale, NEWS2 National Early Warning Score II, DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, SAVEAHAART/KATAMARAN Vigilance test, OSLA Observational Scale of Level of Arousal, mRASS Modified Richmond Agitation Sedation Scale, DMSS4 Delirium Motor Subtype Scale 4.

a Clinical frailty scale missing in 11 patients; 4 in PLM group and 7 in PRM group.

b IQCODE missing in 20 patients; 11 in PLM group and 9 in PRM group

c NEWS2 missing in 2 patients in PLM group

d DMSS4 missing in 1 patient in PLM group

e Frailty Index missing in 3 patients

Feasibility Outcomes

The average recruitment rate was 3 participants per month (Table 2). The retention rates for the participants in PLM and PRM groups were 64% and 33% respectively. Most withdrawals were due to worsening of the participants' health condition, but none withdrew their consent to use the data collected prior to withdrawal.

The total adherence to the study protocol (both interventions and assessments) was 29% in the PLM (n=4 patients), and 17% in the PRM group (n=2 patients). Five additional participants in the PLM group met the per-protocol criteria but were excluded because their assessments occurred outside of the assessment window.

The total number of conducted music sessions, including those with deviations, was 55 out of the planned 78 (PLM=42; PRM=36). Common reasons for missing sessions were: 1) minimum dosage of 10 minutes was not met, 2) unavailability of assessor/music therapist to assess/treat, 3) patient became palliative, or 4) patient was discharged. The percentage of adherence to the PLM and PRM protocols were 83% and 58% respectively. Of the 21 completed PRM sessions, 17 were delivered with some deviations (81%), of which the most common were the unwanted interaction between the patient and the therapist, and in some cases changing the order of songs from one intervention day to another. No significant protocol deviations were registered during the PLM, and most sessions were delivered as intended.

The success of TF was 93% for the PLM, including satisfied complementary items 4-6 in the checklists, and 83% for the PRM, with one of the complementary items not satisfied. As planned, music preferences were assessed with input from the legal guardians and participants. Only two participants were not able to contribute to music preference assessments due to their worsened health condition at the time of assessment (Table 2).

Of the planned 78 pre-post delirium assessments in both groups, 34 were successfully completed (44%). Adherence to the assessment procedures in PLM was 62%. Ten pre-post assessment were not completed due to unavailable assessor, patient discharged or becoming palliative: six of the pre-post assessments were out of the assessment window. Adherence to the assessment procedures in PRM was 50%, with 15 pre-post assessments missing due to the unavailable assessor, patient discharged or becoming palliative, and three pre-post assessments were conducted outside of the assessment window.

One serious adverse event (death) occurred during the intervention period but was unrelated to the interventions. Minor, potentially intervention-related events such as patients falling asleep while listening to music, as well as showing signs of boredom and restlessness or wanting to switch faster to the next song, were recorded during the PRM sessions.

Measure	Total (n=26)	PLM group (n=14)	PRM group (n=12)
Recruitment rate	3/month		
Participants who completed the study (Retention), n (%)	13 (50)	9 (64)	4 (33)
Participants who discontinued the study (Attrition), n (%)	11 (42)	3 (21)	8 (67)
Intervention sessions completed (Adherence to interventions) n (%)	56 (72)	35 (83)	21 (58)
Pre-post assessments completed (Adherence to assessments), n (%)	34 (45)	26 (62)	18 (50)
Participants who completed the study procedures as per protocol [a] (Adherence to study protocol), n (%)	6 (23)	4 (29)	2 (17)
TF (%)[b]	NR	93%[c]	83%[d]

Table 2. Feasibility outcomes

PLM Preferred Live Music group; *PRM* Preferred Recorded Music group; *TF* Treatment Fidelity

[a] Patients who completed interventions and assessments as per protocol

[b] Treatment Fidelity average success rate per condition

[c] Compulsory items 4-6 in checklists are satisfied.

[d] Compulsory item 6 in checklists was not satisfied

Secondary clinical outcomes

This feasibility trial did not intend to draw conclusive findings on the effects of MIs on delirium symptoms, and did not need to be adequately powered. Initially aimed to recruit 60 participants, 30 in each arm, to obtain sufficient data to examine the main objectives of the study, while allowing for potential dropouts. An intention-to-treat principle was used to analyse efficacy outcomes, such that the analysis included also those participants who were discharged prior to completion of the three music sessions, or were not able to receive the interventions as per protocol for other reasons. We also intended to complete a per-protocol analysis, but with few participants completing the interventions as described we ultimately opted not to undertake this analysis.

Comparing baseline, and pre-intervention scores showed that delirium symptoms varied during the first three days of the intervention, with measures of level of arousal, attention, orientation and short-term memory fluctuating for most individuals. On average, the participants' level of arousal was similar across the three assessment days. However, their performance on attention tests improved on day 3 comparing baseline and pre-intervention scores, and was statistically significant for counting from 20 to 1, weekdays backwards, digit span memory test and SAVEAHAART vigilance tests (Table 3).

Measure[b]	Day	Mean (95 % CI)[a]	Mean difference (95 % CI)[a]	p-value
OSLA	Baseline	4.2 (3.1 to 5.3)	Ref.	
	Day 1	4.4 (3.3 to 5.5)	0.1 (-1.3 to 1.4)	0.930
	Day 2	4.9 (3.7 to 6.1)	0.3 (-1.1 to 1.7)	0.659
	Day 3	3.4 (2.0 to 4.8)	-0.6 (-2.3 to 1.1)	0.502
mRASS	Baseline	-0.6 (-0.9 to -0.3)	Ref.	0
	Day 1	-0.8 (-1.2 to -0.5)	-0.2 (-0.7 to 0.3)	0.379
	Day 2	-1.0 (-1.4 to -0.6)	-0.3 (-0.8 to 0.2)	0.189
	Day 3	-0.4 (-0.9 to 0.0)	0.2 (-0.4 to 0.7)	0.546
Count 20 to 1	Baseline	8.7 (5.8 to 11.6)	Ref.	0
	Day 1	9.5 (6.4 to 12.6)	0.7 (-2.7 to 4.2)	0.687
	Day 2	9.3 (6.1 to 12.6)	0.5 (-3.1 to 4.1)	0.776
	Day 3	13.9 (10.2 to 17.6)	4.8 (0.5 to 9.0)	0.027
Days of the week	Baseline	3.2 (2.2 to 4.3)	Ref.	
	Day 1	4.0 (2.9 to 5.1)	0.7 (-0.6 to 1.9)	0.287
	Day 2	3.5 (2.3 to 4.6)	0.2 (-1.1 to 1.5)	0.779
	Day 3	5.4 (4.1 to 6.8)	2.1 (0.6 to 3.6)	0.006
Months of the year	Baseline	3.1 (1.8 to 4.5)	Ref.	
	Day 1	2.7 (1.2 to 4.1)	-0.6 (-2.1 to 1.0)	0.493
	Day 2	3.3 (1.8 to 4.9)	0.2 (-1.5 to 1.8)	0.825
	Day 3	3.3 (1.6 to 5.1)	-0.1 (-2.1 to 1.8)	0.882
Digit span	Baseline	2.8 (2.1 to 3.5)	Ref.	
	Day 1	4.0 (3.3 to 4.7)	1.2 (0.4 to 2.0)	0.003
	Day 2	3.2 (2.5 to 4.0)	0.5 (-0.3 to 1.4)	0.205
	Day 3	4.4 (3.6 to 5.3)	1.7 (0.8 to 2.7)	0.001
SAVEAHAART	Baseline	4.1 (2.9 to 5.4)	Ref.	
	Day 1	3.6 (2.3 to 5.0)	-0.5 (-1.9 to 1.0)	0.523
	Day 2	3.6 (2.2 to 5.0)	-0.7 (-2.2 to 0.9)	0.398
	Day 3	1.8 (0.2 to 3.3)	-2.3 (-4.1 to -0.6)	0.010
Orientation	Baseline	3.4 (2.5 to 4.3)	Ref.	
	Day 1	3.8 (2.9 to 4.7)	0.5 (-0.6 to 1.6)	0.355
	Day 2	3.6 (2.6 to 4.6)	0.2 (-0.9 to 1.3)	0.699
	Day 3	4.8 (3.6 to 5.9)	1.2 (-0.1 to 2.5)	0.073

Table 3. Daily mean score for clinical delirium outcomes and change from baseline

OSLA Observational Scale of Level of Arousal, m*RASS* Modified Richmond Agitation Sedation Scale *SAVEAHAART/KATAMARAN* Vigilance test.

[a] Marginal means and mean differences estimated using mixed linear model.

[b] Recall is not presented in this table because linear regression was not suitable (see Additional file 5).

There was no significant change in delirium symptoms pre to post MIs on each day. Analysing the data without considering the specific intervention day or group but still considering that each person had up to 7 measures did not show significant change either (Table 4). The individual trajectories showed that some symptoms for given participants did change from pre to post MIs, but these changes were in the negative direction. The residuals for delayed recall score were so skewed that linear modelling of this outcome was not appropriate, and we instead calculated the proportion of the participants who could successfully recall at least one word. The total percentage of the participants who could recall at least one word on the delayed recall test was only 19% (95% CI: 8.2 – 38.9) (Additional file 5).

Measure	Day	Before	After	Mean difference (95 % CI)	p-value
OSLA	1	4.4 (3.3 to 5.5)	3.7 (2.6 to 4.9)	-0.6 (-2 to 0.8)	0.414
	2	4.9 (3.7 to 6.1)	3.1 (1.9 to 4.4)	-1.4 (-2.9 to 0.2)	0.077
	3	3.4 (2 to 4.8)	3.5 (2.0 to 4.9)	-0.2 (-2.2 to 1.8)	0.837
	Any[c]	4.2 (3.3 to 5.0)	3.5 (2.6 to 4.4)	-0.6 (-1.6 to 0.3)	0.206
mRASS	1	-0.8 (-1.2 to -0.5)	-0.7 (-1 to -0.3)	0.2 (-0.3 to 0.7)	0.401
	2	-1 (-1.4 to -0.6)	-0.6 (-1 to -0.2)	0.3 (-0.2 to 0.8)	0.238
	3	-0.4 (-0.9 to 0)	-0.6 (-1 to -0.1)	-0.1 (-0.7 to 0.6)	0.805
	Any	-0.8 (-1 to -0.5)	-0.6 (-0.9 to -0.4)	0.1 (-0.2 to 0.5)	0.378
Count 20 to 1	1	9.5 (6.4 to 12.6)	8.7 (5.5 to 11.9)	-0.3 (-3.9 to 3.4)	0.889
	2	9.3 (6.1 to 12.6)	11.7 (8.3 to 15.2)	2 (-2 to 5.9)	0.332
	3	13.9 (10.2 to 17.6)	10.9 (6.9 to 14.9)	-3.2 (-8.3 to 2)	0.228
	Any	10.6 (8.2 to 13.1)	10.4 (7.9 to 12.9)	-0.2 (-2.7 to 2.4)	0.904
Days of the week	1	4 (2.9 to 5.1)	4.1 (2.9 to 5.3)	0.2 (-1.1 to 1.5)	0.744
	2	3.5 (2.3 to 4.6)	4.6 (3.4 to 5.8)	1.1 (-0.4 to 2.5)	0.142
	3	5.4 (4.1 to 6.8)	4.7 (3.4 to 6.1)	-0.8 (-2.6 to 0.9)	0.339
	Any	4.2 (3.3 to 5.1)	4.5 (3.5 to 5.4)	0.3 (-0.6 to 1.1)	0.538
Months of the year	1	2.7 (1.2 to 4.1)	3.0 (1.5 to 4.5)	0.5 (-1.1 to 2.2)	0.526
	2	3.3 (1.8 to 4.9)	4.7 (3.1 to 6.3)	1.5 (-0.3 to 3.3)	0.104
	3	3.3 (1.6 to 5.1)	4.2 (2.3 to 6.0)	0.9 (-1.4 to 3.3)	0.435
	Any	3.1 (2 to 4.3)	4.0 (2.8 to 5.2)	1.0 (-0.1 to 2.1)	0.080
Digit span	1	4.0 (3.3 to 4.7)	3.3 (2.6 to 4.1)	-0.6 (-1.5 to 0.3)	0.171
	2	3.2 (2.5 to 4.0)	3.8 (3.0 to 4.6)	0.5 (-0.4 to 1.4)	0.294
	3	4.4 (3.6 to 5.3)	3.7 (2.8 to 4.5)	-0.9 (-2.0 to 0.3)	0.139
	Any	3.8 (3.3 to 4.4)	3.6 (3.0 to 4.2)	-0.3 (-0.8 to 0.3)	0.357
SAVEAHEART	1	3.6 (2.3 to 5.0)	4.0 (2.6 to 5.4)	0.1 (-1.4 to 1.7)	0.869
	2	3.6 (2.2 to 5.0)	3.5 (2.1 to 5.0)	-0.1 (-1.7 to 1.6)	0.915
	3	1.8 (0.2 to 3.3)	2.1 (0.5 to 3.7)	0.3 (-1.7 to 2.3)	0.797
	Any	3.1 (2.1 to 4.2)	3.3 (2.2 to 4.4)	0.1 (-0.9 to 1.1)	0.874

Measure	Day	Before	After	Mean difference (95 % CI)	p-value
Orientation	1	3.8 (2.9 to 4.7)	3.5 (2.5 to 4.5)	-0.4 (-1.6 to 0.7)	0.476
	2	3.6 (2.6 to 4.6)	4.5 (3.4 to 5.5)	0.8 (-0.4 to 2.1)	0.190
	3	4.8 (3.6 to 5.9)	4.2 (2.9 to 5.4)	-0.5 (-2.1 to 1.1)	0.559
	Any	4.0 (3.3 to 4.8)	4 (3.2 to 4.8)	-0.1 (-0.8 to 0.7)	0.894

Table 4. Before and after music intervention each day

OSLA Observational Scale of Level of Arousal, *mRASS* Modified Richmond Agitation Sedation Scale *SAVEAHAART/KATAMARAN* Vigilance test.

[a] Marginal means and mean differences estimated using mixed linear model.

[b] Recall is not presented in this table because linear regression was not suitable.

[c] "Any" lines combine information from all days, across the intervention groups, taking into account that each person has up to 7 measures.

There was no evidence of a difference between the participants' delirium symptoms in PLM or PRM groups on day 3 of the intervention (Additional file 4). Group differences on days 1 and 2 were not examined on the assumption that the potential difference in the effect of the interventions would be most relevant on day 3. The participants' average length of hospital stays in PLM was 11 days (SD=8.95) and in PRM 13 days (SD=8.94); there was no statistically significant group difference between the PLM and PRM (U=82.500, p=0.94). The results of Fisher's exact test did not indicate statistically significant difference between the number of patients receiving PRM medication in the two intervention groups (Additional file 6). There was no sufficient data in the medical journals to estimate changes in delirium duration.

Discussion

Feasibility outcomes

This feasibility study demonstrated that implementing PLM and PRM with vulnerable delirium patients at the AG ward was feasible and that the MT could successfully conduct music preference assessments. Obtaining music preferences from the legal representatives before engaging in direct, interactive assessments with the patients helped the MT establish a potentially familiar starting point for further assessment based on the dialogic approach and recognition of music examples. Such an approach helped create a personalized environment in which recognition memory could be activated and musical memories retrieved (54). The interactive assessments might also have impacted delirium outcomes prior to the commencement

of the MIs and created a confounding variable. They could also have generated expectations regarding upcoming interventions and impacted the participants' test performance.

Additionally, our study reaffirms prior research indicating hypoactive delirium as the predominant subtype (55, 56), with 68% of our participants exhibiting hypoactive symptoms. Since distinct delirium subtypes present varying symptoms and necessitate different care approaches, it was previously recommended to explore treatment options separately for each subtype (57). This recommendation aligns with our suggestions for further investigation into MIs.

Robust adherence, high TF, relatively high retention rate, consistent dosage delivery, and minimal protocol deviations that PLM demonstrated indicate this intervention is feasible and well accepted. No intervention-related adverse events or unusual treatment effects were recorded, and no refusals further suggest that the PLM is likely safe. Additionally, descriptive data from the MT's session notes and checklists indicate that PLM might also be engaging, with patients singing, moving to music or reminiscing with the therapist in nearly all the sessions. As 77% of the participants in the PLM had hypoactive delirium, the last finding might be particularly relevant for further exploration of PLM in the treatment of the hypoactive delirium subtype.

PRM exhibited lower adherence, retention, and inconsistent delivery and duration (from 10 to 33 minutes). As discontinuations were mainly associated with patients' health decline, palliative status and discharge rather than refusals, low adherence and retention might not indicate the PRM's low acceptability. However, the data from the MTs notes showed that the patients were actively engaged in only about 50% of the sessions and that they more often expressed signs of restlessness, lack of interest in music, desire to fast-forward or switch to the next song, and requested to end the sessions earlier. Such responses suggest that PRM may be experienced as less engaging and monotonous for the patients due to either the non-interactive MT or the delivery format. This finding aligns with our previous assumption that prolonged exposure to complex musical stimuli delivered from a loudspeaker could lead to habituation and boredom in delirium patients (37, 58).

Despite the 83% success rate, PRM did not satisfy TF due to a persistent breach of one of the protocol's compulsory items regarding prohibited patient-therapist interaction. The interaction was always patient-initiated and related to their confusion, pain, distress, or the need to converse about their experience of music. Although ethically justifiable for addressing patients' safety and needs, interactions lowered the overall consistency of treatment delivery. Excluding the MT from the room could mitigate this issue in further research. However, it would raise concerns regarding patients' safety, as unsupervised music exposure may lead to

increased confusion and adverse events. Replacing the MT with another health practitioner could be another alternative, in which case any interaction would represent what could be expected in any other setting.

The trial demonstrated that recruitment and assessment procedures were feasible and accurately identified patients with delirium for inclusion. While ensuring a high level of expertise on the patients and the ward, the involvement of the internal assessors, with their high workload and other commitments, resulted in the participants being recruited only when an assessor was available – two workdays during day shifts, to ensure the completion of the assessments/interventions before the weekend. Coupled with strict inclusion criteria, the internal assessors' limited availability resulted in a low recruitment rate. The engagement of external assessors available in most shifts seven days a week is advised for future research.

The recommended test battery for the pre-post assessments was efficient, accurate in assessing delirium and its features, and suitable for application at the AG ward. However, the completion time varied among the assessors. There is currently no definitive diagnostic test for delirium, so its detection depends on assessing key features, combining observation, cognitive testing, patients' medical history and clinical interviews (59). Aside from giving a more specific insight into the trajectory of delirium severity by combining continuous (symptom-related) and dichotomous (delirium yes-no) variables, using harmonized test batteries such as ours contributes to developing more robust, reliable and standardized assessments for delirium and its severity in the future (59). The test battery was also well-accepted by delirium patients, with very few refusals, usually related to the severe worsening of their condition. Deviations from the assessment manuals were few and related to either the assessors missing a one-hour time window for assessments or unintentionally omitting some of the tests. However, the lack of post-intervention effects could indicate that time-window for assessments might have been too long and that potential post-intervention effects could have been better captured closer to the end of the interventions. Engaging more flexible external assessors could help address this issue in the future.

Despite the test battery's high accuracy, efficiency and suitability, the total adherence to the three-day, multiple measures, follow-up protocol was low. However, the assessments were mostly missing due to the unavailable assessors and patients becoming palliative or discharged from the ward. Thus, low adherence might not be the right indicator of the feasibility of the follow-up protocol. Individual trajectories of delirium symptoms showed that some participants had a substantially worse post-intervention performance on some of the cognitive/attention tasks. While the MIs might have caused this worsening, it may also be correlated with the multiple measurements; while providing a large amount of data, the comprehensive

three-day, follow-up protocol might have presented a burden for this vulnerable patient group, causing exhaustion, tiredness or boredom, thus negatively impacting their test performance. Therefore, the suitability of the repeated measures design and the length of the follow-up period should be carefully considered in future research.

Clinical outcomes

Our results showed that the participants' performance on the attention tests improved significantly on day three, when comparing baseline and pre-interventions scores, while most of their other symptoms were similar to baseline. However, without a control group, the observed changes are difficult to attribute to the MIs delivered the previous day, as delirium usually is usually reversed by treatment of underlying causes (7, 60). Nevertheless, the summary evaluation of individual DSM-5 criteria showed that most participants still had delirium at the end of the intervention period.

No statistically significant pre-post intervention changes or inter-group changes in delirium symptoms were observed for any of the measures. However, the trial was underpowered to detect preliminary effectiveness properly. Accordingly, the CIs for mean differences were wide for most measures, and we cannot exclude the possibility of changes in delirium symptoms associated with the interventions. The percentage of participants who could recall at least one word on the delayed recall tests was very low. With small samples in addition, testing pre-post intervention and between the groups change in proportion would have provided no conclusive findings and was omitted. No significant differences in LOS and intake of PRN medication between the groups were expected, as the study was underpowered to provide conclusive findings in this regard, and changes in these measures could be correlated with many other factors. The follow-up of delirium duration after the intervention period was unsuccessful due to the transient and fluctuating delirium nature, making it difficult to ascertain whether it had been recovered.

Despite not showing sensitivity to the MIs, clinical outcomes tested in this trial are still highly relevant for detecting changes in delirium progression and severity and should be included in the future. However, to capture the potential effects of the MIs, other complementing outcomes, such as biomarkers, patient-centred outcomes (emotional responses and engagement), or environmental outcomes related to the medical ward and staff, should be considered and explored. Data from the MT's session notes and checklists indicated that relevant intervention-related changes might also have occurred during the MI sessions, and it is, therefore, recommended that future trials consider assessing these changes more systematically.

Testing clinical outcomes did not provide sufficient information to discern which of the two MIs could more effectively impact delirium symptoms. The wide CIs are mainly associated with small samples but indicate that the potential effect of PLM and PRM interventions cannot be ruled out.

Strengths and limitations

This trial was sufficiently powered to evaluate feasibility outcomes. However, it was underpowered to investigate the preliminary efficacy and between the groups differences, for which a sample of a minimum of 30 patients per group is recommended (61). The control group was omitted, and comparing two active arms was prioritized due to our primary aim of evaluating the feasibility and uncertainties regarding delirium diagnosis and recruitment. As the design of the previous music and delirium trials has shown to be of low to moderate methodological quality (62), with feasibility appraisals mostly missing, the main strength of our trial is its focus on feasibility and providing valuable insights improving future trials' design.

Other strengths of this study are: 1) the use of previously validated and recommended delirium assessment procedures (2, 41, 43, 44, 59), 2) training assessors, and 3) involving an experienced delirium researcher to interpret the assessed features. Subtyping delirium is also a strength, and it has been previously recommended for its clinical and prognostic significance in treatment studies (63-65). However, due to small samples, we were not able to conduct separate subgroup analyses with hypoactive and hyperactive delirium patients. We recommend that future studies address delirium subtypes separately, as they may need to be managed differently. Using the staff employed at the site during their usual working hours was a limitation; it resulted in slow recruitment and missed assessments as they were dealing with competing priorities.

Using detailed, standardized intervention protocols with theoretical rationale for comparison, and evaluating TF is also a strength, as it increases the generalizability of effect findings (33). Other strengths are engaging a trained MT and conducting music preference assessments to personalize the interventions and increase relevance and safety, which aligns with previous recommendations (33).

In conclusion, the feasibility of recruitment procedures, music preference assessments, MIs and assessment protocols were indicated, and the results showed that PLM intervention is more engaging, better accepted, and potentially more suitable for further testing with acutely ill older patients with delirium. Recommended next steps are to undertake a pilot study with a comparative group, assess preliminary efficacy, estimate the size of the treatment effects, and to further explore different intervention dosages and frequency of delivery.

List of abbreviations

AG – Acute Geriatrics
APMP – Assessment of Personal Music Preference tool
CAM-ICU – Confusion Assessment Method for the Intensive Care Unit scale.
CI – Confidence Interval
CONSORT – Consolidated Standards of Reporting Trials.
CSF – Clinical Frailty Scale.
DMSS-4 – Delirium Motor Subtyping Scale.
DOWB – Days of the Week Backwards.
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.
FI – Frailty Index.
ICU – Intensive Care Unit.
IQCODE – Informant Questionnaire on Cognitive Decline in the Elderly.
LOS – Length of stay.
MAT – Music Assessment Tool.
MDAS – Memorial Delirium Assessment Scale.
MI – Music Interventions.
MOYB – Months of the Year Backwards.
mRASS – Modified Richmond Agitation Sedation Scale.
MT – Music Therapist
NEWS2 – National Early Warning Score 2.
OSLA – Observational Scale of Level of Arousal.
OUH – Oslo University Hospital.
PLM – Preferred Live Music.
PRM – Preferred Recorded Music.
PRN – Pro Re Nata, non-prescribed psychopharmacological medication.
SAVEHAART – ten-letter vigilance "A" test.
TF – Treatment Fidelity.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Regional Ethics Committee in Norway (REK 457017). The ability to give informed consent was individually evaluated for each participant, and the consents were obtained by the experienced physicians, either directly from the patient, or supplemented or replaced by the consents from the legally assigned representatives (LAR) if the patient's ability to consent was reduced. Three different consent forms informing of the study objectives personal data collection methods, benefits and potential risks, data management and the right to withdraw from the study were used. Consents in written format were prioritized, but verbal consents via phone-call were also approved by REK in cases where LAR were not physically present, and the written confirmation was acquired at the first possible occasion.

Consent for publication

All the authors have consented to the publication of this article.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors meet the criteria for authorship stated in the Uniform Requirements

for Manuscripts Submitted to Biomedical Journals, have read the last draft of the manuscript and agree with the findings presented. JG, BE, FAB, and MRS developed the protocol. FB generated random allocation sequences, and JG randomized the participants, performed the

music preference assessments and interventions, and recorded videos for treatment fidelity (TF) evaluation. JG monitored the data collection process. JG assessed and analysed all the feasibility outcomes. JG randomly selected 20% of the participants who completed three sessions and for whom videos were available for TF evaluation using a previously generated randomization sequence. KJ evaluated video recordings and scored treatment delivery checklists, and JG calculated percentages of TF success. JG plotted pre-post delirium data in SPSS, MRS converted some of the data to STATA files, and BEN collected and plotted the medical variables from the electronic journals. Based on the collected pre-post intervention data, BEN completed summary evaluations of delirium, and JG plotted the new variable into the SPSS files. MRS developed a statistical analysis plan and performed the analyses of the pre-post delirium data (mixed linear regression models); JG performed the analysis of all the baseline measures and some of the clinical outcomes (length of hospital stay, medication intake). JG wrote the manuscript with FAB, BEN, MRS, and KJ contributions. All the authors have read and agreed to the published version of the manuscript.

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Additional files

Additional file 1. Assessment tools and their properties

Additional file 2. Diagnostic algorithm for DSM-5 delirium evaluation

Additional file 3. Checklists for treatment fidelity evaluation (PLM, PRM)

Additional file 4. Group PLM versus Group PRM difference on Day 3

Additional file 5. Proportion of participant who could recall any words in delayed recall test

Additional file 6. Between the groups difference in Length of hospital stay and PRN medication

Additional file 1. Assessment tools and their properties

Type of data	Assessment Tools	Scale-Properties/Cut-off
Sociodemographic and clinical background data (assessed at baseline)		
Age Gender Place of residence Level of medical care before hospitalisation Past and current medical conditions Prescribed medication	Electronic medical journals	N.R.
Pre-admission cognitive status	IQCODE: Informant Questionnaire of Cognitive Decline	The short version of the validated Informant Questionnaire on Cognitive Decline in the Elderly. Consists of 16 questions scored from 1-5, with a score of ≥ 3.3 indicating worsening (49)
Frailty status	CFS: Clinical Frailty Scale	A nine-point scale, evaluations based on the descriptions of functional status and activity, and scores ranging from 1 (very fit) to 9 (terminally ill) (50).
	FI: Frailty index	Scores below 0.12 indicate the person is fit; higher scores indicate greater frailty (0.12-0.24, mildly frail, 0.24 to 0.36, moderately frail, 0.36 and above, severely frail) (51).
Severity of acute illness	NEWS2: National Early Warning Score 2	Routinely allocates recorded scores of physiological parameters (e.g. respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness/new confusion, and temperature), with a cut-off of ≥ 5 points for clinical deterioration in acutely ill patients (52, 53).
Clinical outcomes (assessed pre-post interventions and at discharge)		
1. Trajectory of delirium symptoms:	DSM-5 criteria	DSM-5 diagnostic algorithm and test battery, comprising validated scales and tests for evaluating each DSM-5 criteria (37).
AROUSAL	OSLA: Observational Scale of Level of Arousal	OSLA is a reliable and validated instrument for assessing arousal by observing eye opening, eye contact, posture and movement, and the scores range from 0 to 15 (42). The score ≥ 3 is the cut-off for abnormal arousal, for which OSLA scale has sensitivity of 0.85 (95% CI [72-93]), and specificity of 0.82 (95% CI [71-91] (42).
	mRASS: Modified Richmond Agitation Sedation Scale	mRASS measures changes in sedation and agitation by observing the duration of eye contact following verbal and physical stimulation (55, 56). mRASS has strong validity and reliability in geriatric and critically ill populations (57). The scores

	‘	range from −5 (comatose state) to +5 (combativeness), with negative scores indicating more hypo-aroused states, and positive scores indicating hyper-arousal (56). With a cut-off ≠ 0 for abnormal sedation/agitation, the sensitivity of the mRASS scale is 0.90 (95% CI [56-100]), and the specificity 0.85 (95% CI [62-97]).
ATTENTION	Digit span test	The digit span test has scores ranging between 0-7.
	Backwards tests: • Months of the year • Days of the week • Counting 20-1	• Months of the Year Backwards (MOYB) has scores ranging from 0-12. • Days of the Week Backwards (DOWB) has scores ranging between 0-7. • Backwards counting from 20-1 has scores ranging from 0-20 (41, 44).
	Vigilance test (SAVEHAART)	A ten-letter vigilance “A” task (SAVEHAAART) is taken from the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale and has scores ranging from 0-4 (41, 44).
ORIENTATION and SHORT TERM MEMORY	Recall tasks Orientation questions	• The orientation test consisted of 10 predefined questions for the patients (ranging from 0-10) • Short term memory and delayed recall test involved repeating 3 words after a series of other tasks and had scores ranging from of 0-3(58). Orientation, short-term memory, and recall tests originate from the validated MDAS scale assessing the severity of delirium (58). Cut-offs of the tests indicating inattention, disorientation, and impaired short-term memory may be found in Appendix 2 and in our published protocol (37)
2. Duration of delirium	DSM-5 assessments Medical journals	N.R.
3. Length of hospital stay	Electronic medical journals	N.R.
4. Use of PRN medication	Electronic medical journals	N.R.
Feasibility outcomes		
Treatment fidelity	Author-developed checklists for PLM and PRM.	The six checklist items (no = 0, yes = 1 point) were calculated, and the threshold for satisfied treatment fidelity for each participant was ≥80 % averaged across the three intervention days, including satisfied compulsory items 4-6 for each session. The intervention was considered not to have met fidelity if the compulsory items were not satisfied even if the total score was ≥80 %.

Additional file 2. Diagnostic algorithm for DSM-5 delirium evaluation

<table>
<tr><th>DSM-5 Criteria</th><th>Tests to be performed and information to be collected</th><th colspan="2">Is DSM-criteria fulfilled?</th></tr>
<tr><th></th><th></th><th>YES</th><th>NO</th></tr>
<tr><td>A. Disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment</td><td>
<table>
<tr><th>Evaluation</th><th>Attention-tests</th><th>Cut off (definition of inattention)</th></tr>
<tr><td rowspan="5">Daily</td><td>SAVEAHAART/ KATAMARAAN</td><td>2 or more errors</td></tr>
<tr><td>Days of the week in reversed order</td><td>Any error</td></tr>
<tr><td>Months of the year in reverse order</td><td>Unable to reach July</td></tr>
<tr><td>Count backwards from 20 to 1</td><td>Any error</td></tr>
<tr><td>Digit span forward</td><td>Less than 5 forward</td></tr>
</table>
<u>Observation:</u>
Easily distracted? Collaborative? Has a tendency to “loose thread” in the conversation?</td><td></td><td></td></tr>
<tr><td></td><td>Arousal: OSLA >3 and/or mRASS other than 0?</td><td></td><td></td></tr>
<tr><td>B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.</td><td>Informant history from patient’s carers and nursing staff. Questions to carer/nursing staff or derived from clinical notes:
➢ Has there been a sudden change in the patient’s mental state?
➢ Does the patient seem to be better at any period in the day compared to other times?
➢ Has the level of consciousness been altered (drowsy/not responsive, or agitated)?
➢ Sleep-wake cycle disturbances?</td><td></td><td></td></tr>
<tr><td>C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).</td><td><u>Questions to the patients:</u>
Orientation-tests: Orientation to time, place and person; Why are you in hospital? Will a stone float in water? Are there fish in the sea? (any error=disorganized thinking)
Recall (3 words)
<u>Questions to carers/nursing staff/clinical notes:</u>
Has there been any…Perceptual disturbances? Sleep-wake cycle disturbances? Memory disturbances? Psychotic episodes? Psychomotor disturbances?</td><td></td><td></td></tr>
<tr><td>D. The disturbances in criteria A and C are not</td><td>Information from history/chart/clinical assessment.</td><td></td><td></td></tr>
</table>

explained by another preexisting, established			
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.			
Delirium, based on the tests and information above?	All DSM-5 criteria are fulfilled		
Subsyndromal delirium, based on the tests and information above?	Defined as evidence of change, in addition to any of the following: (a) altered arousal, (b) attention deficits, (c) other cognitive change, (d) delusions or hallucinations. Criteria D and E must be fulfilled.		

Additional file 3. Checklists for treatment fidelity evaluation (PLM, PRM)

PREFERRED LIVE MUSIC (PLM)				
Study ID:	**Intervention day:**	**Criteria satisfied**		**Score**
1.	MT delivered the intended minimum dosage (participant was in attendance for 10 min or longer).	YES	NO	
2.	MT used the assessed preference songs in the session. *	YES	NO	
3.	MT presented the preference songs in the same order as intended/planned (relevant for sessions 2 and 3 only)	YES	NO	
4.	MT delivered the intervention by voice only, or voice and accompaniment (e.g. guitar, tone-chimes, percussions).	YES	NO	
5.	MT cued the participant to sing along or move to music, used the elements of improvisation and attunement to the patient. **	YES	NO	
6.	MT had physical (holding hands, stroking, etc.), verbal, or non-verb verbal interaction with the participant (eye-contact, face expressions, smiling).	YES	NO	
			Total:	

Intervention manual:
In PLM intervention music therapist should chose the music for the sessions from patients' assessed preferences and make sure not to change their order of deliverance. MT should enter the room, say hi to the patient, introduce the intervention, and if appropriate, offer the participants small percussion instruments that they can play on during the session. Thereafter MT should deliver the intervention live, by singing/playing the songs either A Capella, or accompanied by a guitar, tone-chimes, or percussion instruments. The intervention may involve interaction with the patients (e.g. physical, musical, verbal), the songs are not expected to be delivered in a way that is identical to their original versions, and elements of improvisation are both allowed and expected, as well as other forms of attunement to the patients. After max. 30 minutes, the MT should collect the instruments, say good bye to the patient, and leave the room.

Instructions for scoring:
YES: I agree with the statement (score 1)
NO: I disagree with the statement (score 0)
NR: Not relevant

* Item 2 is only relevant for sessions 2 and 3 and not relevant for sessions 1. Should be scored as NR.
** Item 5 is related to the presence of improvisation elements, such as repetition, variation, extension, mirroring, matching, imitation, etc. as well as other musical or non-musical elements and forms of attunement to the patient (cuing, humming, whistling, scatting, snapping fingers, laughing together etc. The rater should score YES if there is at least one of the aforementioned elements present, and as long as there is a minimum variation in the performance of the songs compared to the original.

PREFERRED RECORDED MUSIC (PRM)					
Study ID:	**Intervention day:**		**Criteria satisfied:**		**Score**
1.	MT delivered the intended minimum dosage (participant was in attendance for the minimum of 10 min).		YES	NO	
2.	MT used the assessed preference songs in the session. *		YES	NO	
3.	MT presented the preference songs in the same order as intended/planned (relevant for sessions 2 and 3 only).		YES	NO	
4.	MT delivered the intervention by the speaker and Bluetooth musical device.		YES	NO	
5.	MT did not cue the participant to sing along or move to music.		YES	NO	
6.	MT did not have physical (holding hands, stroking, etc.), verbal, or non-verb verbal interaction with the participant (eye-contact, face expressions, smiling etc.).		YES	NO	
				Total:	

Intervention manual:
In the PRM intervention, music therapist (MT) should chose the songs for the sessions from the patients' assessed preferences (and not vary their order each of the three intervention days). MT should enter the participant's room, and after saying hi and shortly introducing the music that will be played, start the music from a musical device and a Bluetooth speaker. MT should refrain from engaging with the patient while the music is played, and any engagement should be registered as the disruption from the protocol. The MT should not engage with the patient neither verbally, non-verbally, physically while the music is played. Any engagement should be registered as the disruption of the protocol. After 30 minutes the MT should stop the music, say good bye to the patient and leave the room.

Instructions for scoring:
YES: I agree with the statement (score 1)
NO: I disagree with the statement (score 0)
NR: Not relevant

*Item 2 was only relevant for sessions 2 and 3. Should be scored as NR for session 1.

Additional file 4. Group PLM versus Group PRM difference on Day 3

Measure	Before/after	PLM	PRM	Mean difference (95 % CI)	p-value
OSLA	Before	3.0 (1.4 to 4.5)	4.1 (1.4 to 6.9)	1.2 (-2.0 to 4.3)	0.463
	After	3.9 (2.3 to 5.5)	2.8 (0.0 to 5.6)	-1.1 (-4.3 to 2.1)	0.514
mRASS	Before	-0.5 (-0.9 to 0)	-0.4 (-1.2 to 0.4)	0.1 (-0.9 to 1)	0.874
	After	-0.9 (-1.4 to -0.4)	-0.1 (-0.9 to 0.7)	0.7 (-0.2 to 1.7)	0.125
Count 20 to 1	Before	14.1 (9.8 to 18.4)	13.6 (6.8 to 20.3)	-0.6 (-8.5 to 7.4)	0.890
	After	11.8 (7.3 to 16.2)	9.6 (2 to 17.2)	-2.2 (-11 to 6.6)	0.625
Days of the week	Before	5.4 (3.9 to 7.0)	5.4 (3.0 to 7.8)	-0.1 (-2.9 to 2.8)	0.972
	After	5.3 (3.6 to 6.9)	3.9 (1.5 to 6.3)	-1.4 (-4.3 to 1.6)	0.358
Months of the year	Before	4.3 (2.3 to 6.3)	1.8 (-1.3 to 4.9)	-2.4 (-6.1 to 1.3)	0.195
	After	4.7 (2.6 to 6.8)	3.3 (0.0 to 6.8)	-1.5 (-5.5 to 2.6)	0.485
Digit span	Before	3.9 (2.9 to 4.9)	5.2 (3.6 to 6.7)	1.2 (-0.6 to 3.1)	0.197
	After	3.5 (2.4 to 4.5)	3.9 (2.3 to 5.5)	0.4 (-1.5 to 2.3)	0.657
SAVEAHEART	Before	1.9 (0.0 to 3.7)	1.6 (0.0 to 4.4)	-0.3 (-3.6 to 3.1)	0.881
	After	2.6 (0.7 to 4.5)	1.3 (0.0 to 4.2)	-1.3 (-4.7 to 2.1)	0.458
Orientation	Before	5.0 (3.7 to 6.3)	4.3 (2.3 to 6.4)	-0.7 (-3.1 to 1.7)	0.576
	After	4.0 (2.7 to 5.4)	4.4 (2.0 to 6.7)	0.3 (-2.4 to 3.0)	0.813

PLM Preferred Live Music, *PRM* Preferred Recorded Music

[a] The estimated confidence intervals from the linear mixed models had lower limits below zero, however the scores do not go below zero and the lower limit has therefore been adjusted to zero.

Additional file 5. Proportion of participant who could recall any words in delayed recall test

Day	Before/after	Proportion (95 % CI)
Baseline		19.2 (8.2 to 38.9)
Day 1	before	9.1 (2.3 to 30.2)
Day 1	after	15.0 (4.9 to 37.9)
Day 2	before	15.8 (5.1 to 39.4)
Day 2	after	11.8 (2.9 to 37.2)
Day 3	before	20.0 (6.5 to 47.3)
Day 3	after	7.7 (1.1 to 39.5)

Additional file 6. Between the groups difference in Length of hospital stay and PRN medication

Variable	**PLM (n=14)**	**PRM (n=12)**	**Mann-Whitney test *(U)***	**Significance *(p)***
Length of hospital stay, Mean (SD) [a]	11 (8.95)	13 (9.94)	82.500	0.940
Number of patients receiving PRN medication during hospital stay, n (%) [b]			**Fisher Exact test *(p)***	
Benzodiazepines[b]	7 (43)	4 (33)	0.431	
Opioids[b]	9 (64)	6 (50)	0.422	
Antipsychotics[b]	5 (36)	2 (17)	0.286	

PLM Preferred Live Music, *PRM* Preferred Recorded Music *PRN* Pro-re-nata, psychopharmacological "rescue" medication.
[a] Mean ranks
[b] Number and percentage of patients who got the PRN medication during hospital stay

Appendices

Appendix 1	Ethical approval documentation
Appendix 2	1: Forenklet informasjonsskriv 2: Fullstendig informasjonsskriv til pasient 3: Fullstendig informasjonsskriv til pårende 4: Short Information Sheet 5: Information Sheet and Declaration from Patients 6: Information Sheet and Declaration from Legal Guardians
Appendix 3	Diagnostic algorithm for DSM-5 delirium evaluation
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Appendix 1

Ethical approval documentation

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst D	Silje U. Lauvrak	22845520	09.04.2022	457017

Bjørn Erik Neerland

Prosjektsøknad: Musikkterapi til akuttinnlagte eldre pasienter med delirium
Søknadsnummer: 457017
Forskningsansvarlig institusjon: Oslo universitetssykehus HF
Samarbeidende forskningsansvarlige institusjoner: Norges musikkhøgskole

Prosjektsøknad godkjennes

Søkers beskrivelse

Dette prosjektet er en gjennomførbarhetsstudie som inngår i et doktorgradsarbeid hvor bruk av musikkterapi som intervensjon ved delirium utforskes hos akuttinnlagte eldre pasienter. Delirium kjennetegnes av en akutt endring i bevissthet, oppmerksomhet og kognitive funksjoner og oppstår i forløpet av akutt sykdom, gjerne med agitasjon, desorientering, persepsjonsforstyrrelse (hallusinasjoner, vrangforestillinger). Delirium er en stor belastning for pasienter, deres pårørende og helsetjenesten og medfører betydelige kostnader for samfunnet. Det finnes ingen effektiv medikamentell behandling og ikke-medikamentelle tiltak er viktigst i forebygging og behandling av tilstanden.

Målet med dette prosjektet er å utforske musikkterapi som behandling for delirium gjennom to eksperimentelle
studier:
1) sammenligning av ulike musikkterapeutiske intervensjoner;
2) sammenligning av ulike doser musikkterapi.
Vi vil også utforske hvilke spesifikke deliriumsymptomer musikkterapi-intervensjonene bør rette seg mot, hvilke intervensjoner som best påvirker hvilke symptomer, sensitivitet av ulike vurderingsverktøy, og praktiske forhold knyttet til rekruttering av pasienter.
Prosjektet har en kvantitativ metodologi og vil baseres på objektive tester, og en statistisk behandling av datamaterialet.
Prosjektet består av to kliniske intervensjonsstudier med 30 deltakere i hver. Effekt måles hos samme pasient før- og etter intervensjonene.
Målet med studien er å evaluere umiddelbare effekter kort tid etter intervensjon(er) og sammenligne med utgangsverdier. Data vil bli samlet ved bruk av standardiserte tester for vurdering av symptomer ved delirium, ved systematisk observasjon og andre objektive målinger. Hensikten med prosjektet er å samle viktig data som kan informere design av en mer konklusiv studie senere.
Hele studie 1 gjennomføres før studie 2 kan starte, og disse vil involvere ulike deltakere. Deltakere i denne studien vil være voksne personer i en akutt forvirringstilstand, og vi forventer derfor at de fleste aktuelle deltakere vil ha en redusert evne til å gi samtykke. Pasienter med delirium er en meget sårbar gruppe samtidig som standard behandling ikke gir tilfredsstillende resultater (særlig den farmakologiske). For å kunne få generaliserbare

resultater og få frem viktig kunnskap om nye behandlingsalternativer er det derfor både viktig og nødvendig å inkludere pasienter med redusert samtykkekompetanse. Vi vil legge vekt på grundig og utfyllende informasjon (til både pasienter og pårørende/verge), og ivaretakelse av deltakernes integritet.
Musikkterapi-intervensjonene som vi ønsker å utforske vil basere seg på musikkpreferanser som er kartlagt på forhånd for hver deltaker, og vil innebære både reseptive og ekspressive metoder (musikklytting, interaktiv musikkterapi). Effekten antas og forklares gjennom nevrobiologiske mekanismer, som forbindelsen mellom musikk og emosjoner, musikkens virkning på våkenhet/oppmerksomhet og generell aktivering, samt virkning på nevrokjemi, nevroplastisitet. Musikkens forbindelse med personlig identitet og dens ulike funksjoner i et sosialt felleskap er også vesentlige.
Både intervensjonene og undersøkelsene i dette prosjektet medfører svært liten risiko og ubehag for deltakerne.

Vi viser til søknad om forhåndsgodkjenning for ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK) i møtet 16.03.2022. Vurderingen er gjort med hjemmel i helseforskningsloven § 10.

REKs vurdering

Prosjektets formål er å undersøke musikkterapi som tillegg til ordinær behandling for delirium. Umiddelbare effekter kort tid etter intervensjonen skal sammenlignes med utgangsverdier. Studien er delt i to deler, der del 1 skal sammenligne ulike musikkterapeutiske intervensjoner, mens del 2 skal sammenligne ulike doser musikkterapi. Del 1 skal ferdigstilles før del 2 starter.

I tillegg til musikkintervensjonen, innebærer deltagelse at det gjøres observasjon av våkenhetsgrad, distraherbarhet, forståelse og tendens til å «miste tråden» i samtale. Det vil bli tatt videoopptak av musikkterapeuten under intervensjonene. Pasienten skal ikke filmes, men lyden fra pasienten vil kunne høres. Deltagelse innebærer også at det innhentes opplysninger fra pasientjournal om demografi, hjelpebehov i dagliglivet, skrøpelighetsvurdering, kroniske sykdommer, faste legemidler, liggetid, fysiologiske variabler, alvorlighetsgrad av sykdom (NEWS2).

Utfallsmål i studien er blant annet vurdering av symptomer ved delirium, og komiteen mener dermed at prosjektet kan fremskaffe ny kunnskap om helse og sykdom og at det faller innenfor helseforskingslovens virkeområde, jamfør lovens § 2 og § 4 bokstav a).

Det skal inkluderes 60 pasienter innlagt på akuttgeriatrisk sengepost ved Ullevål sykehus (30 pasienter i hver studiedel). Gjennomsnittsalder for pasientene er ca. 85 år. Mange av pasientene har en demenssykdom og forekomsten av delirium er høy.

Det oppgis følgende om rekrutteringsprosedyren: «Det forventes at de fleste aktuelle deltakere vil ha en redusert evne til å gi samtykke. Behandlingsansvarlige leger vil individuelt vurdere samtykkekompetansen. I de tilfellene der det er nødvendig at pårørende/verge samtykker på vegne av pasienten, ønskes det å innhente samtykke muntlig per telefon. Skriftlig samtykke vil deretter innhentes så snart det lar seg gjøre.»

Slik komiteen oppfatter prosjektet, skal det gjennomføres på pasienter som mer eller mindre akutt kommer i en tilstand av delir. Prosjektet omfattes følgelig av helseforskningsloven § 19, som regulerer forskning i kliniske nødssituasjoner der pasienten ikke er i stand til å avgi samtykke og der det er umulig å innhente samtykke fra vedkommendes nærmeste pårørende. Det stilles da krav om at forskning bare kan skje dersom

a. eventuell risiko eller ulempe for personen er ubetydelig,

b. personen selv ikke motsetter seg det, og det ikke er grunn for forskere eller øvrig personell til å tro at vedkommende ville ha motsatt seg dette dersom vedkommende hadde hatt samtykkekompetanse,

c. det bare er mulig å utføre forskningen i kliniske nødssituasjoner, og

d. forskningen utvilsomt er berettiget på grunn av utsikten til resultater med stor forebyggende, diagnostisk eller terapeutisk verdi.

Komiteen vurderer at alle vilkår er oppfylt, og at foreslåtte rekrutteringsprosedyre er akseptabel i de tilfeller der pårørende ikke er tilstede ved innleggelse. Komiteen forutsetter at det muntlige samtykke fra pårørende per telefon dokumenteres og observeres av en person som ikke er knyttet direkte til studien, og at skriftlig samtykke innhentes så snart som mulig i etterkant. Dersom pasienten gjenvinner samtykkekompetanse skal samtykke også innhentes fra pasienten.

I de tilfeller der pasientens pårørende er tilstede ved innleggelse, skal skriftlig samtykke innhentes i forkant av musikk-intervensjonen. Også i disse tilfellene skal samtykke innhentes fra pasienten selv dersom denne gjenvinner sin samtykkekompetanse.

Komiteen finner prosjektet interessant og anser det som nyttig å undersøke om musikkterapi kan fungere som et ikke-farmakologisk behandlingsalternativ for pasienter med delirium. Det presiseres i søknaden at musikkterapien skal vektlegge personlige preferanser og valg, og komiteen vurderer det som en fordel for deltagerne å få en individuelt tilpasset behandling i tillegg til den vanlige oppfølgingen på avdelingen. Risikoen forbundet med deltagelse anses minimal, da musikk-intervensjonen er lite invaderende og dermed ikke forventes å kunne gi alvorlige negative bivirkninger.

På denne bakgrunn vurderer komiteen at det er forsvarlig å gjennomføre prosjektet som beskrevet i søknad og protokoll.

Vedtak

REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven § 10.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2026. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2031. Forskningsfilen skal oppbevares atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Komiteens avgjørelse var enstemmig.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 31.12.2026, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Pål Aukrust
Prof.em. Dr. med
Leder

Silje U. Lauvrak
Seniorrådgiver

Kopi til:

Oslo universitetssykehus HF
Norges musikkhøgskole

Appendix 2

1: Forenklet informasjonsskriv
2: Fullstendig informasjonsskriv til pasient
3: Fullstendig informasjonsskriv til pårende
4: Short Information Sheet
5: Information Sheet and Declaration from Patients
6: Information Sheet and Declaration from Legal Guardians

Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter. Kort informasjonsskriv. Versjon 1. 11.02.2022.

Oslo universitetssykehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

"Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter"

Dette er et spørsmål til deg om å delta i et forskningsprosjekt som utforsker musikkterapi som behandling for *delirium* (akutt forvirring).

HVA INNEBÆRER PROSJEKTET FOR DEG?

Dersom du deltar, vil du få behandling med musikkterapi mens du er på sykehuset.

- Musikkterapeuten vil finne ut hvilken musikk du liker
- Du vil enten få høre, spille og synge noen av de yndlingssangene dine sammen med musikkterapeuten, eller så vil musikken spilles for deg fra en høyttaler

All annen behandling vil være slik du ellers ville fått.

Vi vil også

- registrere noen opplysninger om deg fra journalen din
- snakke med dine nærmeste pårørende om hvordan du har klart deg den siste tiden
- gjøre noen enkle oppgaver og tester sammen med deg
- observere hvordan musikken påvirker deg og hvordan du har det
- lagre opplysninger om din helsetilstand

Vi ønsker også å filme (video) musikkterapibehandlingen. Du vil ikke selv bli synlig på filmen, men lyden fra deg kan kanskje høres.

Opplysninger om deg vil bli ikke bli tilgjengelig for andre enn oss som deltar i studien.

All informasjon vil bli behandlet konfidensielt, og resultatene vil bli presentert i fagtidsskrift og/eller fagkonferanser i anonymisert form. Informasjonen lagres til år 2031.

MULIGE FORDELER OG ULEMPER

Det er trygt og enkelt for deg å få musikk-behandlingen. Vi vil alltid ta hensyn til hvor mye du orker og hva du liker. Kanskje vil du ønske mer musikkterapi enn vi kan gi deg den dagen.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet og du har full anledning til å trekke deg senere uten å oppgi grunn til det. Du vil få betenkningstid om du vil delta eller ikke.

GODKJENNINGER OG RETTIGHETER

Regional komité for medisinsk og helsefaglig forskningsetikk har gjort en forskningsetisk vurdering og godkjent prosjektet. [XXX XXX]

Etter ny personopplysningslov har dataansvarlig (Oslo Universitetssykehus, ved avdelingsleder), og prosjektleder (Bjørn Erik Neerland) et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Studien har lovlig grunnlag for behandling av person- og helseopplysninger i GDPR art. 6 nr. 1 e) og art. 9 nr. 2 j).

Dersom du har spørsmål om personvernet i prosjektet, kan du kontakte personvernombudet ved institusjonen: personvern@ous-hf.no

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet eller ønsker å trekke deg fra deltakelse, kan du kontakte prosjektleder: Overlege og forsker Bjørn Erik Neerland, Geriatrisk avdeling, Oslo Universitetssykehus. Tlf. 90078979. E-post bjonee@ous-hf.no

Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter. Kort informasjonsskriv. Versjon 1. 11.02.2022.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg samtykker også til at det gjøres videoopptak mens musikkterapibehandlingen pågår, som beskrevet over

Sted/dato

Deltakers signatur

LEGE

Jeg bekrefter at pasienten er samtykkeredusert og har fått forenklet skriftlig informasjon. Det er lagt vekt på tydelig muntlig informasjon. Pårørende har fått fullstendig informasjonsskriv. Pasienten har fått betenkningstid.

Navn med blokkbokstaver:

Sted og dato

Signatur

Rolle i prosjektet

Oslo universitetssykehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

"Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter"

FORMÅLET MED PROSJEKTET OG HVORFOR DU BLIR SPURT

Dette er et spørsmål til deg om å delta i et forskningsprosjekt hvor vi utforsker musikkterapi som mulig behandling for *delirium* hos akuttinnlagte eldre pasienter. Vi spør deg da du er lagt inn akutt ved Oslo Universitessykehus, Ullevål.

Noen pasienter kan oppleve forvirring, uro eller andre akutte mentale endringer når de er syke og innlagt på sykehus. Dette kalles *delirium*. Det finnes per i dag ingen effektiv behandling for delirium og mange opplever dette ubehagelig. Vi vil studere om musikkterapi kan være en egnet behandling for eldre personer med delirium.

HVA INNEBÆRER PROSJEKTET FOR DEG?

Dersom du deltar i prosjektet vil du først få møte en musikkterapeut som vil kartlegge hva slags musikk du liker. Deretter vil du få en av to forskjellige behandlingsopplegg med musikk:

1. Enten lytting til musikk/sanger fra en høyttaler, eller
2. Musikkterapeuten presenterer musikken for deg.

Dette vil skje en eller flere ganger om dagen, flere dager på rad i løpet av sykehusoppholdet. Det er tilfeldig om du vil få musikken fra musikkterapeuten eller fra høyttalerne. Dette vil vi bestemme ved loddtrekning.

Om du samtykker til dette, vil vi også lage videoopptak av musikkterapisesjonene. Du kommer ikke til å bli filmet selv, kun musikkterapeuten, men lyden av deg kan høres.

Deltakelse innebærer ikke noen endring i behandlingen for øvrig, og du vil få akkurat samme oppfølging på avdelingen enten du deltar i studien eller ikke.

Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter. Informasjonsskriv. Versjon 1. 11.02.2022.

I prosjektet vil vi innhente og registrere noen personlige opplysninger om deg fra pasientjournalen din her på sykehuset (kjønn, alder, sivilstatus, medisiner du tar osv.). En lege vil også gjøre noen tester sammen med deg før og etter musikkterapisesjonene. Testene vil kunne hjelpe oss å se hvordan du har det før og etter musikken og hvordan musikkterapien påvirker deg. Noen av testene vil bestå av spørsmål som du vil bli bedt om å svare på, mens resten er observasjoner av hvordan du har det, i noen minutter.

Ved deltagelse i dette prosjektet, samtykker du at vi kan bruke personlige informasjon om deg til forskning. Alle opplysninger vi samler om deg vil bli avidentifisert og ingen andre enn oss som deltar i studien vil få tilgang på dem.

MULIGE FORDELER OG ULEMPER

Det er helt trygt for deg å få musikkterapi-behandlingen i dette prosjektet. Vi vil alltid passe på at behandlingen foregår på dine premisser og at du ikke må høre på musikken for lenge, og heller ikke hvis du ikke orker det den dagen. Musikken i dette prosjektet vil alltid være valgt fra dine ønsker, og vi vil ikke til å tvinge deg til å høre på noe du ikke ønsker.

En ulempe kan være at du kanskje ikke får høre musikken så lenge du kanskje ønsker, fordi vi skal følge en plan som er laget for at vi skal kunne måle bedring hos deg.

Det vil ikke være krevende for deg å motta musikkterapi, og du trenger ikke å ha drevet med musikk for å kunne delta. Hvis du liker musikk, er det mer enn nok.

Erfaringene fra studien vil gi oss ny og nyttig kunnskap som vi håper kan gi både deg og fremtidige pasienter med delirium en bedre og mer tilpasset behandling.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Det vil ikke ha noen negative konsekvenser for deg eller din behandling hvis du ikke vil delta eller senere velger å trekke deg. Dersom du trekker tilbake samtykket, vil det ikke forskes videre på dine helseopplysninger. Du kan også kreve at dine helseopplysninger i prosjektet slettes eller utleveres innen 30 dager. Adgangen til å kreve destruksjon, sletting eller utlevering gjelder ikke dersom opplysningene er anonymisert. Denne adgangen kan også begrenses dersom opplysningene er inngått i utførte analyser.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte prosjektleder *Bjørn Erik Neerland*, Overlege og forsker ved Geriatrisk avdeling, Oslo Universitetssykehus, tlf 90078979, e-post bjonee@ous-hf.no

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet under formålet med prosjektet, og planlegges brukt til 2031. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra REK og andre relevante myndigheter. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Du kan klage på behandlingen av dine opplysninger til Datatilsynet og institusjonen sitt personvernombud.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun personell med ansvar for studien som har tilgang til denne listen.

Opplysningene om deg vil bli oppbevart i fem år etter prosjektslutt av kontrollhensyn, og deretter slettet.

FORSIKRING

Alle deltakere omfattes av de generelle pasientforsikringsordningene, og i henhold til Pasientskadeloven, ved Oslo Universitetssykehus.

GODKJENNINGER

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning xxx xxx.

Etter ny personopplysningslov har dataansvarlig (Oslo Universitetssykehus, ved avdelingsleder), og prosjektleder (Bjørn Erik Neerland) et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Studien har lovlig grunnlag for behandling av person- og helseopplysninger i GDPR art. 6 nr. 1 e) og art. 9 nr. 2 j).

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet eller ønsker å trekke deg fra deltakelse, kan du kontakte prosjektleder: Overlege og forsker Bjørn Erik Neerland, Geriatrisk avdeling, Oslo Universitetssykehus. Tlf. 90078979. E-post bjonee@ous-hf.no

Dersom du har spørsmål om personvernet i prosjektet, kan du kontakte personvernombudet ved institusjonen: personvern@ous-hf.no

Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter. Informasjonsskriv. Versjon 1. 11.02.2022.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

Jeg samtykker også til at det gjøres videopptak mens musikkterapibehandlingen pågår, som beskrevet over

Sted/dato

Deltakers signatur

Jeg bekrefter å ha gitt informasjon til deltakeren om prosjektet.

Navn med blokkbokstaver: _____

Sted og dato

Signatur

Rolle i prosjektet

Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter. Informasjonsskriv og erklæring fra pårørende. Versjon 1. 1.02.2022.

Oslo universitetssykehus

FORESPØRSEL TIL PÅRØRENDE OM PASIENTENS DELTAKELSE I FORSKNINGSPROSJEKTET

"Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter"

Dette er et spørsmål til deg om å la den du er pårørende til delta i et forskningsprosjekt. **Vi ber deg som nærmeste pårørende om å svare det du tror pasienten selv ville ha svart dersom han/hun var i stand til det.** Du blir spurt fordi pasienten selv kan ha redusert forståelse for hva denne studien innebærer og fordi studien ikke lar seg gjennomføre på annen måte. Dersom du har innvendinger til at pasienten deltar, så vil dette bli respektert. Pasienter som senere i sykdomsforløpet blir i stand til å svare, vil selv bli spurt om samtykke til videre deltakelse i studien.

Noen pasienter kan oppleve forvirring, uro eller andre akutte mentale endringer når de er syke og innlagt på sykehus. Dette kalles delirium. Det finnes per i dag ingen effektiv behandling for delirium og mange opplever dette ubehagelig. Vi vil studere om musikkterapi kan være en egnet behandling for eldre personer med delirium.

HVA INNEBÆRER PROSJEKTET?

Pasientene som deltar i prosjektet vil først få møte en musikkterapeut som vil kartlegge hva slags musikk pasienten liker. Deretter vil de få en av to forskjellige behandlingsopplegg med musikk:

1. Enten lytting til musikk/sanger fra en høyttaler, eller
2. Musikkterapeuten presenterer musikken for deg.

Dette vil skje en eller flere ganger om dagen, flere dager på rad i løpet av sykehusoppholdet. Det er tilfeldig om pasienten vil få musikken fra musikkterapeuten eller fra høyttalerne. Dette vil vi bestemme ved loddtrekning.

Deltakelse innebærer ikke noen endring i behandlingen for øvrig, og pasientene vil få akkurat samme oppfølging på avdelingen enten den deltar i studien eller ikke.

I prosjektet vil vi innhente og registrere noen personlige opplysninger om pasienten fra pasientjournalen (kjønn, alder, sivilstatus, medisiner pasienten tar, tidligere sykdommer osv.). En lege vil også gjøre noen tester sammen med pasienten før og etter

musikkterapisesjonene. Testene vil kunne hjelpe oss å se hvordan pasientene har det før og etter musikken og hvordan musikkterapien påvirker dem. Noen av testene vil bestå av spørsmål som pasienten vil bli bedt om å svare på, mens resten er observasjoner av hvordan pasienten har det, i noen minutter.

Vi ønsker også å lage videoopptak av musikkterapisesjonene. Pasienten kommer ikke til å bli filmet selv, kun musikkterapeuten, men lyden av pasienten vil kunne høres. Vi lager videoopptakene for å evaluere selve utførelsen av musikkterapien. Kun studiepersonell vil ha tilgang til videoene, som lagres sikkert.

Alle opplysninger vi samler om pasienten, vil bli avidentifisert og ingen andre enn oss som deltar i studien vil få tilgang på dem.

MULIGE FORDELER OG ULEMPER

Det er helt trygt for pasienten å få musikkterapi-behandlingen i dette prosjektet. Vi vil alltid passe på at behandlingen foregår på pasientenes premisser, og at pasientene ikke må høre på musikken for lenge, og heller ikke hvis de ikke orker det den dagen. Musikken i dette prosjektet vil alltid være valgt fra pasientenes ønsker, og vi vil ikke til å tvinge dem til å høre på noe de ikke ønsker.

En ulempe kan være at pasientene kanskje ikke får høre musikken så lenge de ønsker, fordi vi skal følge en plan som er laget for at vi skal kunne måle bedring hos pasienten.

Det vil ikke være krevende å motta musikkterapi, og pasientene trenger ikke å ha drevet med musikk for å kunne delta. Hvis de liker musikk, er det mer enn nok.

Erfaringene fra studien vil gi oss ny og nyttig kunnskap som vi håper kan gi både den du er pårørende til og fremtidige pasienter med delirium en bedre og mer tilpasset behandling.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet. Siden vi ikke kan spørre pasienten selv om deltakelse i studien nå, **ber vi deg som nærmeste pårørende om å svare det du tror pasienten selv ville ha svart dersom han/ hun var i stand til det**. Dersom du ikke ønsker at pasienten skal delta i studien, trenger du ikke å oppgi noen grunn, og det får ingen konsekvenser for deg eller pasienten. Du vil få betenkningstid, og **dersom du ikke har innvendinger til at pasienten deltar, undertegner du erklæringen på siste side**.

Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for deg eller pasientens videre behandling. Dersom du senere ønsker å trekke samtykket, kan du kreve å få slettet innsamlet informasjon, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Dersom du senere ønsker å trekke samtykket eller har spørsmål til prosjektet, kan du enkelt kontakte prosjektleder *Bjørn Erik Neerland*, kontaktopplysninger under

HVA SKJER MED OPPLYSNINGENE OM DELTAKEREN?

Opplysningene som registreres om pasienten skal kun brukes slik som beskrevet i hensikten med prosjektet, og planlegges brukt til 2031. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra REK og andre relevante myndigheter.

Pasienten har rett til innsyn i hvilke opplysninger som er registrert om ham/henne og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Pasienten har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Pasienten kan klage på behandlingen av sine opplysninger til Datatilsynet og institusjonen sitt personvernombud.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter pasienten til sine opplysninger gjennom en navneliste. Det er kun personell med ansvar for studien som har tilgang til denne listen.

Opplysningene om pasienten vil bli oppbevart i fem år etter prosjektslutt av kontrollhensyn, og deretter slettet.

FORSIKRING

Alle deltakere omfattes av de generelle pasientforsikringsordningene, og i henhold til Pasientskadeloven, ved Oslo Universitetssykehus.

GODKJENNINGER

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning xxx xxx.

Etter ny personopplysningslov har dataansvarlig (Oslo Universitetssykehus, ved avdelingsleder), og prosjektleder (Bjørn Erik Neerland) et selvstendig ansvar for å sikre at behandlingen av deltakerens opplysninger har et lovlig grunnlag. Studien har lovlig grunnlag for behandling av person- og helseopplysninger i GDPR art. 6 nr. 1 e) og art. 9 nr. 2 j).

Pasienten har rett til å klage på behandlingen av sine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet, kan du kontakte prosjektleder:

Bjørn Erik Neerland, Overlege og forsker ved Geriatrisk avdeling, Oslo Universitetssykehus
Tlf. 90078979 E-post: bjonee@ous-hf.no

Dersom du har spørsmål om personvernet i prosjektet, kan du kontakte personvernombudet ved institusjonen: personvern@ous-hf.no

Musikkterapi for behandling av delirium hos akuttinnlagte eldre pasienter. Informasjonsskriv og erklæring fra pårørende. Versjon 1. 1.02.2022.

ERKLÆRING FRA PÅRØRENDE

Pårørendes navn (blokkbokstaver): _____

Pasientens navn (blokkbokstaver): _____

1. Jeg har ingen innvendinger til at den jeg er pårørende til deltar i studien

Jeg er selv villig til å delta i prosjektet med opplysninger om pasienten

---

(Signert av pårørende, dato)

2. Jeg har ingen innvendinger til at det gjøres videoopptak mens musikkterapibehandlingen pågår, som beskrevet over

---

(Signert av pårørende, dato)

Jeg bekrefter å ha gitt muntlig og skriftlig informasjon om studien til pårørende. Jeg vurderer pasienten selv som ikke samtykkekompetent. Pårørende har fått betenkningstid.

Navn med blokkbokstaver: _____

Sted og dato Signatur

_____

Rolle i prosjektet

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Short Information Sheet. v/1, 08.02.2022.

OSLO UNIVERSITY HOSPITAL

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

"Music therapy for the treatment of delirium in acutely hospitalized elderly patients"

This is a question inviting you to participate in a research project exploring music therapy as a treatment for delirium (acute confusion).

WHAT DOES THE PROJECT ENTAIL FOR YOU?

If you participate, you will receive music therapy treatment while you are in the hospital.

- The music therapist will find out what music you like.
- You will either listen to, play, and sing some of your favorite songs together with the music therapist, or the music will be played for you from a speaker. All other treatments will be as you would otherwise receive. We will also:
- record some information about you from your medical record.
- talk to your closest relatives about how you have been doing lately.
- do some simple tasks and tests with you.
- observe how the music affects you and how you are feeling.
- store information about your health condition. We also wish to record (video) the music therapy treatment. You will not be visible on the video yourself, but the sound from you might be heard. Information about you will not be accessible to anyone other than those involved in the study. All information will be treated confidentially, and the results will be presented in professional journals and/or conferences in anonymized form. The information will be stored until the year 2031.

FORESEEABLE BENEFITS AND PREDICTABLE RISKS AND BURDENS OF TAKING PART

It is safe and simple for you to receive the music treatment. We will always consider how much you can handle and what you enjoy. Perhaps you'll want more music therapy than we can provide on that day.

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Short Information Sheet. v/1, 08.02.2022.

VOLUNTARY PARTICIPATION AND POSSIBILITY TO WITHDRAW YOUR CONSENT

Participation in the project is voluntary, and you have the full opportunity to withdraw later without needing to provide a reason. You will be given time to consider whether you want to participate or not.

ETHICAL APPROVAL AND RIGHTS

The Regional Committee for Medical and Health Research Ethics has conducted an ethical assessment and approved the project. [XXX XXX]

Under the new Personal Data Act, the data controller (Oslo University Hospital, represented by the department head) and the project leader (Bjørn Erik Neerland) have an independent responsibility to ensure that the processing of your information has a lawful basis. The study has a lawful basis for processing personal and health information under GDPR Article 6(1)(e) and Article 9(2)(j).

If you have questions regarding privacy in the project, you can contact the privacy ombudsman at the institution: privacy@ous-hf.no

You have the right to lodge a complaint about the processing of your information with the Data Protection Authority.

CONTACT INFORMATION

If you have any questions about the project or wish to withdraw from participation, you can contact the project leader: Geriatrician and Researcher Bjørn Erik Neerland, Geriatric Department, Oslo University Hospital. Phone: 90078979. Email: bjonee@ous-hf.no

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Short Information Sheet. v/1, 08.02.2022.

I CONSENT TO PARTICIPATING IN THE RESEARCH PROJECT AND THAT MY PERSONAL DATA CONCERING HEALTH CAN BE USED AS DESCRIBED ABOVE

.....

Place and Date

Participant's signature

.....

Participant's name (IN BLOCK LETTERS)

I also consent to video recordings being made during the music therapy treatment, as described above.

.....

Place/Date

Participant's Signature

DOCTOR

I confirm that the patient lacks capacity to consent and has been provided with simplified written information. Emphasis has been placed on clear verbal communication. Relatives have received the complete information leaflet. The patient has been given time for consideration.

.....

Place and Date

Signature

.....

Role in the research project

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Complete Information Sheet. Version 1.

OSLO UNIVERSITY HOSPITAL

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

"Music therapy for the treatment of delirium in acutely hospitalized elderly patients"

THE PURPOSE OF THE PROJECT AND WHY YOU ARE BEING ASKED

This is an invitation for you to participate in a research project where we explore music therapy as a possible treatment for delirium in acutely admitted elderly patients. We ask you because you are admitted acutely at Oslo University Hospital, Ullevål. Some patients may experience confusion, restlessness, or other acute mental changes when they are sick and hospitalized. This is called delirium. Currently, there is no effective treatment for delirium, and many find it uncomfortable. We will study whether music therapy may be a suitable treatment for elderly individuals with delirium.

WHAT DOES THE PROJECT ENTAIL FOR YOU?

If you participate in the project, you will first meet with a music therapist who will assess what kind of music you like. Then you will receive one of two different music treatment approaches:

- Either listening to music/songs from a speaker, or
- The music therapist presenting the music to you.

This will happen once or several times a day, over several consecutive days during your hospital stay. It will be random whether you receive the music from the music therapist or from the speakers. This will be determined by drawing lots.

If you consent to this, we will also make video recordings of the music therapy sessions. You will not be filmed yourself, only the music therapist, but the sound of you may be heard.

Participation does not involve any changes in your treatment otherwise, and you will receive the same care on the ward whether you participate in the study or not.

In the project, we will gather and record some personal information about you from your patient record here at the hospital (gender, age, marital status, medications you take, etc.). A doctor will also conduct some tests with you before and after the music therapy sessions. The tests will help us see how you are before and after the music and how music therapy

affects you. Some of the tests will consist of questions that you will be asked to answer, while the rest are observations of how you are doing, for a few minutes.

By participating in this project, you consent to us using personal information about you for research. All information we collect about you will be anonymized, and only those of us involved in the study will have access to it.

FORESEEABLE BENEFITS AND PREDICTABLE RISKS AND BURDENS OF TAKING PART

It is completely safe for you to receive music therapy treatment in this project. We will always ensure that the treatment takes place on your terms and that you do not have to listen to the music for too long, and neither if you don't feel up to it on a particular day. The music in this project will always be chosen based on your preferences, and we will not force you to listen to anything you do not wish to hear.

One drawback may be that you may not get to listen to the music for as long as you might like because we will follow a plan designed to measure improvement in you.

Receiving music therapy will not be demanding for you, and you do not need to have a background in music to participate. If you enjoy music, that is more than enough.

The experiences from the study will provide us with new and valuable knowledge that we hope can provide both you and future patients with delirium with better and more tailored treatment.

VOLUNTARY PARTICIPATION AND POSSIBILITY TO WITHDRAW YOUR CONSENT

Participation in the project is voluntary. If you wish to participate, you sign the consent form on the last page. You can withdraw your consent at any time and without providing any reason. It will not have any negative consequences for you or your treatment if you choose not to participate or later decide to withdraw. If you withdraw your consent, no further research will be conducted on your health information. You can also request that your health information in the project be deleted or disclosed within 30 days. The right to demand destruction, deletion, or disclosure does not apply if the information is anonymized. This right may also be limited if the information is included in completed analyses.

If you later wish to withdraw or have questions about the project, you can contact the project leader Bjørn Erik Neerland, Geriatrician and Researcher at the Department of Geriatrics, Oslo University Hospital, tel. 90078979, email bjonee@ous-hf.no

WHAT WILL HAPPEN TO YOUR PERSONAL DATA CONCERNING HEALTH?

The information recorded about you will only be used as described under the purpose of the project and is planned to be used until 2031. Any extensions in use and storage time can

only occur after approval from the Regional Committee for Medical and Health Research Ethics (REK) and other relevant authorities. You have the right to access which information is recorded about you and the right to have any errors corrected in the information that is recorded. You also have the right to access the security measures for the processing of the information. You can complain about the processing of your information to the Norwegian Data Protection Authority (Datatilsynet) and the institution's data protection officer.

All information will be processed without names, social security numbers, or other directly identifying information (=coded information). A code links you to your information through a name list. Only the project leader, Bjørn Erik Neerland, has access to this list.

The information about you will be stored for five years after the end of the project for control purposes, and then deleted.

INSURANCE

All participants are covered by the general patient insurance schemes, and according to the Patient Injury Act, at Oslo University Hospital.

ETHICAL APPROVAL

The Regional Committee for Medical and Health Research Ethics has reviewed the project and has given prior approval XXX XXX.
Under the new Personal Data Act, the data controller (Oslo University Hospital, represented by the department head), and the project leader (Bjørn Erik Neerland) have independent responsibility to ensure that the processing of your information has a legal basis. The study has a legal basis for processing personal and health information under GDPR Article 6(1)(e) and Article 9(2)(j).
You have the right to complain about the processing of your information to the Norwegian Data Protection Authority (Datatilsynet).

CONTACT INFORMATION

If you have any questions about the project or wish to withdraw from participation, you can contact the project leader: Geriatrician and Researcher Bjørn Erik Neerland, Department of Geriatrics, Oslo University Hospital. Phone: 90078979. Email: bjonee@ous-hf.no

If you have any questions about privacy in the project, you can contact the institution's data protection officer: privacy@ous-hf.no

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Complete Information Sheet. Version 1.

I CONSENT TO PARTICIPATING IN THE RESEARCH PROJECT AND THAT MY PERSONAL DATA CONCERING HEALTH AND BIOLOGICAL MATERIAL CAN BE USED AS DESCRIBED ABOVE

.....

Place and Date Participant's signature

.....

Participant's name (IN BLOCK LETTERS)

I also consent to video recordings being made during the music therapy treatment, as described above.

……..

Place/Date Participant's Signature

DOCTOR

I confirm that I have provided information to the participant about the project.

……

Place and Date Signature

…….

Role in the research project

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Information Sheet and Declaration from Legal Guardians. Version 1. 08.02.2022.

OSLO UNIVERSITY HOSPITAL

INQUIRY TO LEGAL GUARDIANS REGARDING THE PATIENT'S PARTICIPATION IN THE RESEARCH PROJECT

"Music therapy for the treatment of delirium in acutely hospitalized elderly patients"

THE PURPOSE OF THE PROJECT AND WHY YOU ARE BEING ASKED

This is a question for you regarding allowing the person you are a caregiver for to participate in a research project. We ask you, as the closest caregiver, to answer what you believe the patient themselves would have answered if they were able to. You are being asked because the patient themselves may have reduced understanding of what this study entails, and because the study cannot be carried out in any other way. If you have objections to the patient participating, these will be respected. Patients who later become capable of answering will be asked for their consent to continue participating in the study.

Some patients may experience confusion, restlessness, or other acute mental changes when they are sick and hospitalized. This is called delirium. Currently, there is no effective treatment for delirium, and many find it uncomfortable. We will study whether music therapy may be a suitable treatment for elderly individuals with delirium.

WHAT DOES THE PROJECT ENTAIL?

The patients participating in the project will first meet with a music therapist who will assess what kind of music the patient likes. Then they will receive one of two different music treatment approaches:

- Either listening to music/songs from a speaker, or
- The music therapist presenting the music to them.

This will happen once or several times a day, over several consecutive days during their hospital stay. It will be random whether the patient will receive the music from the music therapist or from the speakers. This will be determined by drawing lots.

Participation does not involve any changes in treatment otherwise, and patients will receive exactly the same follow-up on the ward whether they participate in the study or not.

In the project, we will gather and register some personal information about the patient from their medical record (gender, age, marital status, medications the patient is taking, previous illnesses, etc.). A doctor will also conduct some tests with the patient before and after the

music therapy sessions. The tests will help us see how the patients are before and after the music and how music therapy affects them. Some of the tests will consist of questions that the patient will be asked to answer, while the rest are observations of how the patient is doing, for a few minutes.

We also want to make video recordings of the music therapy sessions. The patient will not be filmed themselves, only the music therapist, but the sound of the patient will be audible. We make the video recordings to evaluate the execution of music therapy itself. Only study personnel will have access to the videos, which are securely stored.

All information we collect about the patient will be anonymized, and only those of us participating in the study will have access to it.

FORESEEABLE BENEFITS AND PREDICTABLE RISKS AND BURDENS OF TAKING PART

It is completely safe for the patient to receive music therapy treatment in this project. We will always ensure that the treatment is conducted on the patient's terms, and that they do not have to listen to the music for too long, especially if they don't feel up to it on a particular day. The music in this project will always be chosen according to the patients' preferences, and we will not force them to listen to anything they do not wish to hear.

One drawback may be that patients might not get to listen to the music for as long as they'd like because we have to follow a plan designed to measure improvement in the patient.

Receiving music therapy will not be demanding, and patients do not need to have prior musical experience to participate. If they enjoy music, that is more than enough.

The experiences from the study will provide us with new and valuable knowledge that we hope can offer both the person you are caring for and future patients with delirium a better and more tailored treatment.

VOLUNTARY PARTICIPATION AND POSSIBILITY TO WITHDRAW YOUR CONSENT

It is voluntary to participate in the project. Since we cannot ask the patient directly about participation in the study at the moment, we ask you as the closest relative to answer what you believe the patient would have answered if he/she were able to. If you do not wish for the patient to participate in the study, you do not need to provide any reason, and there will be no consequences for you or the patient. You will have time to consider, and if you have no objections to the patient participating, you can sign the declaration on the last page.

You can withdraw your consent at any time and without providing any reason. This will not have any consequences for you or the patient's further treatment. If you later wish to withdraw your consent, you can request to have collected information deleted unless the information has already been included in analyses or used in scientific publications.

If you later wish to withdraw your consent or have any questions about the project, you can easily contact project leader Bjørn Erik Neerland, contact information provided below.

WHAT WILL HAPPEN WITH THE PERSONAL DATA CONCERNING HEALTH?

The information recorded about the patient shall only be used as described in the purpose of the project and is planned to be used until 2031. Any extensions in the use and storage period can only occur after approval from the Regional Committees for Medical and Health Research Ethics (REK) and other relevant authorities.

The patient has the right to access the information recorded about him/her and the right to have any errors corrected in the recorded information. The patient also has the right to access the security measures regarding the processing of the information. The patient can complain about the handling of their information to the Norwegian Data Protection Authority (Datatilsynet) and the institution's data protection officer.

All information will be processed without names, social security numbers, or any other directly identifiable information. A code links the patient to their information through a name list. Only personnel responsible for the study have access to this list.

The patient's information will be stored for five years after the project's end for control purposes and then deleted.

INSURANCE

All participants are covered by the general patient insurance schemes, and according to the Patient Injury Act, at Oslo University Hospital.

ETHICAL APPROVAL

The Regional Committee for Medical and Health Research Ethics has evaluated the project and has given preliminary approval xxx xxx. Under the new Personal Data Act, the data controller (Oslo University Hospital, represented by the department head), and the project leader (Bjørn Erik Neerland) have independent responsibility to ensure that the processing of participant information has a legal basis. The study has a legal basis for processing personal and health information under GDPR Article 6(1)(e) and Article 9(2)(j).

The patient has the right to complain about the processing of their information to the Norwegian Data Protection Authority (Datatilsynet).

CONTACT INFORMATION

If you have any questions about the project, you can contact the project leader:

Bjørn Erik Neerland, Geriatrician and Researcher at the Geriatric Department, Oslo University Hospital

Music Therapy and Delirium in Acutely Admitted Elderly Patients. Information Sheet and Declaration from Legal Guardians. Version 1. 08.02.2022.
Phone: 90078979 Email: bjonee@ous-hf.no

If you have any questions about privacy in the project, you can contact the institution's data protection officer: personvern@ous-hf.no

DECLARATION FROM LEGAL REPRESENTATIVES

Relative's name: _____

Patient's name: _____

1. I have no objections to the participation of the person I am a relative of in the study. I am willing to participate in the project with information about the patient.
2. I have no objections to video recording being conducted during the music therapy treatment, as described above.

……

(Signed by the legal representative, Date)

DOCTOR

I confirm that I have provided verbal and written information about the study to the relatives. I personally assess the patient as lacking capacity to consent. The relatives have also been given time for consideration.

Place and Date

Signature

Role in the project

Appendix 3

Diagnostic algorithm for DSM-5 delirium evaluation

<table>
<tr><th>DSM-5 Criteria</th><th>Tests to be performed and information to be collected</th><th colspan="2">Is DSM-criteria fulfilled?</th></tr>
<tr><th></th><th></th><th>YES</th><th>NO</th></tr>
<tr><td>A. Disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment</td><td>
<table>
<tr><th>Evaluation</th><th>Attention-tests</th><th>Cut off (definition of inattention)</th></tr>
<tr><td>Daily</td><td>SAVEAHAART/ KATAMARAAN</td><td>2 or more errors</td></tr>
<tr><td></td><td>Days of the week in reversed order</td><td>Any error</td></tr>
<tr><td></td><td>Months of the year in reverse order</td><td>Unable to reach July</td></tr>
<tr><td></td><td>Count backwards from 20 to 1</td><td>Any error</td></tr>
<tr><td></td><td>Digit span forward</td><td>Less than 5 forward</td></tr>
</table>
<u>Observation:</u>
Easily distracted? Collaborative? Has a tendency to “loose thread” in the conversation?</td><td></td><td></td></tr>
<tr><td></td><td>Arousal: OSLA >3 and/or mRASS other than 0?</td><td></td><td></td></tr>
<tr><td>B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.</td><td>Informant history from patient’s carers and nursing staff. Questions to carer/nursing staff or derived from clinical notes:
➢ Has there been a sudden change in the patient’s mental state?
➢ Does the patient seem to be better at any period in the day compared to other times?
➢ Has the level of consciousness been altered (drowsy/not responsive, or agitated)?
➢ Sleep-wake cycle disturbances?</td><td></td><td></td></tr>
<tr><td>C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).</td><td><u>Questions to the patients:</u>
Orientation-tests: Orientation to time, place and person; Why are you in hospital? Will a stone float in water? Are there fish in the sea? (any error=disorganized thinking)
Recall (3 words)
<u>Questions to carers/nursing staff/clinical notes:</u>
Has there been any…Perceptual disturbances? Sleep-wake cycle disturbances? Memory disturbances? Psychotic episodes? Psychomotor disturbances?</td><td></td><td></td></tr>
<tr><td>D. The disturbances in criteria A and C are not</td><td>Information from history/chart/clinical assessment.</td><td></td><td></td></tr>
</table>

explained by another preexisting, established			
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.			
Delirium, based on the tests and information above?	All DSM-5 criteria are fulfilled		
Subsyndromal delirium, based on the tests and information above?	Defined as evidence of change, in addition to any of the following: (a) altered arousal, (b) attention deficits, (c) other cognitive change, (d) delusions or hallucinations. Criteria D and E must be fulfilled.		

Appendix 4

1: Checklist for treatment fidelity evaluation and intervention manual (PLM)
2: Checklist for treatment fidelity evaluation and intervention manual (PRM)

PREFERRED LIVE MUSIC (PLM)				
Study ID:	**Intervention day:**	**Criteria satisfied**		**Score**
1.	MT delivered the intended minimum dosage (participant was in attendance for 10 min or longer).	YES	NO	
2.	MT used the assessed preference songs in the session. *	YES	NO	
3.	MT presented the preference songs in the same order as intended/planned (relevant for sessions 2 and 3 only)	YES	NO	
4.	MT delivered the intervention by voice only, or voice and accompaniment (e.g. guitar, tone-chimes, percussions).	YES	NO	
5.	MT cued the participant to sing along or move to music, used the elements of improvisation and attunement to the patient. **	YES	NO	
6.	MT had physical (holding hands, stroking, etc.), verbal, or non-verb verbal interaction with the participant (eye-contact, face expressions, smiling).	YES	NO	
			Total:	

Intervention manual:
In PLM intervention music therapist should chose the music for the sessions from patients' assessed preferences and make sure not to change their order of deliverance. MT should enter the room, say hi to the patient, introduce the intervention, and if appropriate, offer the participants small percussion instruments that they can play on during the session. Thereafter MT should deliver the intervention live, by singing/playing the songs either A Capella, or accompanied by a guitar, tone-chimes, or percussion instruments. The intervention may involve interaction with the patients (e.g. physical, musical, verbal), the songs are not expected to be delivered in a way that is identical to their original versions, and elements of improvisation are both allowed and expected, as well as other forms of attunement to the patients. After max. 30 minutes, the MT should collect the instruments, say good bye to the patient, and leave the room.

Instructions for scoring:
YES: I agree with the statement (score 1)
NO: I disagree with the statement (score 0)
NR: Not relevant

* Item 2 is only relevant for sessions 2 and 3 and not relevant for sessions 1. Should be scored as NR.
** Item 5 is related to the presence of improvisation elements, such as repetition, variation, extension, mirroring, matching, imitation, etc. as well as other musical or non-musical elements and forms of attunement to the patient (cuing, humming, whistling, scatting, snapping fingers, laughing together etc. The rater should score YES if there is at least one of the aforementioned elements present, and as long as there is a minimum variation in the performance of the songs compared to the original.

PREFERRED RECORDED MUSIC (PRM)					
Study ID:		**Intervention day:**		**Criteria satisfied:**	**Score**
1.	MT delivered the intended minimum dosage (participant was in attendance for the minimum of 10 min).		YES	NO	
2.	MT used the assessed preference songs in the session. *		YES	NO	
3.	MT presented the preference songs in the same order as intended/planned (relevant for sessions 2 and 3 only).		YES	NO	
4.	MT delivered the intervention by the speaker and Bluetooth musical device.		YES	NO	
5.	MT did not cue the participant to sing along or move to music.		YES	NO	
6.	MT did not have physical (holding hands, stroking, etc.), verbal, or non-verb verbal interaction with the participant (eye-contact, face expressions, smiling etc.).		YES	NO	
				Total:	

Intervention manual:
In the PRM intervention, music therapist (MT) should chose the songs for the sessions from the patients' assessed preferences (and not vary their order each of the three intervention days). MT should enter the participant's room, and after saying hi and shortly introducing the music that will be played, start the music from a musical device and a Bluetooth speaker. MT should refrain from engaging with the patient while the music is played, and any engagement should be registered as the disruption from the protocol. The MT should not engage with the patient neither verbally, non-verbally, physically while the music is played. Any engagement should be registered as the disruption of the protocol. After 30 minutes the MT should stop the music, say good bye to the patient and leave the room.

Instructions for scoring:
YES: I agree with the statement (score 1)
NO: I disagree with the statement (score 0)
NR: Not relevant

*Item 2 was only relevant for sessions 2 and 3. Should be scored as NR for session 1.

Appendix 5

Co-author statement PhD

Norges musikkhøgskole
Norwegian Academy of Music

Medforfattererklæring ph.d. / *Co-author statement PhD*

Kandidat/*Candidate:* Jelena Golubovic

Tittel på avhandlingen/*Title of the dissertation:*
Music Interventions for Delirium in Older Adults

Denne erklæringen gjelder følgende artikkel / *This statement refers to the following article:*
Music Interventions and Delirium in Adults: A Systematic Literature Review and Meta-Analysis

Medforfatter(e)/ *Co-author(s):*
Jelena Golubovic, Bjørn Erik Neerland, Dagfinn Aune, and Felicity A. Baker

Beskrivelse av bidragene / *Description of the contributions:*

J.G. was responsible for the library of references and the uploading process. J.G., F.A.B., and B.E.N. selected the studies for inclusion, and J.G. extracted the data from the included studies. All the decisions concerning screening, inclusion/exclusion, and data extraction were cross-checked with F.A.B. and B.E.N., J.G., F.A.B., and B.E.N. performed the risk of bias assessment, and J.G. calculated interrater reliability. J.G. extracted the data for the meta-analysis and D.A. conducted the meta-analysis. J.G. wrote the first draft of the paper, with contributions from F.A.B., B.E.N. and D.A., who reviewed it and provided feedback. All authors have read and agreed to the published version of the manuscript.

Dato/*Date:* 02/04/2024

Kandidatens signatur /*Candidate's signature:* Jelena Golubovic

Jeg samtykker med dette til at artikkelen kan benyttes i avhandlingen
I hereby agree that the article may be used in the dissertation.

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Medforfattererklæring ph.d. / *Co-author statement PhD*

Kandidat/*Candidate:* Jelena Golubovic

Tittel på avhandlingen/*Title of the dissertation:*
Music Interventions for Delirium in Older Adults

Denne erklæringen gjelder følgende artikkel / *This statement refers to the following article:*
Live and recorded music interventions for management of delirium symptoms in acute geriatric patients: Protocol for a randomized feasibility trial

Medforfatter(e)/ *Co-author(s):*
Jelena Golubovic, Felicity A. Baker, Melanie R. Simpson & Bjørn Erik Neerland

Beskrivelse av bidragene / *Description of the contributions:*

J.G., F.A.B., B.E.N. and, M.R.S. collaborated on developing the pilot and feasibility trial protocol. J.G. and F.A.B. developed the intervention manuals and fidelity evaluation plan, J.G. developed treatment fidelity checklists, B.E.N. created the diagnostic algorithm, and J.G. and M.R.S. designed the statistical analysis plan. J.G. developed the theoretical framework for the interventions and the theoretical rationale for comparison with feedback from F.A.B. J.G. drafted the initial version of the manuscript, and B.E., F.A.B., and M.R.S. oversaw manuscript development by providing feedback and making corrections along the way. M.R.S. contributed significantly to formulating the statistical analysis sections. All the authors have read and agreed to the published version of the manuscript.

Dato/*Date:* 02/04/2024

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Medforfattererklæring ph.d. / *Co-author statement PhD*

Kandidat/*Candidate:* Jelena Golubovic

Tittel på avhandlingen/*Title of the dissertation:*
Music interventions for Delirium in Older Adults

Denne erklæringen gjelder følgende artikkel / *This statement refers to the following article:*
A Randomized Pilot and Feasibility Trial of Live and Recorded Music Interventions for Management of Delirium Symptoms in Acute Geriatric Patients

Medforfatter(e)/ *Co-author(s):*
Jelena Golubovic, Bjørn Erik Neerland, Melanie R. Simpson, Kjersti Johansson, Felicity A. Baker

Beskrivelse av bidragene / *Description of the contributions:*

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, have read the last draft of the manuscript and agree with the findings presented. J.G., B.E.N., F.A.B., and M.R.S. developed the protocol. F.B. generated random allocation sequences, and J.G. randomized the participants, performed the music preference assessments and interventions, and recorded videos for treatment fidelity (TF) evaluation. J.G. monitored the data collection process. J.G. assessed and analysed all the feasibility outcomes. J.G. randomly selected 20% of the participants who completed three sessions and for whom videos were available for TF evaluation using a previously generated randomization sequence. K.J. evaluated video recordings and scored treatment delivery checklists, and J.G. calculated percentages of TF success. J.G. plotted pre-post delirium data in SPSS, M.R.S. converted some of the data to STATA files, and B.E.N. collected and plotted the medical variables from the electronic journals. Based on the collected pre-post intervention data, B.E.N. completed summary evaluations of delirium, and J.G. plotted the new variable into the SPSS files. M.R.S. developed a statistical analysis plan and performed the analyses of the pre-post delirium data (mixed linear regression models); J.G. performed the analysis of all the baseline measures and some of the clinical outcomes (length of hospital stay, medication intake). J.G. wrote the manuscript with F.A.B., B.E.N., M.R.S., and K.J. contributions. All the authors have read and agreed to the version of the manuscript submitted for publication.

Dato/*Date:* 02/04/2024

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Felicity Baker

Delirium is an acute confusional state marked by sudden changes in arousal, attention, cognition, emotions, and psychomotor functions. Factors like old age or dementia combined with acute illness or surgery contribute to delirium's onset. The prognosis for older adults is poor, leading to cognitive decline, worsening of dementia, increased mortality, longer hospital stays, or the need for long-term care. Non-pharmacological, multifactorial approaches, such as music interventions, show promise.

In this dissertation, Golubovic examines the potential of music interventions for managing delirium in older adults through two interconnected substudies, published as three scientific articles. The overarching goal was to generate knowledge for further efficacy testing of music interventions in this population. Substudy 1 was a systematic review synthesizing available evidence, summarizing effect sizes, and detailing research designs, interventions, outcomes, and psychometric tools. Substudy 2 was a pilot and feasibility trial exploring the design and feasibility of two different music interventions for older patients with delirium in an acute geriatric context.

Jelena Golubovic is a pianist, music therapist, and researcher, and the co-leader of NRK's Dementia Choir. Golubovic's formal specialization and clinical experience are in elderly care, with a special focus on dementia, delirium, depression, and agitation in long-term care settings and acute hospital wards.

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