

The development and evaluation of TIME - Targeted Interdisciplinary Model for Treatment and Evaluation of Neuropsychiatric Symptoms

An effectiveness-implementation cluster randomised hybrid trial in nursing homes

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Some problems are so complex that you have to be highly intelligent and well-informed just to be undecided about them.

Laurence J. Peter (Peter's Almanac, entry on September 24, 1982)

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Attachments

Scientific environment

This thesis was conducted between 2015 and 2018. My work with the thesis was related to the Research Centre for Age-Related Functional Decline and Disease (AFS) at the Department of Psychiatry, Innlandet Hospital Trust, and The Institute of Health and Society, Faculty of Medicine, University of Oslo. The initiation and the elaboration of the project were done in cooperation with the Norwegian National Advisory Unit on Ageing and Health. A three-months period in 2018 was spent collaborating with researchers and clinicians at the Memory Clinic and Research Centre of Lyon, Hospital of Charpennes, University Hospital of Lyon, and the Memory Clinic and Research Centre of Saint Etienne, Neurological Unit, University Hospital of Saint Etienne in France.

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Abstract

This thesis describes the development and the evaluation of TIME, the Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms. TIME is a multicomponent, biopsychosocial and interdisciplinary model to be used by the staff and the nursing homes physician in their approach to neuropsychiatric symptoms (NPS) in dementia. Nearly all persons with dementia will develop some type of NPS like agitation, aggression, anxiety, depression, psychosis and apathy. The prevalence of at least one clinically significant neuropsychiatric symptom (i.e. a score of 4 or higher on the Neuropsychiatric Inventory, Nursing Home Version) is approximately 75% for persons with dementia living in nursing homes in Norway, making them one of the major challenges for the nursing home staff.

NPS can be characterised as complex problems because of their biopsychosocial nature with multiple interactive causes and their instability. In addition, the nursing homes (NH) represent complex systems with different stakeholders. These features suggest that the approach to NPS must be comprehensive, biopsychosocial, and interdisciplinary, and that the approach must be flexible and tailored to the individual resident and the context.

Of the NPS, agitation represents the most frequent and persistent symptoms. Although there is no general agreement on the definition, agitation is usually conceived as behaviour characterised by verbal and physical aggression and excessive motor activity consistent with emotional distress for the person. Agitation results in distress for the residents and their caregivers and is associated with reduced quality of life, institutionalisation, referral to specialist health care and hospitalisation, and a more rapid progression toward severe dementia and death. The prescription rate of psychotropic drugs is high in NH, even if the effects of these drugs for agitation is modest, and their use is associated with major side effects. Although there is conflicting evidence about non-pharmacological interventions for agitation, they are nevertheless recommended in most treatment guidelines as a first-line approach. Thus, safe, effective, and evidence-based approaches targeting agitation in dementia are needed. Such approaches should enable the simple implementation of these recommendations and guidelines in real-world settings.

There is emerging evidence that systematic approaches for agitation using training and supervision of the staff, can have beneficial effects for residents and reduce staff burden. Only a few studies have assessed in depth the staff's experiences of the interventions, but their experiences are important for further dissemination of the interventions. Such in-depth evaluations also have the potential to contribute to causal assumptions on the effectiveness of the interventions. The disadvantage of many of these interventions is that they require a good deal of support from external experts and long-lasting training to ensure implementation. A thorough and detailed description of the interventions and the strategies used for implementation is, therefore, mandatory for others to be able to judge on the interventions' applicability to real-world clinical settings. This can be achieved by performing a systematic process-evaluation alongside a clinical randomised controlled trial. A process

evaluation will also provide valuable information on how to obtain an effective and sustainable implementation.

Aims of the thesis

To address the challenges outlined above, the overarching aim was to describe the development and the evaluation of a Norwegian interdisciplinary model for the assessment and treatment of NPS, TIME. We proposed four single aims:

1. To describe the development of TIME from the conception of the idea of the model to a fully developed testable model. In Paper 1, we described the different components of TIME, and the overall study design of an effectiveness-implementation cluster randomised hybrid trial.
2. To test the hypothesis that TIME could reduce agitation in residents with dementia and moderate to severe agitation living in NH, compared to a control condition consisting of usual care supplemented with a brief educational intervention (Paper 2).
3. To explore in depth the experiences of the staff using TIME in their approach to agitation, with an emphasis on their learning and coping experiences at work (Paper 3).
4. To perform a process-evaluation of the implementation of TIME with an emphasis on facilitators and barriers to the implementation and on possible causal assumptions of the effects of TIME at the residential level (Paper 4).

Methods and results

TIME was developed in 2007-2009 by the author of this thesis in cooperation with the leading ward nurse in a nursing home in the municipality of Rana. The elaboration was a result of a perceived need in the nursing homes for a practical tool for the translation of existing international recommendations for the assessment and the treatment of NPS to their context and their reality. A pilot study was conducted in 2010 by the Centre for Old Age Psychiatric Research, Innlandet Hospital Trust in nine nursing homes, and demonstrated the model's feasibility. The results from this pilot study formed the basis for a revision of the TIME manual and a web-accessible educational film.

TIME is based on the theoretical framework of cognitive behavioural therapy and person-centred care. TIME consists of three overlapping phases: a registration and assessment phase; a guided reflection phase, including one or more case conferences; and an action and evaluation phase. As the actions and treatment measures are supposed to be tailored to each resident, they will display great variations between residents. In this way, TIME serves as a guide for the staff to create actions and treatment measures that are person-centred. These three phases are in line with reviews describing "state-of-the-art" of the management of NPS.

To test the effectiveness of TIME at the resident level and explore the implementation, we chose to perform an effectiveness-implementation cluster randomised hybrid trial. This design combines clinical effectiveness and implementation outcomes in one trial. The main

advantage of the hybrid design is that it can accelerate the translation of research findings into routine practice.

We hypothesised that TIME could reduce agitation in residents with dementia and moderate to severe agitation living in nursing homes, compared to a control condition consisting of usual care supplemented with the education-only intervention. A single-blinded, cluster randomised controlled trial (RCT) in 33 nursing homes (clusters) from 20 municipalities in Norway was conducted to test the effectiveness of TIME. The RCT was conducted from January 2016 to the end of June 2016. In total, 229 residents, 104 residents in 17 NH and 125 residents in 16 NH, were randomised to the intervention or control group, respectively.

The staff in both the intervention nursing homes (INH) and the control nursing homes (CNH) were given a two hour lecture covering dementia and NPS. This lecture represented the education-only intervention for the CNH. The staff in the INH were offered a one-day training programme in TIME with the purpose to implement TIME in the NH.

The primary outcome was the between-group difference in change in the agitation/aggression item of the Neuropsychiatric Inventory Nursing Home (NPI-NH) version between baseline and eight weeks. Secondary outcomes were the between-group difference in change in the same single item between baseline and 12 weeks, in change in agitation measured by the Cohen-Mansfield Agitation Inventory (CMAI) and in change in other NPS, quality of life, and use of psychotropic and analgesic medications between baseline and eight and 12 weeks.

In total, 202 residents (88.2%) and 32 NH (97%) completed the study and the final analysis. For the primary outcome, a significant between-group difference in reduction of agitation at eight weeks (1.1; 95% confidence interval (CI) 0.1 to 2.1; $P=0.031$) in the favour of the TIME intervention was found. For the secondary outcomes a significant between-group difference in reduction of agitation at 12 weeks (1.6; 95% CI 0.6 to 2.7; $P=0.002$) in favour of the TIME intervention was found. In addition, agitation measured by the CMAI at eight and twelve weeks, symptoms of delusions at eight weeks, and depression, disinhibition, and quality of life at 12 weeks, showed significant between-group differences in favour of the intervention group.

To explore the staff's experiences with TIME and how the model meets the challenges when dealing with the complexity of NPS, we used a qualitative explorative design with five focus group interviews. This study was conducted three to six months after the RCT was completed. In these focus groups, we interviewed 32 of the caregivers, leaders and physicians participating in the INH in trial. For the analysis, we used the thematic content analysis, and our approach was mainly inductive and data-driven.

The analysis yielded two main themes: (1) a systematic reflection method enhanced learning at work; (2) the structure of the approach helped staff to cope with NPS in residents with dementia. These results indicated that TIME shifts the way of learning for the staff from a traditional to a more innovative and reflection-based learning through a process of learning

how to learn at work. In addition, the staff experienced increased coping in their approach to complex problems. The third theme that was discussed concerning the implementation process was analysed as a part of the process evaluation in the fourth paper.

To perform a process evaluation on the implementation we used an exploratory and a quasi-experimental design with mixed methods based on the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, Maintenance). The RE-AIM dimensions were explored by questionnaires to 807 staff members and 46 leaders in both INH and the CNH. They were distributed before the start of the intervention (baseline measurements in the RCT), and six and 12 months later. To assess the implementation, we used a checklist for the performance of the main components in TIME and analysed the minutes from 84 case conferences in the INH. To explore the adoption and maintenance, we analysed the results from the five focus group interviews described above.

For the five RE-AIM dimensions, we found a high degree of reach, adoption, implementation, and maintenance in the INH that might have contributed to the effectiveness of TIME at the resident level. There were, however, no between-group differences between the INH and the CNH throughout the study period for the measurements of effectiveness at the staff level. An easy-to-grasp model and an engaged and present leadership facilitated the intervention and its sustainability. Another causal assumption of the effectiveness of TIME is the development in the staff of a new, shared and situated knowledge about each individual resident, which is not reflected by measurements in general knowledge and attitudes. This assumption is supported by the results on the staff's learning and coping experiences from the interviews in the focus groups.

Conclusion

In conclusion, our results show that TIME is a feasible and effective model for reducing agitation in persons with dementia living in NH. The staff experienced increased coping, and a new learning process when approaching the complexity of agitation. Our results emphasise the importance of a structured and biopsychosocial approach to agitation in clinical practice. Future research should explore models for integrating situated learning in the daily routines in NH. Methods for assessing how general knowledge and attitudes are translated into an every-day approach for each individual resident should be developed and evaluated. This research should aim for a more active involvement of the field of practice in developing and implementing new knowledge.

Sammendrag

Denne avhandlingen beskriver utviklingen og evalueringen av TID, Tverrfaglig Intervensjonsmodell ved utfordrende atferd ved Demens (eng. TIME). TID er en multikomponent, biopsykososial og tverrfaglig modell for personalet og lege i sykehjem til bruk i deres tilnærming til nevropsykiatriske symptomer (NPS) ved demens. Nesten alle personer med demens utvikler en eller annen form for NPS som agitasjon, aggresjon, angst, depresjon, psykose og apati. Forekomsten av minst et klinisk betydningsfullt NPS (dvs. en skår på 4 eller høyere på Nevropsykiatrisk intervjuguide, sykehjemsversjonen) er ca. 75% for personer med demens som bor i sykehjem. Dette gjør NPS til en av de største utfordringene for sykehjempersonalet.

NPS kan karakteriseres som komplekse problemer på grunn av symptomenes bio-psykososiale natur med flere interaktive årsaker og deres ustabilitet. I tillegg representerer sykehjemmene komplekse systemer med mange involverte parter. Disse kjennetegnene innebærer at tilnærmingen til NPS bør være bred, bio-psykososial og tverrfaglig, og den bør i tillegg være fleksibel og skreddersydd til den enkelte beboer og konteksten. Av de ulike NPS er agitasjon av de hyppigste og mest persisterende symptomene. Selv om det ikke foreligger noen generell enighet om definisjonen blir agitasjon vanligvis beskrevet som en atferd som inkluderer både verbal og fysisk aggresjon samt uttalt motorisk aktivitet forenelig med emosjonelt ubehag for personen. Agitasjon medfører ubehag for både personen selv og omsorgsgivere, og er assosiert med redusert livskvalitet, institusjonalisering, henvisning til spesialisthelsetjenesten, sykehusinnleggelse, en raskere progresjon av demenstilstanden og tidligere død. Forskrivningen av psykofarmaka er høy i sykehjem til tross for at effekten av psykofarmaka mot agitasjon er beskjeden, og bruken er assosiert med alvorlige bivirkninger. Selv om det er motstridende resultater fra forskning om ikke-farmakologiske intervensjoner, er de likevel anbefalt som førstevalg i de fleste behandlingsretningslinjer. Således er det behov for sikre, effektive og evidensbaserte tilnærminger rettet mot agitasjon ved demens. Slike tilnærminger bør kunne bidra til at retningslinjer og anbefalinger lett lar seg implementere i klinisk praksis.

Ny forskning tyder på at systematisk tilnærming til agitasjon ved opplæring, trening og veiledning av personalet, kan gi god effekt for beboerne og redusere belastningen for personalet. Selv om personalets erfaringer er viktige for å lykkes med å implementere og spre intervensjonene, har bare et fåtalls studier utført evalueringer av disse erfaringene. Slike grundige evalueringer har også potensialet i seg til å bidra til å belyse antatte årsakssammenhenger for effekten av intervensjonene. Ulempen med flere av intervensjonene er at de krever mye støtte fra eksterne spesialister og langvarig opplæring for å sikre implementering. En grundig og detaljert beskrivelse av intervensjonene og strategiene som anvendes for implementeringen er derfor avgjørende for at andre skal kunne vurdere intervensjonens anvendbarhet i vanlig klinisk praksis. Dette kan oppnås ved å gjennomføre en systematisk prosessevaluering ved siden av en randomisert kontrollert

studie. En slik prosessevaluering vil også kunne bidra med verdifull informasjon om hvordan en kan oppnå en effektiv og varig implementering.

Formålet med avhandlingen

For å i imøtekomme de overnevnte utfordringene, var den overordna målsettingen å beskrive utviklingen og evalueringen av en norsk tverrfaglig modell for utredning og behandling av NPS, TID. Vi formulerte følgende fire delmål:

1. Å beskrive utviklingen av TID, og det overordna stuedesignet for en effektivitet-implementerings og klyngerandomisert hybrid studie (artikkel 1).
2. Å teste hypotesen om at TID kan redusere agitasjon hos sykehjemsbeboere med demens og moderat til alvorlig agitasjon (artikkel 2).
3. Å utforske personalets erfaringer med TID i deres tilnærming til agitasjon med vekt på deres lærings- og mestringserfaringer på arbeidsplassen (artikkel 3).
4. Å gjennomføre en prosessevaluering av implementeringen av TID med vekt på faktorer som fremmer og hemmer implementeringen og på mulige kausale antagelser om effekten av TID på beboernivå (artikkel 4).

Metoder og resultater

TID ble utviklet i årene 2007 til 2009 av forfatteren av denne avhandlingen i samarbeid med sykepleier og avdelingsleder ved et sykehjem i Rana kommune. Utviklingen var et resultat av et opplevd behov i sykehjemmene for et praktisk verktøy som kunne overføre eksisterende anbefalinger for utredning og behandling av NPS til sykehjemmenes kontekst og virkelighet. En pilotstudie ble gjennomført i 2010 ved Forskningscenteret for Aldersrelatert Funksjonssvikt og Sykdom (AFS), Sykehuset Innlandet, i ni sykehjem, og dokumenterte gjennomførbarheten av modellen. Resultatene fra pilotstudien danner grunnlaget for en revisjon av TID-manualen og utviklingen av en opplæringsfilm tilgjengelig via internett.

TID er basert på det teoretiske rammeverket til kognitiv terapi og personsentrert omsorg. TID består av tre overlappende faser: en registrering- og utredningsfase, en refleksjon- og veiledningsfase som inneholder ett eller flere refleksjonsmøter, og en tiltak- og evalueringsfase. Siden tiltakene og behandlingen er forutsatt skreddersydd til den enkelte beboer, vil de variere fra person til person. På denne måten blir TID en guide for personalet for å skape tiltak og behandling som er personsentrerte. De tre fasene er i overensstemmelse med det som i dag beskrives som «state of the art» i tilnærmingen til NPS.

For å teste effekten av TID for sykehjemsbeboerne og for å studere selve implementeringsprosessen valgte vi å utføre en effektivitet-implementering- og klynge randomisert hybrid studie. Dette designet kombinerer kliniske effektivitet- og implementeringsmål i en og samme studie. Den viktigste fordelen med hybrid-designet er at den kan bidra til at overføringen av forskningsfunn til klinisk praksis går raskere. Vår hypotese var at TID kunne redusere agitasjon hos sykehjemsbeboere med demens og moderat til alvorlig agitasjon sammenlignet med en kontrollgruppe av sykehjemsbeboere der personalet mottok en enkel undervisningsintervensjon. En enkelblindet,

klyngerandomisert kontrollert studie (RCT) i 33 sykehjem (klynger) fra 20 kommuner i Norge ble gjennomført for å teste effekten av TID. RCT-en ble gjennomført fra januar 2016 til slutten av juni 2016. Totalt ble 229 beboere, 104 beboere i 17 sykehjem og 125 beboere i 16 sykehjem, randomisert til henholdsvis intervensjonsgruppa eller kontrollgruppa. Personalet i både intervensjonssykehjemmene (ISH) og i kontrollsykehjemmene (KSH) mottok en to timers forelesning om demens og NPS. Denne forelesningen representerte den enkle undervisningsintervensjonen for KSH. Personalet i ISH mottok i tillegg et heldags opplæringsprogram om TID med formålet å implementere TID i sykehjemmene.

Det primære effektmålet var forskjellen mellom de to gruppene i endring i symptomene agitasjon/aggresjon i nevropsykiatrisk intervjuguide (NPI-NH) fra baseline til åtte uker. Sekundære effektmål var forskjellen mellom de to gruppene i endring av samme symptomer mellom baseline og 12 uker, i endringer i agitasjon målt med Cohen-Mansfield Agitation Inventory (CMAI) og i endringer i andre NPS, livskvalitet, og bruk av psykofarmaka og analgetika mellom baseline og åtte og 12 uker. 205 beboere (88,2%) og 32 sykehjem (97%) fullførte studien og siste analyser. For det primære effektmålet ble det funnet en signifikant forskjell mellom gruppene i reduksjon av agitasjon/aggresjon ved åtte uker (1,1; 95% konfidensintervall (CI) 0,1 til 2,1; $P=0,031$) til fordel for intervensjonen med TID. For de sekundære effektmålene ble det funnet en signifikant forskjell mellom gruppene i reduksjon av agitasjon/aggresjon målt med NPI-NH ved 12 uker (1,6; 95% CI 0,6 til 2,7; $P=0,002$) til fordel for intervensjonen med TID. I tillegg viste målingene av agitasjon med bruk av CMAI ved åtte og 12 uker, av vrangforestillinger ved åtte uker, og depresjon, manglende hemninger og livskvalitet ved 12 uker, en signifikant forskjell i endring mellom gruppene til fordel for intervensjonsgruppa.

For å utforske personalets erfaringer med TID og hvordan TID håndterer utfordringene med kompleksiteten til NPS valgte vi et kvalitativt eksplorerende design med fem fokusgruppeintervjuer. Denne studien ble gjennomført tre til seks måneder etter at RCT-en var avsluttet. I disse fokusgruppene intervjuet vi 32 pleiere, ledere og leger som deltok i studien fra ISH. For analysen anvendte vi tematisk innholdsanalyse, og vår tilnærming var hovedsakelig induktiv og datadrevet. Analysen avdekket to hovedtemaer: (1) en systematisk refleksjonsmetode øker læring på arbeidsplassen; (2) strukturen i tilnærmingen hjelper personalet til å mestre NPS hos beboere med demens. Disse resultatene tyder på at TID endrer måten personalet lærer på fra en tradisjonell til en mer innovativ og refleksjonsbasert læring gjennom en prosess for å lære hvordan å lære på arbeid. I tillegg erfarte personalet økt mestring i tilnærmingen til komplekse problemer. Et tredje tema som ble drøftet og som omhandlet implementeringsprosessen ble analysert som en del av prosessevalueringen i den fjerde artikkelen.

For å gjennomføre en prosessevaluering av implementeringen anvendte vi en eksplorativ og kvasi-eksperimentell design med «mixed methods» basert på rammeverket RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance). Dimensjonene i RE-AIM ble undersøkt med spørreskjemaer fra 807 av personalet og fra 46 ledere i både ISH og KSH. Spørreskjemaene ble sendt ut før oppstart av intervensjonen (baselinemålinger i RCT-en), og seks og tolv måneder etter. For å undersøke «implementation», anvendte vi en sjekklister for

gjennomføringen av hovedkomponentene i TID og analyserte referatene fra 84 refleksjonsmøter i ISH. Vi undersøkte «adoption» og «maintenance» ved å analysere resultatene fra de fem fokusgruppene som beskrevet over. For de fem RE-AIM dimensjonene fant vi en høy grad av «reach», «adoption», «implementation» og «maintenance» som kan ha bidratt til effekten av TID på beboernivå. Derimot var det ingen forskjell mellom gruppene gjennom studieperioden for målingene av effekt på personalnivå. En lett begripelig modell og en engasjert og tilstedeværende ledelse fremmet implementeringen av intervensjonen og varigheten av den. En annen mulig årsakssammenheng for effekten av TID er utviklingen hos personalet av en ny, delt og situert kunnskap om den enkelte beboer, og som ikke reflekteres i målinger av generell kunnskap og holdninger. Denne antakelsen støttes av resultatene fra personalets læring- og mestringserfaringer som framkommer i fokusgruppeintervjuene.

Konklusjon

For å konkludere viser våre funn at TID er en gjennomførbar og effektiv modell for å redusere agitasjon hos sykehjemsbeboere med demens. Personalet erfarer økt mestring og en ny læringsprosess i tilnærmingen til kompleksiteten av agitasjon. Våre resultater understreker betydningen av en strukturert og biopsykososial tilnærming til agitasjon i klinisk praksis. Framtidig forskning bør utforske modeller for å integrere situert læring i de daglige rutinene i sykehjemmene. Det bør utvikles metoder for å evaluere hvordan generell kunnskap og generelle holdninger overføres i den daglige tilnærmingen til den enkelte beboer. Slik forskning bør i større grad enn i dag inkludere praksisfeltet i både utvikling, og implementering av ny kunnskap.

List of papers

1. Lichtwarck B, Selbæk G, Kirkevold Ø, Rokstad AMM, Benth JS, Myhre J, Nybakken S, Bergh S. TIME-Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms: protocol for an effectiveness-implementation cluster randomised hybrid trial. *BMC Psychiatry*. 2016; 16(233):1-12.
2. Lichtwarck B, Selbæk G, Kirkevold Ø, Rokstad AMM, Benth JS, Lindstrøm JC, Bergh S. Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms: A Cluster Randomised Controlled Trial. *The American Journal of Geriatric Psychiatry*. 2018; 26(1):25-38.
3. Lichtwarck B, Myhre J, Goyal AR, Rokstad AMM, Selbæk G, Kirkevold Ø, Bergh S. Experiences of NH staff using the Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) – a qualitative study. *Aging & Mental Health*. 2018; 1-10.<https://doi.org/10.1080/13607863.2018.1464116>
4. Lichtwarck B, Myhre J, Selbæk G, Kirkevold Ø, Rokstad AMM, Benth JS, Bergh S. TIME to reduce agitation in persons with dementia in nursing homes. A RE-AIM based process evaluation of a complex intervention (submitted).

Abbreviations

AD Alzheimer's disease

ADL activities of daily living

ADQ Approach to Dementia Questionnaire

AHRQ Agency for Health Research and Quality

ARD alcohol-related dementia

BARS Brief Agitation Rating scale

BPSD behavioural and psychological symptoms in dementia

CBT cognitive behavioural therapy

CDR Clinical Dementia Rating Scale

CI Confidence Interval

CMAI Cohen-Mansfield Agitation Inventory

CNH control nursing home(s)

CSDD Cornell Scale for Depression in Dementia

CVD cerebrovascular disease

DCM dementia care mapping

DLB dementia with Lewy bodies

DSM Diagnostic and Statistical Manual of Mental Disorders

FTD frontotemporal dementia

IADL Instrumental Activities of Daily Living Scale

ICC intra-class correlation coefficient

ICD International Classification of Diseases and Related Health Problems

INH intervention nursing home(s)

IPA International Psychogeriatric Association

ISH intervensjonssykehjem

KSH kontrollsykehjem

MCI mild cognitive impairment

MCID minimal clinically important difference

MMSE Mini-Mental State Examination

MRC Medical Research Council

NH nursing home(s)
NPI-NH Neuropsychiatric Inventory Nursing Home Version
NPI-C Neuropsychiatric Inventory Clinician
NPI-Q Neuropsychiatric Inventory Questionnaire
NPS neuropsychiatric symptoms
NS non-significant
OR Odd's ratio
PCC person-centred care
PDD Parkinson's disease with dementia
PSMS Personal Self-Maintenance Scale
QPS-Nordic General Nordic Questionnaire for Psychological and Social Factors at Work
QUALID Quality of Life in Late-Stage Dementia Scale
RCT randomised controlled trial
RE-AIM reach effectiveness adoption implementation maintenance
RU regular unit(s)
SCU special care unit(s)
SD standard deviation
SMD standardised mean difference
SES standardised effect size
SMART Specific Measurable Actual Realistic Time framed
TID Tverrfaglig Intervensjonsmodell ved utfordrende atferd ved Demens
TIME Targeted Intervention Model for Evaluation and Treatment of Neuropsychiatric Symptoms.
UD unspecified dementia
VAD vascular dementia
VIPS value individualised perspective social
WHO World Health Organisation
VPM VIPS practice model

1.0 Introduction

In Norway, approximately 39,600 persons live in NH (1). The mean age of NH residents in Norway is 85 years, and residents usually have several chronic diseases that require continuous treatment (2, 3). About 84% of NH residents in long term care facilities have dementia (3). Nearly 75% of persons with dementia in these NH facilities exhibit clinically significant neuropsychiatric symptoms (NPS), also labelled as behavioural and psychological symptoms of dementia (BPSD), such as psychosis, depression, anxiety, agitation, and apathy (4). Nearly all persons with dementia will experience NPS during the disease course (4-6). Clinically significant NPS are often defined as a score of 4 or more on the Neuropsychiatric Inventory Nursing Home Version (NPI-NH) (7).

NPS are usually conceived as having multiple causes that have the possibility to interact with each other (8, 9). The causes can be attributed to person factors like the neurological changes in the brain and premorbid personality, unmet needs and acute or chronic medical conditions. They can be attributed to the environmental factors, such as over- and understimulation, noisy and complex environments and to caregiver factors such as communication issues, lack of knowledge, and mismatch between expectations and dementia severity (8). In an individual person, it might be difficult to determine which factors are important. All these characteristics make NPS qualify as complex or so-called wicked problems (10). In addition to the complexity of the symptoms, there is a dual complexity because NH can be regarded as complex systems mainly because they consist of different stakeholders, such as professionals, leaders, residents and their relatives in constant interaction (11-13). In summary, these features suggest that the approach to NPS must be comprehensive, interdisciplinary and biopsychosocial, and that treatment measures must be flexible and tailored to the individual resident (14-16).

Agitation, defined as a group of symptoms including verbal and physical aggression and excessive motor activity consistent with emotional distress for the person, is one of the most frequent and persistent of the NPS (5, 6, 17). Agitation is associated with increased patient suffering, reduced quality of life and a more rapid progression toward severe dementia and death, and it is a predictor of referral to specialist health care and institutionalisation (18-20). These symptoms also create a great burden and distress for caregivers and families (21).

Although there is conflicting evidence about their effectiveness, nonpharmacological interventions are recommended as a first-line approach for agitation (15). Psychotropic drugs are associated with serious side effects and safety concerns, and their effects are, at best, modest (22), yet their use is frequent in NH (23, 24). A systematic review by Livingston et al.(2014) concluded that behavioural therapeutic techniques and psychoeducation aimed at altering the caregiver's behaviour seemed to reduce NPS (25). However, the findings regarding other types of treatment were inconclusive and inadequately documented. A systematic review and meta-analysis of nonpharmacological interventions for agitation and

aggression in dementia, published by the Agency for Healthcare Research and Quality in 2016, concluded that the evidence is weak because of methodological limitations. When evidence was sufficient to draw conclusions, the outcomes at the resident level showed no difference between intervention and control groups (26). A disadvantage of many of these interventions is that they are poorly adapted to the conditions in the NH, and they often require a substantial amount of additional resources to NH to be implemented successfully (27). Multicomponent models targeting agitation in dementia that enable simple implementation of evidence-informed recommendations in real-world settings are therefore beneficial (15).

As a response to some of these challenges, The Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) was developed by the author of this thesis, in cooperation with his co-workers in a NH in 2007-2009. TIME represents a biopsychosocial approach and is a multicomponent intervention for NH staff and physicians, based on the theoretical framework of cognitive behavioural therapy (CBT) and person-centred care (28). A pilot study conducted in 2010 in nine NH demonstrated the model's feasibility and formed the basis for a revision of the intervention strategies and the TIME manual (29).

This thesis describes the development of TIME and the testing in a cluster randomised controlled trial of the model's effectiveness to reduce agitation in residents with dementia living in NH. The thesis also reports from the parallel exploratory and quasi-experimental process evaluation of the intervention, to ease further replication and dissemination of the model and clarify possible causal assumptions of its effectiveness.

2.0 Background

2.1 The dementia syndrome

Dementia can be defined as a clinical syndrome characterised by cognitive impairment, usually of a chronic and progressive nature, and caused by various brain diseases (30) . Consciousness is usually preserved. These brain diseases should also cause a reduction in the person's ability to perform activities of daily life compared to a previous level, as well as deterioration in the control of emotion, social behaviour or motivation. Usually the first cognitive domain to be affected is memory, whereas other cognitive domains such as executive functions, orientation, language, calculation, learning capacity and judgement become affected gradually (31, 32).

Tables 1 and 2 present the criteria for the dementia syndrome according to the International Classification of Diseases and Related Health, 10th revision (ICD-10) (31), and the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (32). The two sets of criteria do not differ much, especially not for clinical purposes. In the DSM-5, the term "neurocognitive disorder" is introduced where "major cognitive disorder" is equivalent to dementia in the ICD-10, and "mild neurocognitive disorder" is comparable to mild cognitive impairment (MCI) in the most frequently used definitions of MCI (33). It is, however, noteworthy that the DSM-5 criteria do not require the presence of memory impairment as a part of the cognitive decline, thus broadening the concept of dementia to disorders where the initial symptoms do not encompass memory impairment. Another clarification in the DSM-5 in contrast to the ICD-10 is that the criterion for a need for assistance in everyday activities caused by the cognitive decline could, as a minimum, be accounted for by assistance with complex instrumental activities like paying bills or managing medication. In June 2018, the ICD-11 for Mortality and Morbidity Statistics (ICD-11 MMS) 2018 version was published (34). The ICD-11 MMS introduces the term neurocognitive disorders for the dementia disorders without omitting the term dementia and introduces the term mild neurocognitive disorder for MCI. The criteria for the dementia syndrome in ICD-11 MMS is more in line with the DSM-5 criteria. As in the DSM-5, the criteria for the dementia syndrome in the ICD-11 MMS have no absolute requirement of a cognitive decline in memory. The requirements of a symptom duration of at least six months of, preserved consciousness and impairment in emotional control, motivation and social behaviour have also been abandoned in the ICD-11 MMS (34).

In the context of this thesis where one of the main concerns is how the interpretation of the symptoms of dementia can have a detrimental impact on the care that is offered to people with dementia, it is noteworthy that these descriptive criteria implicitly introduce the clinical features of the syndrome as a direct consequence of the various brain disorders. I will discuss this issue later in Chapter 2.4., when introducing the concept of a biopsychosocial understanding of the neuropsychiatric symptoms in dementia.

Table 1. Dementia according to ICD-10 research criteria (summarised)

1. A decline in memory, especially for new information, objectively verified
2. A decline in other cognitive abilities such as judgment, thinking, planning, organising, and abstraction: <ul style="list-style-type: none">- Mild: the decline influences the activities of daily living- Moderate: the decline makes it impossible to function without help- Severe: the decline results in the need for continuous help
3. Preserved awareness of the environment (consciousness not clouded)
4. A decline in emotional control or motivation or a change in social behaviour: <ul style="list-style-type: none">- Emotional lability- Irritability- Apathy- Coarsening of social behaviour
5. The condition should have been present for at least six months.

Notes: ICD-10: *International Classification of Diseases and Related Health Problems, 10th revision (31)*

Table 2. Diagnostic criteria for Mild and Major Neurocognitive Disorder (NCD) according to the DSM-5 (summarised)

1. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor or social cognition) based on: <ul style="list-style-type: none">a. Concerns related to a significant decline in cognitive function, andb. A documented substantial (major NCD) or modest (mild NCD) impairment in cognitive performance.
2. Cognitive decline that interferes with one's independence in everyday activities.
3. The cognitive decline does not occur exclusively in the context of delirium.
4. The cognitive deficits cannot be explained by another mental disorder.

Notes: DSM-5: *Diagnostic and Statistical Manual of Mental Disorders, 5th edition (32)*

The most prevalent of the degenerative dementia disorders is Alzheimer's disease (AD), which accounts for approximately 60% of the persons with dementia (35-37). Of the other degenerative dementias, Dementia with Lewy bodies (DLB) accounts for 15-20% (36, 37), Parkinson's disease with dementia (PDD) for approximately 5%, and frontotemporal dementia (FTD) 2-4% (35-37). Of the secondary dementia disorders, vascular dementia (VAD) is the most common, which accounts for 20-25% of the persons with dementia (35, 37). Another important secondary dementia is dementia due to excessive alcohol consumption, often labelled alcohol related dementia (ARD) which is part of the spectrum of alcohol-related brain damage (38). Due to the lack of a consensus of diagnostic criteria the prevalence estimates of ARD vary in the literature. In a hospital-based population ARD was found in 1.4% of the patients with diagnosed dementia and in 22% of dementia patients under 65 years (39).

The clinical features of the different types of dementia are most pronounced in the beginning of the disorder. During the progression of the brain disorders with a more extensive involvement of neuronal degeneration, their clinical characteristics tend to be

more homogenous, and it becomes harder to differentiate between them based on their clinical characteristics (37). This is also the case for the expression of the NPS (5).

2.2 Prevalence of dementia

The estimated population of persons with dementia worldwide was 47 million in 2015 (40). This number is expected to double every 20 years, and is estimated to reach almost 132 million in 2050 (40). The number of persons with dementia in Norway is estimated to be approximately 79,000 (41). Since there are no Norwegian studies on the prevalence or incidence of dementia, this number is estimated based on data from the World Alzheimer Report 2015 from Alzheimer's Disease International (40). As in the rest of the world, due to the change in the demographic composition of the population with a growing number of older people, this figure is estimated to rise to 112,000 in 2030 and 176,000 in 2050 (41). Even though many recent reports have estimated a decrease in the incidence in dementia (42, 43), this change in the demographic distribution will undoubtedly create heavy demands on health and care services. An important consequence of this demographic change is the rise of the number of people with multimorbidity (i.e. two or more long term conditions) (44). One approach, amongst others, to address these changes is to create interdisciplinary care programmes that are both evidence-based and biopsychosocial at their core and easy to implement on a large scale in primary care settings without an extensive demand of new resources. The greatest burden will undoubtedly be placed on primary health care services because of the chronic characteristics of many diseases in the elderly, where dementia is one of the most prevalent (45). A newly published report estimated that the number of older people with four or more chronic diseases will double within the next 20 years, and a third of these people will have dementia, depression or a cognitive impairment (44). Multimorbidity including dementia will be a huge challenge for health and care services worldwide over the next 20 years (46).

2.3 Symptoms of dementia

Symptoms of dementia can be divided into four main domains: symptoms of cognitive decline, decline in the ability to perform activities of daily living (ADL), neuropsychiatric symptoms (NPS) and physical symptoms from motor impairment (47).

In the dementia syndrome, a decline in most cognitive symptoms can be observed, although a deterioration of memory is the hallmark of dementia and often one of the first symptoms detected, except for frontotemporal dementia (48, 49). Other cognitive functions affected during the course of the syndrome are orientation, reasoning, spatial orientation, language and executive function (37). There are some differences in the cognitive profile of the dementia disorders, and this is, as mentioned earlier, most pronounced in the first phase of the disorders. AD usually involves a broad spectrum of declining cognitive functions, with

memory often as the first one to be detected. In FTD and ARD, language and executive dysfunction are often the most apparent cognitive symptoms. In DLB and PD, spatial and executive dysfunction are most prominent, and in VAD, a more narrow spectrum of symptoms of cognitive decline often tend to be noted depending on the extent and the part of the brain affected by vascular degeneration (37).

A decline in the ability to perform activities of daily life (ADL) is included in the diagnostic criteria for both ICD-10 and DSM-5 (31, 32). Usually, the functional decline follows the decline in cognitive functions, but with great variations between individuals. Since many dementia disorders develop insidiously, the first symptoms of decline in ADL can be difficult to detect and can easily be misinterpreted as a consequence of normal aging. This is often the case for instrumental activities of daily living (IADL), like taking care of personal economic matters, using new technical devices and administering one's own medication. As mentioned before, this aspect of a decline in the abilities to perform complex instrumental activities, is included in the DSM-5 criteria for dementia. As the disorders progress the functional decline becomes more apparent and will display as a decline in more basic personal activities of daily living (PADL), like the ability to get dressed appropriately, prepare meals, take care of personal hygiene, and to perform toilet activities (37).

Physical symptoms from motor impairment are experienced by nearly all persons with dementia, at least in severe stages of the disorder (37). These symptoms include among others, walking difficulties, postural instability, bradykinesia, impaired co-ordination and incontinence. In DLB and PDD, these features are part of the disorder's diagnostic criteria and are also displayed in mild stages (50, 51).

2.4 The most prevalent dementia disorders: Clinical expression and pathology

The dementia disorders differ in both their clinical expressions and their pathological mechanisms. Since there are great variations amongst individuals in these domains, and since mixed dementias are common, a precise diagnosis of aetiology can be difficult to achieve (52). As mentioned earlier, this can be especially difficult when the diagnostic procedures are performed during severe stages of dementia when mixed dementia is even more common, as for persons living in NH (53). The characteristics of the NPS in dementia disorders will be described in more detail in Chapter 2.6.

2.4.1 Dementia due to Alzheimer's disease (AD)

Dementia due to Alzheimer's disease usually develops insidiously, starting with deficits in episodic memory, and slowly displaying deficits in other cognitive domains, giving rise to a broad decline in cognitive functions. As the disease develops, the person experiences a decline in the ability to independently perform daily functions (47, 54). Pathologically, AD is characterised by the accumulation of aggregates of extra-cellular beta-amyloid and intra-cellular neurofibrillary tangles, which are shown to precede the clinical symptoms by up to 10-20 years. In established dementia caused by AD, brain imaging typically displays medial

temporal lobe atrophy involving both hippocampi and nearby structures, reflecting more severe neuronal loss. In AD the mean survival rate after the first symptoms is between 10-12 years.

2.4.2 Vascular dementia (VAD)

Vascular dementia (VAD) is caused by different cerebrovascular diseases (CVD) like strokes, small-vessel ischemic disease and multiple transient ischemic attacks (54, 55). The broader term vascular cognitive impairment includes the spectrum of deficits from mild cognitive impairment (MCI) due to CVD, to VAD with cognitive deficits causing deficits in the person's daily functioning. The clinical presentation will vary due to the extent and the localisation of the cerebrovascular disease in the brain. In contrast to AD, the cognitive symptoms in VAD often start abruptly, usually have a more step-wise development, and are accompanied by focal neurological signs on examination and traces of vascular changes on cerebral imaging (54). VAD with mainly subcortical symptoms represents another group of VAD, usually due to small vessels diseases incorporating Binswanger's disease and lacunar state (37, 54). The subcortical symptoms develop insidiously with only mild focal neurological findings but with more subtle changes in memory difficulties, speech, psychomotor slowing, apathy, and eventually, urinary incontinence. Orientation is usually preserved longer than the other cognitive domains. The course is progressive, as with AD (47, 54, 55).

2.4.3 Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD)

In both dementia with Lewy bodies (DLB) and in Parkinson's disease with dementia (PDD), the pathological hallmark is the accumulation of alpha-synuclein protein aggregates (Lewy bodies) in neurons and other nerve system cells accompanied by neuronal loss. Due to their shared pathological features and considerable overlap of their clinical symptoms, they are considered as phenomenological expressions of the same disease process known as the Lewy body dementias (LBDs) (56). By convention, PDD is diagnosed when Parkinson disease has been established at least one year before the development of dementia, whilst DLB is diagnosed if the dementia precedes the parkinsonism. Ten years after the diagnosis of Parkinson's disease approximately 50% of the patients develop dementia, as well (56). The core clinical features of DLB are: early presenting visual hallucinations, fluctuating cognition, rapid eye movement sleep behaviour disorder, and symptoms of parkinsonism (i.e. bradykinesia, tremor or rigidity) (50). Compared to persons with AD, persons with DLB seem to have a larger functional disability and a lower level of quality of life (57).

2.4.4 The frontotemporal dementias (FTDs)

The frontotemporal dementias (FTDs) represent a heterogenous group of several pathological disorders that experience neuronal degeneration of different parts of the frontal and rostral temporal lobes (37, 58). The two most prevalent of these are the behaviour variant frontal lobe dementia and a language subtype that is further classified as semantic dementia, primary progressive aphasia or logopenic progressive aphasia. The most prominent clinical features are profound changes in personality traits and behaviour,

changes in speech and language abilities, apathy, and deficits in executive functions. Although the FTDs are less prevalent than dementia due to AD, the FTDs have a huge impact both for society and the persons themselves because these disorders often affect people at a young age with a typical onset in the sixth decade of life (48).

2.4.5 Alcohol-related dementia (ARD)

The pathological mechanisms of the alcohol-related dementia (ARD) are perceived as a combination of a direct toxic effect of alcohol and severe thiamine (Vitamin B1) deficiency (38). The clinical expressions will vary according to the extent of the alcohol related brain damage, rising from mild to severe dementia and with a considerable overlap with Wernicke-Korsakoff syndrome. Typically, the person with ARD shows symptoms from frontal lobe dysfunctions, as seen in the FTDs, often combined with gait disturbances due to damage to the cerebellum (38). The term ARD is still disputed, since 75% of people with alcohol related brain damage considerably improve with appropriate care and if abstinence is maintained over two to three years (38, 59).

2.5 Risk factors for dementia

Age, is above all, the most important risk factor for dementia; the increase in incidence is nearly exponential after the age of 65 and over 80% of people with dementia are aged 75 years or older (60). As for age, genetic risk factors are not modifiable as of now. Their contribution to dementia is complex. The most investigated genetic risk factor increasing the risk of late-onset AD (onset age older than 65 years), is the ApoE ϵ 4 allele. In addition, common variants of approximately 30 genetic loci and more rare variants in several genes have been identified to influence the risk for late-onset AD (61). Heterozygotes and homozygotes for the ApoE ϵ 4 allele have a three and 15 times' higher risk, respectively, of developing late-onset AD compared with ApoE ϵ 3 homozygotes (52). Since the presence of ApoE ϵ 4 alone does not cause AD, testing for the allele is not recommended in clinical practice (52, 62). For young-onset familial AD, mutations linked to the 1th, 14th or the 21th chromosomes are found in approximately half of the cases. Furthermore, in the frontotemporal dementias (FTDs) several contributory genes have been identified. Between one third and half of the FTD cases are classified as familial due to a range of different mutations (63).

Due to the rising number of persons with dementia globally, and the lack of effective disease-modifying agents, there has been a growing interest in the exploration and search for modifiable risk factors. In 2017, the Lancet Commission on Dementia Prevention, Intervention, and Care listed nine potentially modifiable risk factors: low educational level, hearing loss, depression after 65 years, hypertension, diabetes, obesity, physical inactivity, social isolation, and smoking (52). Preventing or delaying dementia by modifying some of these risk factors, even for a small percentage of people, would have a huge impact on the prevalence of dementia.

2.6 Neuropsychiatric symptoms in dementia

Neuropsychiatric symptoms, also labelled behavioural and psychological symptoms of dementia (BPSD), can be conceptualised as disturbances in the person's ability to perceive information and in thought content, mood, or behaviour (8, 64). They are observed in all types and stages of dementia and affect up to 98% of persons with dementia living in NH during the course of the disorders (5, 15, 65, 66). These disturbances are expressed in a variety of symptom clusters like apathy, agitation (also denoted hyperactivity), affective symptoms, and psychosis (9, 15, 65, 67). The results from multiple factor analyses of NPS based on the single items of the NPI, have consistently supported the concept of these four subsyndromes or symptom clusters of NPS (65, 66, 68). The factor structures were not associated with age, gender, or dementia disorder, and were also valid for NH residents (65, 66). The consistency of the subsyndromes in the studies could imply a shared biological mechanism or shared environmental factors for the individual subsyndromes. For clinicians, it should, however, be kept in mind that there is a close inter-relationship and overlap between subsyndromes, and that in a single person one will often find co-existing symptoms from different subsyndromes, changing with time and the evolution of the dementia disorder (65, 69).

In this chapter, I will describe the most prevalent NPS, their determinants, and their course. Patient determinants are here defined in the same way as in the scoping review of the evidence of determinants of NPS by Kolanowski et al. (2017), as individual characteristics that put the person at risk for NPS revealed by research (70). Caregiver and environmental determinants are defined as possible precipitating causes of NPS (70). Theories or frameworks for the development of NPS will be presented and discussed in Chapter 2.6.6 (A biopsychosocial model for neuropsychiatric symptoms). Since agitation, including aggression, is one of the most frequent and persistent NPS and is often regarded as the most distressing and disrupting of the NPS (5, 6, 21, 71), this symptom was chosen as the primary outcome for the cluster randomised controlled trial testing the effectiveness of TIME. For these reasons the symptom complex of agitation/aggression will be discussed more broadly, and in more depth, than the other NPS.

2.6.1 Apathy

Apathy is defined as a loss of motivation accompanied by a reduction in self-initiated goal-directed behaviour and cognitive activity and by a flattening of emotional responses (72, 73). Aside from agitation, it is one of the most frequent and persistent NPS (5, 9). One Norwegian study in NH found a prevalence of clinically significant apathy (defined as a score of 4 or more in the single item apathy on the NPI-NH) amongst persons with dementia of 29%, at baseline with an increase in prevalence to 39%, at a 53-month follow-up (5). Apathy is observed in all dementia types, with only limited evidence suggesting that the symptom occurs more frequently in one dementia type than another (70). Apathy is also frequently associated with other NPS, like depression, irritability, disinhibition, agitation/aggression and aberrant motor behaviour (70, 74). As apathy also frequently accompanies other serious

medical conditions, can be drug-induced, and is one of the core features of hypo-active delirium, it is of importance to perform a thorough medical examination and a critical review of all medication when assessing a person with newly developed apathy (75). Apathy seems to be strongly associated with neurodegeneration and neuroanatomic changes in the thalamic-prefrontal-subcortical circuitry (70, 73), poor physical health, and the severity of the cognitive impairment in dementia (5, 74, 76).

2.6.2 Affective symptoms

Affective symptoms like anxiety and depressive symptoms are common in dementia and often coexist as an expression of a depressive disorder in dementia (77). In contrast to agitation and apathy, these symptoms seem to be less persistent (5, 6, 9). The prevalence of anxiety symptoms in persons with dementia varies in studies from 8 to 71% depending on the scales used to assess the symptoms and the population studied (78). In a Norwegian study in NH the prevalence of anxiety in residents with dementia at baseline was 34.2% (77) and was equally prevalent at a 12-month follow-up (79). In this study, anxiety was defined as a score of 12 or more on the Rating Anxiety in Dementia scale (RAID-N), which corresponds to a clinically significant general anxiety disorder (77, 80). Clinically significant anxiety symptoms as assessed by the NPI-NH, were found to be present in 22% of the NH residents with dementia in another Norwegian NH study by Selbæk et al. (2013), with a decrease in prevalence to 16% at a 53-month follow-up (5). In the same study incidence for anxiety ranged from 11-13% and persistence ranged from 35-44 % for all assessments. Only a few studies have evaluated possible determinants of anxiety separately from depression, but according to these, anxiety seems to be strongly associated with other NPS, impairments in ADL functions and with poor physical health (77, 81).

Depression can be challenging to distinguish clinically from apathy and other symptoms in dementia, since there is considerable overlap between symptoms. In addition, the ICD-10 and DSM-5 criteria for depression rely to a large part on the person's ability to verbally express emotions, thought content and motivation. As the dementia disorder evolves, these abilities diminish, and there is, therefore, a considerable risk in clinical practice to be unaware of depression in persons with dementia (37). "The Provisional Diagnostic Criteria for Depression in AD" have been developed with the aim to present a higher sensitivity for detecting depression in persons with AD, but it is not known to which extent they are used in clinical practice (82). A systematic review of the prevalence of NPS in NH residents with dementia found a weighted mean prevalence of clinically significant depressive symptoms, defined as a score ≥ 4 on the NPI-NH, of 20%, ranging from 10%-26% (71). In the study by Selbæk et al. (2013) the authors found a prevalence of clinically significant depressive symptoms of 22% in NH residents with dementia at baseline, decreasing to 20% at a 53-month follow-up (5). In the same study incidence for depression ranged from 13%-14% and persistence ranged from 42%-52% for all assessments. A review of determinants of NPS revealed a large number of possible determinants for depression both at the patient and the caregiver levels. (70). Amongst patient determinants were female gender, premorbid neuroticism, ApoE $\epsilon 4$ allele carriers, biological changes in the corpus callosum, neuropathology in monoaminergic networks and small vessel disease. Depression is

prevalent in all types of dementia but seems to be most prevalent in VAD (70). Caregiver's burden has been found to be negatively related to depressive symptoms in the person with dementia, whilst enhancement of caregiver skills has been demonstrated to positively affect depressive symptoms. Poorer physical health, higher number of medications and more severe dementia were associated with higher depression score in a large longitudinal study over 74 months in Norwegian NH (83). Depression in persons with dementia living in NH has also been found to be significantly associated with other NPS like disinhibition, irritability, agitation, and anxiety (84). These findings emphasise the need for a broad biopsychosocial concept and understanding of depression in dementia.

2.6.3 Psychosis

Symptoms of psychosis like delusions, hallucinations and persistent misinterpretations are common in all stages and disorders of dementia (85). Hallucinations are for the most part visual, and delusions in dementia usually differs from delusions encountered in schizophrenia by their simple and non-bizarre characteristics (85). Delusions seem to be more prevalent than hallucinations in most studies. According to a systematic review of NPS in NH the weighted mean prevalence of clinically significant delusions in NH residents with dementia was 19% with a range of 11%-26%, whilst it was 9% with a range of 5%-14% for hallucinations as measured by the NPI-NH (71). Symptoms of psychosis have been found to be persistent, especially for delusions with symptoms lasting from three months to more than one year (86, 87). They are associated with a more rapid cognitive decline, increased mortality risk and more severe dementia, although this last association has not been found consistently in persons living in NH (5, 6, 70, 87). One explanation for the large variety in the studies of prevalence of these symptoms might be that in persons with dementia it can be difficult to differentiate between clinical symptoms of cognitive dysfunctions, like disorientation in time and place, and the symptoms of psychosis. Another example is the feeling of being abandoned when the person must leave his or her spouse and move to a NH, and this change in life situation is misinterpreted by the person as infidelity by his or her spouse (88). According to Cohen-Mansfield such symptoms are often classified as delusions whilst they should instead be interpreted as results of the cognitive deficits in orientation and memory (89). The same author found in one study that nearly half of the persons with dementia and psychosis do not exhibit any discomfort or emotional reactions due to the symptoms of psychosis (90). Caregivers should, therefore, not only assess the intensity and frequency of the symptoms, but also thoroughly describe the content of the symptoms of psychosis and to what extent they have a negative impact on the person. Without persistent negative impact from these symptoms, treatment measures should concentrate on reassurance and other communication techniques.

Since symptoms of psychosis are frequently present in delirium, it is especially challenging to differ between psychosis in dementia and delirium in dementia. This is also the case for drug-induced symptoms of psychosis without the person fulfilling all the criteria for delirium (85, 88). As for the other NPS, these features call for a broad biopsychosocial approach to symptoms of psychosis and emphasise the importance of a comprehensive assessment including a physical examination of the person. Hallucinations are especially frequent in DLB,

and visual hallucinations are one of the core diagnostic clinical criteria for DLB (50). Compared to persons with FTD, persons with AD have been found to have more delusions and hallucinations (70). Psychosocial and environmental factors as determinants for psychosis in dementia have been less studied than patient determinants, but sensory deprivation and vision loss as well as inappropriate sensory stimulation has been associated with hallucinations and delusions (88). Most studies on genetic factors for psychosis in dementia have been performed in AD. Several studies have estimated the heritability of psychosis in AD to be between 30%-61%, indicating a substantial genetic component. Different loci on several chromosomes associated with AD and psychosis have been identified such as chromosomes 2, 7, 8 and 15. Interestingly, studies examining the association with the ApoE ϵ 4 allele and psychosis in AD have been negative (85, 91). Available post mortem studies and neuroimaging have suggested that neurobiological changes in distinct neural networks, like in the neocortex and in the frontal regions, are associated with psychosis (92). Delusions in AD and LBD have been found to be significantly associated with an increased level of tau pathology, and recently with decreased levels of the synaptic zinc transporter protein ZnT3 (92, 93).

2.6.4 Agitation

The concept of agitation

There is no general agreement on the definition of the concept of agitation. A variety of different but also overlapping terms, like aggression, signs of irritability, hyperactivity, aberrant motor behaviour and disinhibition are often described and denoted under the term agitation in the literature (67). To be able to perform valid research, to compare and interpret research results on NPS, as well as for clinicians, definitions of NPS are important. For clinical purposes, it is usually more appropriate to describe in detail the observed behaviour instead of using concepts that are poorly defined. As will be discussed later in Chapter 2.6.6 (A biopsychosocial model for agitation), it is also important to remember that these symptoms are not precise disease entities; instead, they represent symptoms of underlying disorders or physical and psychological discomfort that should be further investigated.

In the aforementioned multiple factor analysis of NPS based on the single items of the NPI, agitation/aggression, irritability, disinhibition and, to varying extent, aberrant motor behaviour and euphoria were included in a subsyndrome under the term agitation or hyperactivity (65, 66). The subsyndrome agitation defined this way represents a measurable and a pragmatic conception of agitation that is especially appropriate for research purposes. There is, however an ongoing discussion on whether agitation should encompass aggression or be considered separately (26, 67). Both the provisional consensus clinical and research definition of agitation from The International Psychogeriatric Association (IPA) launched in 2015 (17), and the often mentioned definition from Cohen-Mansfield include aggression as a part of the agitation NPS subsyndrome (94). The definition from IPA defines agitation as verbal and physical aggression and excessive motor activity consistent with emotional distress for the person. Cohen-Mansfield defines agitation as "Inappropriate verbal, vocal or motor activity that is not judged by an outside observer to result directly from the needs or

confusion of the agitated individual". Based on the results from her own study in one NH where she found that different agitated behaviours were highly interrelated, she performed a factor analysis resulting in three subsyndromes of agitation: aggressive behaviour (both physically and verbal), physically non-aggressive behaviour and verbally non-aggressive agitated behaviour (95). Aggressive behaviour includes behaviour like hitting, kicking, pushing, scratching, tearing things, cursing or verbal aggression, grabbing, biting and spitting. Physically non-aggressive behaviour includes pacing, inappropriate robing and disrobing, general restlessness, handling things inappropriately and repetitious mannerisms. Verbally non-aggressive agitated behaviour includes complaining, constant requests for attention, negativism, repetitious sentences, or questions and screaming (95). As Cohen-Mansfield emphasised, many of these symptoms or reactions to the person's environment are not necessarily related to the dementia disorder. The symptoms are also manifested in persons who are not cognitively impaired.

Although the terms aggression and agitation are often used interchangeably, and the behaviours sometimes coexist, the distinction between aggressive agitation and non-aggressive agitation is important both clinically, when deciding upon appropriate treatment strategies, and for research purposes (26, 67, 96). Aggression is usually conceived as more serious than agitation without aggression. It involves at least one other person or an object as targets for the aggression and can represent a real harm for this person, damage to the object and harm for the person performing the aggressive action (26, 96). This implies that actions must be taken in most episodes of aggression to reduce the risk of harm. Although agitation should always be assessed to explore possible causes that might be expressed by this behaviour, it can sometimes be left without intervention and just tolerated if it is not harmful for the person him/herself or others. This distinction is even more important to be aware of if one considers using pharmacological treatment for the behaviours because of the risk of potentially harmful side effects of psychotropic drugs like antipsychotics (22, 97). Consequently, most national and international guidelines for psychopharmacological treatment of agitation in dementia have incorporated this important distinction between aggression and non-aggressive agitation in their recommendations, though the evidence base for this distinction is weak (62, 98, 99). The confusion between agitation and aggression in the literature makes it difficult to interpret and compare research both on frequency and course of agitation and on trials of effectiveness of treatment interventions (26, 100). Most often outcome measures used in research are based on instruments that do not separate these two behaviours (26, 101). Therefore, to be able to better inform clinical guidelines and decision-makers, future research should also use consistent and validated assessment instruments that are capable of distinguishing between aggression and agitation (26).

In the RCT where we tested the effectiveness of TIME at the resident level (the TIME-trial), we used the difference in the change between the intervention group and control group on the single NPI-NH item agitation/aggression as the primary outcome (102). This item includes mostly aggressive behaviours but also some behaviours that are not necessarily aggressive, like getting upset (overlapping with irritability), shouting, rejection of care or "having things his/her way" (7, 102, 103). Another issue in discussing the concept of agitation is if behaviours like "having to have things his/her way and rejection of care"

deserve to be labelled agitation. The labelling becomes a negative moral judgement of what could otherwise be regarded as normal behaviours in healthy people. These issues will be discussed in depth in Chapter 2.6.6 concerning a biopsychosocial model for agitation. Due to the choice of primary outcome in the TIME trial, and its common use in the literature, I will refer to the term agitation for the remainder of this thesis as the NPS agitation subsyndrome, which also includes aggression (65, 66). When referring to aggressive behaviour exclusively, this will be clarified in the text. This is also in line with the aforementioned terminology of different types of agitation developed by Cohen-Mansfield (94) .

Prevalence, course, and the impact of agitation

The prevalence of agitation amongst NH residents with dementia depends on the characteristics of the population studied (e.g. level of dementia, settings, use of psychotropic drugs etc.), the definition used for agitation, and finally which instruments are used for the assessment and measurement of the behaviours. In a recent systematic review by Selbæk and colleagues, the mean prevalence of any agitation symptom as measured by the Cohen-Mansfield Agitation Inventory (CMAI), was 79%, ranging from 66%-83% (71, 95). In the same review, using the NPI-NH, the mean weighted prevalence (range) of a clinically significant score was 30% for the item agitation/aggression (24-48), 18% for disinhibition (9-21), 31% for irritability (24-48) and 25% for aberrant motor behaviour (15-39). Two studies on the prevalence of NPS from Norwegian NH showed estimates for these agitation items of the NPI-NH to be comparable with the weighted means from this review (68, 104). In longitudinal studies of the course of NPS in NH residents with dementia, agitation seems to be one of the most persistent symptoms that also increases in severity with increasing severity of dementia, aside from apathy (5, 6, 105, 106). In one study that followed residents for 53 months using NPI-NH as the assessment instrument, agitation/aggression, irritability, disinhibition, and apathy showed a persistence rate of $\geq 50\%$ at all assessments (5). In the same study, apathy, and the agitation subsyndrome encompassing irritability, agitation/aggression, disinhibition, and aberrant motor behaviour were the symptoms with the highest incidence rate ($\geq 20\%$). Agitation has serious consequences for the person with agitation, his or her family, and the caregivers. Several studies have shown that agitation is associated with increased patient suffering, reduced quality of life and a more rapid progression toward severe dementia and death, as well as serving as a predictor of referral to specialist health care and hospitalisation (18, 19, 106-108). These symptoms also create a heavy burden and disruption for both formal and informal caregivers (21, 109). Aggressive agitation is found to be more disruptive than non-aggressive agitation when controlled for the frequency of the behaviour (109).

Determinants of agitation

As for the other NPS, several determinants have been identified for agitation. Only a few studies have explored aggression independently of agitation. This was done in the scoping review on determinants on NPS by Kolanowski and colleagues (2017) (70), where they found a higher severity of dementia, male gender, reduced functional ability, sadness, and premorbid neuroticism as the main patient determinants for aggression. Greater caregiver

burden was associated with aggression, but no evidence was found for environmental determinants. For agitation (probably also including aggression, since they used the definition of agitation proposed by Cohen-Mansfield), the authors found seven patient determinants: younger age, male gender, type of dementia, dementia severity, premorbid personality traits, the presence of pain and boredom. Caregiver communication issues such as negative communication styles were the caregiver determinants, and music and balanced sensory stimulation were the environmental determinants for agitation in this review. As the authors emphasised, several determinants, but not all, were common for the different NPS. Interestingly for agitation, there were no significant findings related to neuroanatomic structure or specific cognitive domains. These results on biological determinants contrast with findings suggesting an association between agitation and the left hippocampus, right superior frontal cortex, right amygdala, and bilateral insula, as demonstrated with magnetic resonance imaging (MRI) in a study of 426 persons with AD by Trzepacz et al. (2013). In the same study, frontal lobe atrophy was found to correlate with agitation across different dementia disorders. These brain areas have a crucial role in the regulation and processing of behaviours (110). As for delusions, agitation has been found to be associated with increased level of tau pathology and with decreased levels of the synaptic zinc transporter protein ZnT3 (92, 93). Studies on the role of the neurotransmitters serotonin, dopamine and norepinephrine for agitation have found conflicting results (67). Regarding genetic risk factors, one large study with 1,120 persons with AD found no association between agitation and the ApoE ϵ 4 allele (111). Conflicting results from research on biological mechanisms for agitation could be explained by methodological issues and the lack of consistent definitions across studies of the behaviours (67). Another plausible explanation is that these changes mainly display themselves as clinical symptoms in the interaction with other physical, psychological, and social determinants of agitation, which are difficult to control for.

Physical conditions in persons with dementia can give rise to behavioural changes like agitation (8). Kiley et al. (2000) found that aberrant motor behaviour like wandering was associated with pneumonia (OR = 3.15), constipation (OR = 1.82) and pain (OR = 1.65) (112). In addition, delirium superimposed on dementia often remains underdiagnosed because of the challenges of differentiating between the two conditions, especially when there is a lack of knowledge of the person's baseline mental status (113, 114). Rapidly developing aggression or motor agitation could be the presentation of hyperactive or mixed delirium and should always prompt for thorough physical examination and review of all medication in the search for precipitating reversible causes (113, 114). A randomised controlled trial using a systematic pharmacological pain treatment approach for persons with dementia living in NH compared with usual care showed a significant reduction in agitation after eight weeks. It should, however, be noted that the trial did not include persons with severe agitation or aggression (i.e. a score on the NPI-NH item agitation/aggression \geq 8) (115).

2.6.5 How to assess and measure agitation

Instruments to assess agitation and other NPS are fundamental not only for research purposes; they are also important for clinicians as a support in the diagnostic workup of NPS and for longitudinal monitoring and evaluation of treatment actions (67, 101). The confusion

of the concept of agitation and the difficulties in differentiating amongst overlapping NPS described in Chapter 2.6.4 are reflected in the number of different instruments for the assessment of NPS. A systematic review of instruments for assessing NPS by Gitlin et al. from 2014 revealed 85 instruments, of which 44 had adequate psychometric properties and were developed for persons with dementia (101). Some of these assessment instruments include agitation and other NPS as a part of a general instrument for the assessment of NPS, whilst others are specific instruments assessing specific symptoms or NPS subsyndromes like agitation. Only a few instruments measure solely aggression without other agitation symptoms like, for example, the Aggressive Behaviour Scale and the Rating Scale for Aggressive Behaviour in the Elderly (RAGE) (116, 117).

One of the most commonly used general instruments for the assessment of NPS is the NPI-NH (7, 118). The NPI-NH screens for 12 symptoms or behaviours, of which irritability, aggression/agitation, disinhibition and aberrant motor behaviour can be regarded as part of the agitation subsyndrome as discussed in Chapter 2.6.4. The instrument assesses both severity and frequency of the behaviours over the preceding month. Although severity is harder to quantify than frequency, assessing both frequency and severity is an advantage, since a rare but severe degree of a behaviour can be as disruptive as a frequent but less severe degree of a behaviour (109). Two other versions of the NPI have been developed: NPI-Q, which is a shorter version of the NPI measuring only severity of NPS, and NPI-Clinician (NPI-C), which takes into account not only the proxy observation but also allows patient information to inform the rating for each item whenever possible (119). Interestingly, the NPI-C separates aggression from agitation and also introduces a new domain called “aberrant vocalisations”. Another widely used specific instrument for the assessment of agitation is the Cohen-Mansfield Agitation Inventory (CMAI) (95). CMAI is like the NPI-NH and NPI-Q based on an interview with a proxy. It assesses the frequency, but not the intensity, of 29 different types of agitation and amongst those, aggressive behaviours. The psychometric properties of the CMAI, NPI and the other instruments used in the TIME trial will be discussed in Chapter 3.4.

Most scales only report on observed behaviour from a proxy, without any concern about the context in which the behaviour arose. In addition, when there is a lack of a shared framework for defining agitation, there is a risk that normal reactions from the person in some instances will be assessed as a pathological, direct consequence of the dementia disorder (101). There is no sharp distinction when normal behaviour like, for example, restlessness, irritability and stubbornness becomes agitation *symptoms*. In this way, assessment instruments decontextualise behaviour and, to some extent introduce the notion of moral judgement masked as a clinical assessment instrument. When using these instruments for clinical purposes and for labelling behaviour for a person with dementia, these features of the instruments call for extreme caution. The assessment instruments should not be used as a replacement for a detailed description of the behaviour at stake, but rather as a necessary supplement to provide a broader support for clinical decisions and as a means to ease communication in the assessment workup. They should, in one way or another be followed by a reflexion on possible causes, including contextual contributions to the behaviour (67, 120).

Since the different NPS are highly associated and often coexist (69, 84), when choosing an assessment instrument for clinical purposes, it might be useful to start with a general screening instrument of NPS and then, when discovering clinically significant symptoms, proceed with an assessment instrument that specifically targets the revealed symptoms (121).

2.6.6 A biopsychosocial model for neuropsychiatric symptoms

The different, overlapping concepts of NPS are highly associated, exhibiting several common biological, psychological and social determinants that reflect the complexity and multifactorial aspects of these symptoms. Several theoretical frameworks in the medical and nursing field, so-called middle range theories, have been launched to give a coherent explanation of NPS with the purpose to guide research and clinical practice (122, 123).

Kitwood constructed a comprehensive model, called the “dialectical model of dementia” to describe dementia symptoms, including NPS, as the constant interaction between neurological impairment (NI), social psychology (SP), personality (P), biography (B) and physical health (H) in the equation: Dementia (D)=P + B + H +NI + SP (124). According to Kitwood, malignant social psychology, which includes different negative behaviours from the surroundings towards the person with dementia like infantilisation, labelling, intimidation, ignoring etc., could have detrimental effects on the development on the person’s dementia and thereby the person’s symptoms. As he states it: “a malignant social psychology may actually be damaging to nerve tissue” (125).

In an overview paper by Geda et al. (2013) from the NPS-Professional Interest Area within the International Society to Advance Research and Treatment, possible theoretical mechanisms for the link between NPS and AD were elucidated (126). First, they outlined an etiologic pathway where NPS through activation of neuroendocrine axes lead to AD. Secondly, there might be a shared risk factor (genetic and/or environmental) for both NPS and AD. Thirdly, NPS are caused either by a psychological reaction to the cognitive and functional decline or by the same neurodegenerative process as in AD but involving brain areas responsible for controlling behaviour and emotion. Finally, a synergistic process between NPS (e.g. depression) and a biological factor (e.g. ApoE ε4 allele) starts the process of neurodegeneration leading to AD. The authors emphasised that these mechanisms may act together and are not mutually exclusive and, therefore, invite a more non-linear approach to NPS as complex phenomena.

NPS can also be conceptualised as an expression of unmet needs as espoused in the need-driven-compromised behaviour model (NDB) (127). In this framework, Algase et al. (2016) argued for a view that so called disruptive behaviour like verbal agitation, aggression and wandering represents different ways of expressing important needs or frustration and anger from not being properly understood due to reduced verbal communication abilities. These unmet needs could be social or psychological, like lack of social engagement or anxiety, or physical, like hunger, fatigue, or lack of relief from pain. The authors are reluctant to use the concept of disruptive behaviour since this label just reflects the caregiver’s view on the symptoms. NPS should not be *managed* as symptoms of dementia, but first of all understood

and interpreted (127). The symptoms and behaviours are merely a logical response to difficult and unpleasant situations and pain, not necessarily related to the dementia disorder.

In contrast, Zwijsen et al. (2016) emphasised the importance of not neglecting the influence of neurological damage and other physical factors like comorbidities when interpreting the causes of NPS in dementia (128). The authors' literature review conveyed that persons with dementia have important changes in their neuropsychological functioning that could have an impact on their ability to recognise, interpret and respond to their surroundings, and as consequence develop inappropriate behaviour responses. Focusing primarily on psychosocial factors could lead to the neglect of co-morbid physical diagnoses. It could also overestimate the potential for reducing the behaviour, leading to more distress for the staff and carers by signalling that they should just try harder, that is, work in a more person-centred way (128). A biopsychosocial approach should, therefore, take a broader view as outlined by Spector and Orrell (2010) in their paper, "Using a biopsychosocial model of dementia as a tool to guide clinical practice" (129). In this model psychosocial and biological domains are divided in fixed factors and tractable factors. Fixed factor aspects relate to early life events, medical history, personality traits, genetic factors and neurological damage. These factors are not amenable to change, whilst tractable factors like mood, social psychology, social and physical environment, physical health and sensory impairment have the potential to be changed. Interventions addressing tractable factors could reduce what they label "excess disability" i.e. the difference between the person's current functional level and the potential functional level with optimal interventions and support. The authors' ambition was to encompass other theories on symptoms related to dementia, across disciplines, and construct a tool that could inform clinicians when comprehending individual cases. Spector and Orrell relied strongly on the original concept by Engel (1977) of a biopsychosocial model in contrast to a purely medical model of illness (14).

To summarise, there is growing evidence of a multifactorial and complex view on the causes of NPS, including agitation. The NPS appear as a result of a multitude of different and interacting factors of a biological, psychological and social nature, making the person with dementia vulnerable to inner stimuli and the demands of the physical and social environment (15). In other words, there is a consensus on the biopsychosocial conception of NPS as an overarching theoretical framework, though different frameworks emphasise different aspects. Therefore, according to Verdelho and Goncalves-Periera (2017), it is time leave the "keyhole" perspectives and encourage interdisciplinary approaches to dementia and NPS (123). This is easier said, than done, as there is still a lack of evidence-informed standardised approaches to managing NPS that integrates biological, psychological and social factors in real-world clinical settings (15). Although there is a consensus on the biopsychosocial approach to NPS, the model has been criticised to be merely an *idea* of an integrated approach, rather than offering a theory on the interconnections between biological, psychological, and social factors (130). An alternative theory that could elucidate the understanding of NPS and, yet, still encompass NPS as biopsychological phenomena, is the theory of complexity and non-linear dynamical systems (131). This theoretical approach will be presented in Chapter 2.10.1, Complexity in agitation and NH.

2.7 Dementia care in nursing homes

2.7.1 Nursing homes

Organisation

In 2017 approximately 39,600 persons lived in NH in Norway, a number that has been relatively stable over the last 10 years (1). A total of 89% of the NH are run by the municipalities and 11% are run by non-profit organisations or private enterprises. In both cases, the annual costs for staying in a NH for the residents are the same, with an annual fee equal to 75% of the person's national age pension, with an additional 85% of other revenues aside from the pension (132). However, no one should pay more than the actual cost for the stay, which, in 2015 was an average of 814,166 in Norwegian Kroner (91,220 Euros). Of this sum, the resident paid an average of 17% (41). As these charges cover all expenses, including medical services, with the exception of clothes and personal consumption, the access to a NH stay does not depend on the economic status of the person or his or her family.

Type of wards

The NH are usually organised in different wards depending on the type of services they are supposed to offer the residents. In addition, the wards may be differentiated into smaller units, but the terms "wards" and "units" are often used interchangeably. In this thesis, I will use the term ward, defined as the smallest group of residents in a NH having the same administrative leader (the leading ward nurse) and their own care staff during the day time. The main type of wards are special care wards (units) (SCU) for persons with dementia, regular wards (units) (RU) for persons with mainly severe physical disorders though most of them also have dementia, wards for short-term rehabilitation and respite care, wards for short-time stay for the assessment and evaluation of both mental and physical disorders and for the determination of the level of future care, and wards for palliative care (133). The SCU were first established in the second half of the 1980s as a response to the awareness of special needs for persons with dementia of a physical environment that could enhance the implementation of person-centred care (134). Following the national regulations, the SCU should have between 4-12 residents, residents should be diagnosed with dementia before admission and they should have access to common activities (133). A national survey in 2015 showed that 93% of the municipalities in Norway had established at least one SCU in their NH with an average size of 7.9 residents (range 3-20) (135). Of the SCU, 86% had access to a secured outside area or a garden. A subtype of SCU are the "strengthened" SCU. They usually have more staff per residents than the ordinary SCU and are intended for residents with dementia and severe NPS. In the same survey from 2015, 26% of the municipalities in Norway claimed they had such "strengthened" SCU.

Staff

The Norwegian NH must follow national specific regulations from the Ministry of Health and Care Services regarding staff, leadership, SCU and rights for the residents (133). Amongst these regulations it is stated that each NH should have an administrative manager, a registered nurse responsible for the nursing care, a NH physician, and adequate staffing to ensure necessary care for the residents. Most physicians working in NH are general

practitioners in part-time positions. The size of their position depends largely on the number of residents in the NH, and the type of units where they are working, with an average of 0.55 hours per resident per week in 2017 (1). Only a small portion of the NH physicians have any formal qualification in geriatrics or elderly healthcare (136).

A total of 24% of the staff in the NH lacked formal health or social care education in 2009 (137). In contrast, in 2014, 8% of the staff in the SCU lacked formal health or social care education (135); the staff were otherwise composed of 60% auxiliary nurses, 30% registered nurses and 2% social educators. At the daytime shift in the SCU, there were 3.1 residents per staff and 3.9 during evening shift, whilst in the “strengthened” SCU, the figures were 2.0 and 2.2 residents per staff, respectively. The physicians were engaged for 0.3 hours per resident per week in the SCU and 0.5 hours in the “strengthened” SCU (135).

2.7.2 Persons with dementia living in nursing homes

The average age of NH residents in Norway is 85 years, and residents usually have several chronic diseases that require continuous treatment representing a severe degree of multimorbidity (2, 3, 41, 138). Approximately 84% of NH residents have dementia (3), and up to 75% of residents with dementia have clinically significant neuropsychiatric symptoms (4). In the report from the project Resource Use and Disease Course in Dementia (REDIC, 2015) in Norway, the authors estimated that 85-90% of people with dementia will be admitted to care in a NH during the course of the disease (41). The estimate reflects the important role of the NH in dementia care in Norway, and that the progressive nature of the dementia disorders usually makes the person completely dependent of a caregiver in the last stage of the disorder. The mean duration of NH stays was 2.1 years, and the time elapsed from onset of symptoms of dementia to NH admission was 6.0 years (41).

Pharmacological treatment in nursing homes

NH residents in Norway in 2011 were prescribed an average of 6.9 different drugs, an increase from 4.7 in 1997 based on cross-sectional data (139, 140). The authors suggested that this change may reflect more comorbidity and the possibility of using new drugs for treatment and prevention, like prescribing bisphosphonates for osteoporosis and statins for cardiovascular diseases. They also remarked that this trend was seen internationally. According to two cohort studies, the use of psychotropic drugs in Norwegian NH has been relatively stable between 2004 and 2011, except for the prescription of antipsychotics where the rate has dropped from 24% of the residents to 17% (23). The frequency of the prescription of any psychotropic drugs was 73% and 69%, respectively, a non-significant reduction. Included in these figures are anti-dementia drugs, with a use of 11% of the residents in 2004 and 15% in 2011, also a non-significant change. The use of antidepressants was 38% and 36%, respectively, also a non-significant change. For these studies, the authors of the paper adjusted for disease severity and NPS, so the change in the prescription of anti-psychotics suggests a change in clinical practice. A comparison of the prescription of anti-psychotic and antidepressant drugs in NH in Western European countries found that Norway had the lowest prescription of anti-psychotics for residents with dementia but amongst the

highest number for the prescription of antidepressants (24). The literature review in this study was limited to abstracts published between 2004 and 2015.

Quality of care

NH for residents with long-time stays have a dual task. They are intended to serve as a home for their residents, usually for the last period of their lives and, at the same time, provide them with health and social care. These tasks are complex and encompassing and put heavy demands on the staff. The quality of care in Norwegian NH was assessed in a study in 2006 (141). Overall, most of the residents were judged to receive good basic care, but the opportunities to go out for a walk and perform leisure activities were often restricted. A high staff/resident ratio was strongly associated with better quality of care. These results are in line with a more recent study exploring the perspective of residents with dementia living in NH. Twelve residents with dementia, 11 with moderate dementia and one with severe dementia from three NH were interviewed and asked about their views on their lives in the NH. They expressed that they were content with life in general, but they often felt bored. Acceptance of reality and adjustments of expectancy were key components of their contentment (142). Person-centred care (PCC) is nationally and internationally advocated as the main framework for promoting good quality of care (15, 62, 143). In a cross-sectional study in Norway with a convenience sample of 45 NH in 29 municipalities, the authors explored the association between PCC and organisational, staff and unit characteristics. The main results showed that a high job satisfaction and care organized in small specialized units (SCU) were strongly associated with a high level of PCC (144). Another important issue is the association between quality of care and staff/resident ratio. In a systematic review by Rapaport et al. (2017) on the effective components of psychosocial interventions for people with dementia in NH, the authors found that a low staff/resident ratio was one of the main barriers for the staff to engage with residents at a slower pace and deliver PCC (145). In a comprehensive report in 2011 from the Norwegian Institute for Labour and Social Research (FAFO), 53% of the 2,303 registered nurses from the participating NH stated that the residents' needs for feeling secure, social contact and meaningful activities were not addressed in the institution where they worked; 93% of the nurses claimed that their institution was not properly staffed (137). In 2014, the Norwegian Social Research (NOVA) published a report on staffing based on a survey of 431 employee representatives who are members of The Norwegian Nurses Organisation, employed at either a NH (56%) or an in-home care service. This report supported the association between low levels of staffing and perceived low quality of services, especially regarding possibilities for social activities (146).

To summarise, as the largest institutional health care system in Norway (1, 147), NH are supposed to fulfil a variety of aims, from performing a multitude of complex healthcare services to creating a home for the residents. Nearly one-quarter of the staff lack formal healthcare-related education, and only a minority of the physicians have formal qualifications in geriatrics or elderly health care. Reports have indicated the occurrence of understaffing, which also can impact the quality of care. A consequence of these characteristics is that interventions in NH must be adapted to these challenges to be able to

produce desirable effects and be sustainable. The implementation of complex interventions in NH will be discussed in Chapter 2.10.2.

2.8 Non-pharmacological interventions for agitation

Although there is conflicting evidence about non-pharmacological interventions for agitation, they are recommended in treatment guidelines as a first line-approach (26, 62, 148). The main reason for the recommendation of non-pharmacological interventions is that the effects of psychotropic drugs are modest, and the use of these drugs is associated with major side effects (22). Pharmacological interventions for agitation will be discussed in detail in Chapter 2.9.

Nomenclature and classification of interventions

Non-pharmacological and pharmacological interventions are terms often used in the literature to classify interventions aiming at preventing or treating agitation (26, 149, 150). It is, of course, problematic to define a phenomenon by what it is not, “non-pharmacological” (150). Some have used the term “psychosocial” interventions, but it is not clear if this term covers the entire range of interventions that do not use pharmacological agents as the main “active ingredients”. What about interventions like bright light therapy and aromatherapy? What about biopsychosocial multicomponent interventions like TIME, with a broad spectrum of personalised treatment actions, including a physical examination of the resident to treat somatic issues and a review of the resident’s total pharmacotherapy? New emerging treatments for dementia that are still experimental, like electroconvulsive therapy and repetitive transcranial magnetic stimulation, do not fit easily into either of these two broad categories (150). Since “non-pharmacological interventions” as a broad term encompasses extremely different approaches it would perhaps be better to describe the interventions using multiple terms covering narrower and more precise categories. For pragmatic reasons, to classify interventions that do not use pharmacological agents as the main active ingredients in the interventions, in this thesis, I will use the terms “resident-level interventions” and “care delivery-level interventions”, as they were used in a recent and comprehensive comparative effectiveness review from the Agency for Healthcare Research and Quality (AHRQ, 2016) (26) (Table 3). This classification is based on the intervention-level (primarily residents or caregivers) and has been further subdivided with a description of the intervention type, with goals for the intervention and examples. However, this type of classification also has drawbacks, since multicomponent interventions like TIME and other person-centred based interventions, like Dementia Care Mapping (DCM) and the VIPS practice model, are examples of care delivery models that also involve multiple intervention types (28, 151). Some of the other examples might also fit in several categories, but the classification gives us an overview of the diversity of possible interventions and an attempt to classify them. Experimental treatments will not be covered in this presentation,

and pain-treatment to reduce agitation will be discussed in Section 2.9, Pharmacological treatment for agitation in NH.

Table 3. Categories of non-pharmacological interventions addressing agitation in dementia in nursing homes (adapted from AHRQ Comparative Effectiveness Review, 2016 (26))

Intervention Level	Intervention Type	Goals	Examples
Resident-level	Sensory	Preventing incidents	Music therapy (listening), aromatherapy, bright light therapy, multisensory stimulation
	Structured activities	Preventing incidents	Dancing, exercise, social interaction, music therapy (playing, singing), art therapy, outdoor walks
	Complementary and alternative medicine	Preventing incidents, treating incidents	Aromatherapy, reflexology, acupuncture, acupressure, massage, Reiki
	Psychological	Preventing incidents	Validation therapy, reality orientation, reminiscence therapy, support groups
Care delivery-level	Care delivery models	Preventing incidents, treating incidents	Dementia care mapping, person-centred care
	Staff training and education	Preventing incidents, treating incidents	Specific curriculums for communication, managing behaviours
	Environmental	Preventing incidents	Walled-in-areas, wandering areas, way-finding enhancement, reduced-stimulation areas, enhanced environments

Selection of studies and research question

In this section, I will present results restricted to randomised controlled trials (RCTs) testing the effectiveness of the interventions for agitation in NH. The main research question to be answered by the trials is the effectiveness of an intervention to prevent or reduce agitation as a primary outcome, amongst persons with dementia living in NH or NH-like settings. Secondary outcomes in these studies will also be reported for some of the studies but should only be regarded as suggestive results or results supporting the primary outcome (152, 153). Reporting of secondary outcomes as positive effects of an intervention, raises the risk of reporting outcomes that are false-positive resulting from the statistical testing of many outcomes (153). The RCT design is recommended because of its robust method to prevent selection bias between the intervention group and the control group (154). However, there are some major challenges when using the RCT design for complex interventions, especially regarding the balance between standardisation required by the RCT design and the need for adaption to the complexity of the settings. This issue will be discussed in detail in Chapter 2.10.2 on complexity and complex interventions. Another issue is the continuum between the efficacy and effectiveness RCTs and how to judge where on

this continuum a trial is located (155, 156). This will also be further discussed in Chapter 2.10.2.

Conflicting evidence from existing literature

This summary of previous studies will mainly be based on two comprehensive recent systematic reviews, one by Livingston and colleagues (2014) and the other from the Agency for Health Care Research and Quality (AHRQ, 2016); the latter also consists of results from a meta-analysis (25, 26). Results from a few recent reviews and some individual RCTs on interventions for agitation in NH will also be presented. Since TIME represents a care delivery-level intervention, examples of individual RCTs in this category aiming at reducing agitation will be presented in more detail in Table 4.

The Livingston review included 160 papers of quantitative studies, published up to June 2012, of which 33 were RCTs. Most of them were studies on NH residents. The AHRQ review included 129 papers published up to July 2015, all RCTs, of which 84 were from studies on NH residents. In summary, according to the Livingston review, PCC, communication skills and DCM (all with supervision) reduced agitation in care home dementia residents. These interventions can broadly be characterised as care delivery-level interventions. Resident-level interventions like activities, individualised or in groups; and trained therapist led music therapy decreased overall agitation, though not severe agitation. In addition, sensory intervention decreased clinically significant agitation during the intervention, and resident-level interventions like aromatherapy and light therapy did not demonstrate efficacy. However, findings regarding other types of treatment were inconclusive and inadequately documented (25). The review from the AHRQ in contrast, concluded that the evidence was weak because of methodological limitations of trials conducted on agitation in NH. In their summary, the authors claimed that when the evidence was sufficient to draw conclusions, the outcomes at the resident level showed no difference between the intervention and control groups (26).

Reasons for conflicting evidence from reviews

The conclusions in these two comprehensive reviews are, as discussed above, conflicting regarding the effectiveness of these interventions to prevent or reduce agitation amongst persons with dementia living in NH or NH-like settings. The authors of the AHRQ review commented on these conflicting results by stating that Livingston and colleagues included studies other than RCTs (higher risk of selection bias), did not perform meta-analysis and may, in some instances, make conclusions about effectiveness based on changes in agitation from baseline in the absence of differences in the intervention group from the control group. Meta-analyses that pooled results from a mix of homogenous studies with no effect and studies with small effects, may turn out as having no effect, even if these latter studies showed statistical significant effects (157). This was the case for the three trials using DCM included in the AHRQ review and will be discussed in more detail in the paragraph dealing

with care delivery interventions (151, 158, 159). Importantly, two of the studies using DCM included in the AHRQ were both published in 2013 and, therefore, not included in the Livingston review. Another issue related to the interpretations of results from RCTs in these two reviews is whether a statistically significant difference means that the difference is clinically meaningful. The question was not addressed in the appraisal of the trials in the Livingston review, but it was frequently posed in the AHRQ review, though it was not clearly stated how the authors performed this judgement. The difference between a statistical significant difference and a clinical significant difference is a controversial topic (160). As such, the term Minimal Clinically Important Difference (MCID) has been introduced. It is often defined as a fraction of the standard deviation (SD) of the changes from baseline and calculated as $MCID=0.4 \times SD$, but it could also be decided upon using an expert consensus for each assessment instrument (160, 161). The NPI manual (<http://npitest.net/faqs.html>), for instance, suggests that a 30% decrease in NPI scores from baseline is generally clinically meaningful, and the same per cent reduction has been proposed as clinically meaningful for the CMAI (162, 163). To judge the effect size of a result in an RCT, the Standardised Mean Difference (SMD) (also called the Standardised Effect Size, SES) is commonly used (164). SMD in an RCT is calculated by dividing the difference between the outcome means in the two groups to be compared, by the pooled standard deviation of the changes in the two groups. Cohen's term *d* is an example of this type of effect size index of the SMD. Cohen classified effect sizes as small ($d=0.2$), medium ($d=0.5$), and large ($d=0.8$) (164). However, one cannot infer directly from the SMD if a result is *clinically* meaningful. The SMD effect size is, therefore, best suited to compare the effect size between studies, having used different scales (e.g. the NPI and the CMAI for agitation), where no direct comparison is possible (164).

2.8.1 Resident-level interventions for agitation in nursing homes

Structured activities

According to the Livingston review, activities in care homes reduced agitation with a standardised effect size (SES) of 0.8 to 0.6. but with no evidence for severe agitation. The review based these results on 10 studies implementing a group activity and three studies on individualised activities. There were no differences between these two types of interventions. The authors of the AHRQ review concluded that the evidence was insufficient to draw conclusions about the effectiveness of interventions of both group activities or individualised activities due to methodological limitations and imprecise estimates.

Music interventions

In the Livingston review, the authors concluded, based on 10 studies, that music therapy by protocol (therapist-led) decreased agitation level immediately but has no long-term effect or effect for severe agitation; SES was between 0.5 to 0.8. Evidence was judged insufficient to conclude regarding music therapy without a specific protocol (11 studies). A recent review and meta-analysis by Pedersen et al. from 2017 including 12 studies on music interventions mainly in NH, found evidence for the effectiveness of the interventions with an overall SES of

0.6; 95% CI, 0.38 to 0.84 (165). Based on four trials comparing music therapy with usual care and four studies comparing music therapy with other therapies, the AHRQ review concludes that music therapy is similar to usual care or no treatment in decreasing agitation. Evidence was insufficient to draw conclusions in the comparative studies. The meta-analysis of these trials confirmed these narrative conclusions. The AHRQ review excluded several studies included in the two above mentioned reviews because they were judged as having a high risk of bias, mainly because there were no blinding and no intention to treat analysis. A Cochrane review published in July 2018 that included 22 studies, all with high risk of performance bias, with 1097 randomised participants from NH, concluded that music interventions have little or no effect on agitation or aggression (166).

Sensory interventions

Sensory interventions include massage, therapeutic touch, etc. Therapeutic touch refers to a method in which a therapist sits next to a patient and places her hands near or on the patient and is presumed to transfer energy. According to the Livingston review based on 13 studies, sensory interventions improved all levels of agitation during the intervention; SES was between 0.6 to 1.3. However, there was insufficient evidence of long-term effects. The studies included typically had a small number of participants, and some were not RCTs. In the AHRQ review, the three trials they assessed for massage were judged to have methodological limitations, inconsistent findings and imprecise estimates. Only two studies for therapeutic touch were found to be without an acceptable risk of bias; one of them found no difference between the intervention and control group, and the other did not specifically report on an agitation outcome. The authors of the review concluded that the evidence was insufficient to draw conclusions.

Bright light therapy

Both reviews performed meta-analysis (this was the only meta-analysis in the Livingston review) on the effect of bright light therapy for agitation. The Livingston review included three trials and the AHRQ review four trials, and both reviews concluded no effect of bright light therapy on agitation for persons with dementia in NH.

Aromatherapy

Most of the studies used lavender oil, and a few used Melissa oil. Both reviews concluded, based on six studies each, that aromatherapy is similar to a placebo in managing agitation in this group of residents. The AHRQ review added that the evidence regarding Melissa aromatherapy was insufficient to draw conclusions.

Exercise

Both reviews concluded that there was insufficient evidence to draw conclusions on exercise interventions on agitation due to methodological limitations. Most referred studies were relatively small.

Tailored versus non-tailored interventions

This was a category of interventions examined only in the AHRQ review, based on four trials with an acceptable risk of bias. Tailoring interventions can rely on different concepts like residents' preferences and abilities, unmet needs etc. Only the trial by Cohen-Mansfield et al. found a decrease in agitation compared with usual care. This intervention used what was referred to as the TREA (Treatment Route for Exploring Agitation) intervention, which is based on the assessment from multiple sources of possible unmet needs for each resident. All the observations and the recommendations for each resident were guided by a trained research assistant as a part of the research team. All trials had, according to the review, methodological limitations and imprecise estimates (167). The authors concluded that there was insufficient evidence to draw conclusions.

Animal assisted and robot seal interventions

Results from animal-assisted interventions were included only in the Livingston review. The review concluded, based on three small studies, that there was insufficient evidence of the effectiveness of these types of interventions. In a recent systematic review by Yakimicki et al. 2018, animal-assisted interventions resulted in a significant decrease of agitation in nine of 15 studies. In this review, only two of the studies used an RCT design (168). One recent Norwegian study on robot-assisted activity showed a reduction in agitation three months after the end of the three-month intervention but not immediately after the intervention (169). It is unclear from the paper whether the primary outcome was predetermined to be a reduction in agitation after the end of the intervention or after three months. The assessors of the outcomes were not blinded to the randomisation. A selection bias might be present, since one of the inclusion criteria was that residents showed an interest in the robot-seal Paro when it was demonstrated during recruitment. It is not clear if this selection happened before or after randomisation. In conclusion, this study had a high risk of bias.

2.8.2 Care delivery-level interventions for agitation in nursing homes

Dementia Care Mapping (DCM)

DCM was developed as a tool for the observation of care settings with a goal to develop person-centred care and improve quality of care with the perspective of the person with dementia as the focus (170). In DCM, systematic in-depth observations of both the residents and the staff following a standardised coding system is used. The observations are analysed, and feedback is then given back to the staff in feedback sessions. In these sessions, the observations are discussed with the staff, and care plans are elaborated to improve practice. The observations are performed by trained and certified professionals (171). In the AHRQ review, three trials were found with a total of 643 NH and with an acceptable risk of bias (151, 158, 159). These three trials are displayed in detail in Table 4. Of these, only Chenoweth and colleagues reported a significant reduction in agitation as a primary outcome (158). In this trial, the difference in change in agitation as measured by the CMAI was 10.9; 95% CI, 0.7 to 21.1, in favour of DCM compared to usual care at follow-up four months after the end of the four-months intervention (i.e. eight months after baseline). There was no significant change immediately after the end of the intervention. It is not clear from the paper which of these outcomes were the predetermined primary outcome. The authors of

the AHRQ review questioned whether this change was clinically meaningful. They also performed a metaanalysis of the three trials by using the SMD and concluded that the effect of DCM in agitation in dementia is similar to usual care. In the Livingston review the authors concluded that DCM is effective immediately and after four months with an SES=1.4 to 0.6. The possible reasons for this conflicting evaluation have been discussed earlier in this chapter.

Person-Centred Care (PCC)

Interventions grouped under the term PCC consist of training the staff and leadership in NH in approaches based on the same principles as DCM, but with the use of other types of structured methods for implementing changes to care services (25, 26, 172). The core concept of PCC is personhood, developed by Kitwood and further defined as the VIPS framework (Valuing the person with dementia, Individualised approach, understanding the Perspective of the person, and promoting a positive Social psychology) (125, 172, 173). Since principles derived from PCC represent one of the main theoretical underpinnings for TIME, the concepts from PCC will be discussed in more detail in Chapter 2.12.5.

The Livingston review claimed, based on four RCTs, that there is convincing evidence for the effect of training and supervising staff in NH in PCC and communication skills for reducing agitation immediately and up to six months after the end of the interventions, with an SES=1.8 to 0.3. However, the AHRQ review concluded based on three RCTs, by evaluating them individually and performing a metaanalysis, that person-centred care and usual care have similar effects on agitation in dementia in NH (151, 158, 174). Only one of the RCTs was included in both the two reviews, since the two other RCTs in the AHRQ review were published too late to be included in the Livingston review. In the study included in both the two reviews, Chenoweth and colleagues compared PCC with usual care over a period of four months (see Table 4 for details) (158). They found a significant reduction in agitation measured by CMAI at four months after the four-month intervention had ended (mean between-group difference in change of CMAI score of 13.6; 95% CI, 3.30 to 23.9). According to the AHRQ review, the SMD for this trial was 0.44. The authors of the AHRQ review stated that this difference between the intervention and usual care is unlikely to be clinically meaningful. The second study in the AHRQ review was the trial by Fossey et al. (174). However, here the primary outcome was reduction in the use of antipsychotics with agitation as a secondary outcome. This study compared a staff training programme to reduce the prescription of antipsychotics and to promote person-centred care, with usual care as the control. After adjusting for baseline antipsychotic use and region, the authors found no difference between the intervention and the control group in the use or dosing of antipsychotics at 12-months' postintervention. There were no effects on agitation, either. In the third study in the AHRQ review under the PCC heading, Rokstad et al. compared an intervention with PCC with usual care for a period of 10 months (see Table 4 for details) (151). The intervention used the VIPS practice model (VPM) to introduce the VIPS framework to implement PCC. The core element of the VPM is a consensus meeting in the NH using prespecified indicators to analyse challenging resident-staff interactions. There were no significant differences in the change in agitation between the groups in the primary

agitation outcome, the Brief Agitation Rating Scale (175), but a small difference in the NPI-Q agitation sub scale (mean difference 0.9; 95% CI, 1.6 to 0.1) was noted as a secondary outcome.

Other care delivery interventions

Two other RCTs by Zwijsen et al. and Rapp et al., were presented in the AHRQ review under the heading “Protocols to Reduce Use of Antipsychotics” (176, 177). Both these interventions used a staff-training programme (for description see Table 4) and found a significant reduction in agitation in the intervention group compared to the control group. For the Zwijsen study, there was a mean difference in the change in agitation measured by CMAI between the groups of 2.4; 95% CI, 4.30 to 0.6 at eight months’ follow-up. The authors of the review judged this result as possibly not clinically significant. However, there was a significant reduction in the prescription of antipsychotics (secondary outcome). Rapp et al. found a mean difference of 6.24; 95% CI, 2.03 to 14.44 in the change between the intervention and the control group in agitation measure by the CMAI at 10 months’ follow-up. The authors of the AHRQ review questioned whether this difference was clinically meaningful. There was also a significant reduction in the prescription of antipsychotics in favour of the intervention group.

Table 4. Randomised control trials (RCT) of care delivery-level interventions aiming at reducing agitation in persons with dementia in nursing homes

Study, country, comparison, n	Intervention description, intensity, duration, qualification of those who performed the intervention	Primary outcome results	Main secondary outcomes results
Chenoweth et al. 2009¹ , Australia, DCM ² versus (vs) usual care, n=159	-staff training and implementation of DCM; -DCM 6 hours a day for 2 days per site -study investigators together with 2 care staff from NH ⁵ trained by Bradford trained experts + regular telephone support for 4 months	Directly after the 4-month intervention, mean between group difference in change (MC ⁷) in CMAI: non-significant (NS). At 4 months' follow-up: significant MC in CMAI 10.9 (95% CI:0.7 to 21.1)	MC in reduction of use of psychotropic drugs NS. MC in reductions in accidents or injuries NS.
³Rokstad et al. 2013 .Norway DCM vs. usual care (5 DVDs with lectures on dementia), n=308	-staff received 3-hour lecture of DCM -DCM, beginning of study and at 6-months -2 care staff members from each NH were trained in DCM (certified) -DCM by researchers and certified staff	At 10 months' follow-up: MC in BARS: NS	NPI-Q sum score, -agitation, and -psychosis scores, and quality of life showed a significant MC in favour of DCM
Van de Ven et al. 2013 , Netherlands, DCM vs. usual Care, n=180	-all staff given a 3-hour lecture on DCM -at least 2 DCM cycles over 4 months -2 staff members from each NH trained (and certified) for DCM performed DCM	Directly after the 4-month intervention, and at 8 months' follow-up: MC in CMAI NS	MC in NPI-NH scores, reduction of use of psychotropic drugs and quality of life NS
Fossey et al. 2006 , England, PCC ⁴ , and a protocol for reduction of antipsychotics vs. usual care, n=346	-staff training in the delivery of PCC -weekly supervision over 10 months -psychologist, occupational therapist, or study investigators provided weekly supervision; prescribers worked with psychiatrist 2-days a week	At 12 months' follow up: MC for the use of antipsychotics NS (after adjusting for baseline and region antipsychotic use)	At 12 months' follow up MC in CMAI NS
Chenoweth et al. 2009¹ , Australia, PCC vs. usual care, n=159	-staff training in PCC using the Bradford University's training manual -2-days training session for 2 of the staff + 2 visits by study investigators per nursing home + conference calls between investigators and staff for 4 months -study investigators	Directly after the 4 month intervention, MC in CMAI NS At 4 months' follow-up after intervention is completed: a significant MC in change in CMAI score of 13.6 (95% CI:3.30 to 23.9) in favour of DCM	MC in reduction of use of psychotropic drugs NS. MC in reductions in accidents or injuries NS.
Rokstad³ et al. 2013 , Norway PCC vs. usual care, n=288	-staff training in a 24-indicator framework to evaluate PCC (VPM ⁶), 45-60 min. weekly meetings to analyse resident-staff interactions -3 nurses (including the leader) from each ward attended a 3-day basic course, then led the intervention (meetings) -3-hour lectures to staff by the 3 nurses	At 10 months' follow-up: MC in BARS: NS	NPI-Q sum score, -NPI-Q-agitation, and NPI-Q psychosis scores and reduction in depression symptoms showed significant MC in favour of PCC
Zwijzen et al. 2014 , Netherlands, (stepped-wedge design) clinical protocol vs. usual care, n=659	-staff training in using a structured analytic approach to analyse behaviours and develop individual treatment goals -1-day training at study commencement -post-intervention meetings 2 weeks later -nursing staff, physicians, psychologist	Directly after the 4-month intervention, MC in CMAI NS. At 8 months' follow-up: a significant MC in CMAI of 2.4 (95% CI:0.60 to 4.30) in favour of the intervention	MC in reduction of use of psychotropic drugs was significant in favour of the intervention
Rapp et al. 2013 , Germany, clinical protocol vs. usual care, N=258	-staff training on the uses of individualised activity-based interventions; implemented 1-2 days a week for 45 min. -staff trained in 2 4-hour sessions; -prescribers trained individually for 4 hours - occupational therapists, prescribers	At 10 months' follow-up: a significant MC in change in CMAI score of 6.24 (95% CI:2.03 to 14.44) in favour of the intervention	At 10 months' follow-up MC in reduction of use of psychotropic drugs was significant in favour of the intervention. MC in NPI-NH scores NS

Notes: ^{1,3}Each of the two studies are composed of two different interventions (DCM and PCC) compared with usual care. To simplify this presentation the two interventions versus usual care are separated in this table for each study; ²DCM, dementia care mapping; ⁴PCC, person-centred Care; ⁵NH, nursing home; ⁶VPM, VIPS practice model; ⁷MC, mean between-group difference in change

2.9 Pharmacological treatment of agitation in dementia

One main challenge when translating the results from RCTs and reviews reporting from pharmacological trials to clinical situations is that many trials only report outcomes on total NPS scores as the primary outcome (22, 62). In clinical practice, psychotropic drugs are usually used to treat specific symptoms like psychosis or aggression and treating total NPS burden as a clinical entity is usually considered as meaningless. Another challenge is that the patients included in many trials often have a less severe symptom burden than would usually be the case in clinical practice when treatment with drugs are considered necessary. This could lead to a bias in trials in the estimation of the efficacy of pharmacological agents (62, 178). Another issue concerning agitation is that most trials do not distinguish between agitation with or without aggression, even though the clinical consequences of a patient displaying aggression usually are far more serious than without aggression as discussed in Chapter 2.6.4 on the concept of agitation (26, 62). Most trials are of short duration, especially for antipsychotics where follow-up typically is between 10-12 weeks, meaning there are fewer data on long-term efficacy and side effects (22, 62). Recommendations regarding treatment of agitation should, therefore, include judgements considering the aforementioned limitations. In this chapter, I will present the main results from some recent systematic reviews and meta-analyses of the most used classes of psychotropic drugs and conclude with a summary of national and international recommendations.

2.9.1 Effectiveness of pharmacological agents on total NPS burden

A systematic review by Wang et al.(2015) with RCTs comparing the efficacy of antidepressants, cholinesterase inhibitors, memantine, atypical antipsychotics and anticonvulsants with placebo indicated that atypical antipsychotics have the best efficacy on total NPI scores (22). The pooled standardised mean difference (SMD) for antipsychotics was 0.21; 95% CI, 0.12 to 0.29, which is modest. For the acetylcholinesterase inhibitors and memantine, the statistical effect was even smaller and may not be clinically meaningful. Regarding the antidepressants, there were no differences between placebo and active agents, and for anticonvulsants, there was a significant efficacy in favour of the placebo group. There were not enough studies to conclude for typical antipsychotics. Patients in this review had Alzheimer's disease and the mean age for the participants varied from 73 to 86 years. The range of the mean MSSE-score in the studies was between 4.5 and 21.2. One limitation in this review is that the authors only included trials that used the NPI for the measurements of NPS. These results are in line with other systematic reviews (179-181).

2.9.2 Antipsychotics for the treatment of agitation

A systematic review from 2011, from the Agency for Healthcare Research and Quality (AHRQ) reported on the data of the efficacy of atypical antipsychotics on agitation and psychosis in dementia (182). The review included mostly patients with dementia due to AD but also patients with VAD and mixed AD and VAD. They had moderate to severe NPS, mainly psychosis and agitation with and without aggression. The agents studied were aripiprazole, olanzapine, quetiapine and risperidone. The SMD for pooled results was 0.12 (95% CI 0.04 to 0.19) regarding psychotic symptoms and 0.20 (95% CI 0.12 to 0.27) for

agitation. Risperidone showed the best efficacy on both agitation and psychosis. Aripiprazole, with markedly fewer studies included, had an equivalent effect on agitation, but lesser on psychosis. Olanzapine showed a significant effect on agitation but not for psychosis, and quetiapine demonstrated no effect for psychosis or agitation. All these efficacy results can be classified as modest independently of the type of antipsychotics. The American Psychiatric Association (APA) Practice Guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia included the studies from the AHRQ review but with an update for studies up to 2015. The conclusions regarding the efficacy of atypical antipsychotics had not changed (98). Only a few systematic reviews have examined the effects of typical antipsychotics on agitation in dementia (62). The systematic review by Sink et al. (2005) demonstrated no significant effects on total NPS score or agitation (183). A Cochrane review from 2002 showed a statistical effect of haloperidol only for aggression but not for agitation in general and with a considerable risk of serious side effects (184). Patients included in these two reviews were patients with AD, VAD or mixed AD and VAD. There is insufficient evidence to conclude the effects of antipsychotics for agitation in patients with FTD (62). For persons with PD or DLB, the evidence base for the use of antipsychotics is also weak, and due to the considerable risk of extrapyramidal side effects, delirium, and malignant neuroleptic syndrome they should be avoided (50, 62).

Harm and side effects of antipsychotics

In 2008, the USA Food and Drug Administration published a warning against the use of both typical and atypical antipsychotics for the treatment of elderly persons with dementia due to the increased risk of stroke, coronary disease, death and other serious side effects (185). Although there is conflicting evidence on the risk of death and the size of the risks for vascular events, this warning remains active (97, 182, 186-188). In a retrospective case control study including 90,786 persons with dementia, the increased risk of death compared to non-users was 3.7% for risperidone over a six month period, 2.5% for olanzapine and 2.0% for quetiapine (97). Other common side effects associated with antipsychotics are extrapyramidal symptoms (most pronounced with typical antipsychotics), drowsiness, fatigue, urinary tract infections and urine incontinence (182, 184).

2.9.3 Other pharmacological agents for the treatment of agitation

For specific pharmacological treatments of agitation in dementia aside from antipsychotics, the evidence base is sparse (62, 189). The clinical decision support resource, UpToDate (October 2017), has recommended the use of antidepressants, as agitation can be an expression of depression, but warns against side effects, especially the risk of QTc interval prolongation (measured on an electrocardiogram) and the subsequent development of arrhythmia (189). A recent randomised trial including 186 patients with AD and frequent or severe agitation demonstrated that the antidepressant citalopram (target dose 30 mg daily) significantly reduced agitation compared with placebo (190). However, the use of citalopram was strongly associated with QTc interval prolongation which is a known side effect of the drug. There were insufficient data to conclude on the efficacy of lower dosages than 30 mg. Sub-group analyses of predictors of efficacy and risks with this treatment showed that the

efficacy of citalopram to reduce agitation was less in those with severe agitation and greater cognitive impairment and they were also at a greater risk for side effects (191).

UpToDate has also recommended the use of cholinesterase inhibitors for agitation in persons with mild to moderate dementia, even though the evidence-base for their use is weak (189). It should, however, be noted that side effects are common in cholinesterase inhibitors; in particular nausea, vomiting, diarrhoea, headache and syncope are significantly more frequent in the treatment groups than in placebo groups when prescribed to patients with mild to moderate dementia with AD (192). Data are insufficient to conclude on the efficacy of memantine and anticonvulsant for the treatment of agitation (189). A recent Cochrane review on the efficacy of the anticonvulsant valproate for treating agitation in persons with dementia, concluded that valproate was ineffective and the use was associated with a high risk of adverse effects (193).

As discussed in Chapter 2.6.4 on the determinants of agitation, pain is an important source of agitation in persons with dementia (70, 112) and should, therefore, be a compulsory part of the assessment of persons with agitation and dementia. Since many persons with moderate to severe dementia have difficulties in verbally reporting pain, this assessment can be challenging and will rely heavily on the caregivers' observation skills. A randomised controlled trial comparing systematic treatment of pain with analgesics with usual care (no placebo drug comparison) for persons with dementia and mild to moderate agitation living in nursing homes showed that the treatment of pain reduced agitation after eight weeks but not 12 weeks (115). The authors did not predetermine if the primary outcome was the difference in change in agitation between groups at eight or at 12 weeks.

2.9.6 Guidelines for pharmacological treatment of agitation

Due to the evidence of the modest effects of psychotropic drugs on agitation and the considerable risk of serious side effects, guidelines and expert recommendations are rather consistent (15, 62, 98, 99, 143, 194). All guidelines emphasise the importance of a biopsychosocial approach with a comprehensive assessment with the goal to uncover potential treatable causes of agitation, including physical causes and pain. Pharmacological treatment of agitation should be reserved for patients whose symptoms are severe or can cause serious harm to the patient or others in his or her surroundings. In practice, this will most often apply to agitation with aggression. Non-pharmacological approaches that apply principles from PCC should precede pharmacological treatment, except in dangerous emergency situations, and non-pharmacological approaches should co-exist with pharmacological treatment. Continuous assessments of the efficacy and possible side effects of psychotropic drugs with well-established clinical instruments should be part of an individual treatment plan. Decisions about treatment should also be based on the understanding of the person's preferences and values if possible and, if not possible, with inputs from the person's next-of-kin. Preferred duration of treatment with antipsychotics vary in recommendations between six weeks to four months. If the use of antipsychotics is deemed necessary, the atypical antipsychotics risperidone, aripiprazole and olanzapine are recommended as first-line agents before typical antipsychotics.

Although national and international guidelines for the treatment of agitation in dementia recommend the use of non-pharmacological strategies as the first-line approach, the use of psychotropic drugs remains frequent, as outlined in Chapter 2.7.2 (23, 24, 139). There are several reasons for this. Clinicians, caregivers and even patients and their next-of-kin, may be overly confident in the efficacy of psychotropic drugs and may not be sufficiently aware of their risks. Furthermore, translation of effective non-pharmacological approaches into standard care remains a challenge (15, 26). Clinicians and caregivers may lack knowledge of non-pharmacological interventions and their efficacy, and they are often perceived to be time-consuming and resource-demanding (26, 195). Another reason is that the evidence of non-pharmacological is conflicting, and when evidence is shown, many trials only prove clinical efficacy several months after the end of a lengthy intervention (26). Some of the non-pharmacological interventions developed in research trials circumvent the increased time and resource use by using the research team or research assistants to deliver the interventions, including frequent and intensive follow-ups (15, 27). These non-pharmacological resource demanding strategies will thus remain outside possible standard clinical practices and may contribute to the lack of interest from clinicians, caregivers and decision-makers. Dissemination and implementation of simple, evidence-based, non-pharmacological approaches for agitation, which are easy to implement in clinical settings without heavily relying on continuous extra resources or expert inputs, should, therefore, be prioritised by the health authorities.

2.10 Complexity and complex interventions

2.10.1 Agitation and nursing homes with perspectives from complexity sciences

Agitation as wicked problems

As described in the previous chapters, agitation represents a group of overlapping and fluctuating symptoms with considerable interactions between them. The confusion described about the symptom definitions in the literature might reflect a reality that at its core, is difficult to refine, hard to predict and changes over time. It can be that striving for classification and order does not comply with this reality. We have seen that the causes of agitation are multiple and of biological, psychological and social character. There is no consensus of which causes are the most influential, and results from studies on determinants of agitation at a group level are not easily translated to an individual level. The biopsychosocial model seems to be a fruitful approach for the understanding of agitation, with its aim to account for all these possible causal factors. However, the model does not construct a theory revealing plausible mechanisms for the interaction between the biological, the psychological and the social (130). From my clinical experience, agitation often seems unpredictable, even after the most cautious investigation for causes and possible triggers. Rittel and Weber (1973) used the term “wicked problems” about complex problems that are hard to refine and understand (196). They characterised wicked problems as evolving and changing over time. Solutions often need to be tested first to bring about an understanding of the problems. Context is essential for the understanding, and there is no definitive set of solutions that are right or wrong. Any problem can be perceived as a

symptom of another problem, and every wicked problem is essentially unique and novel. Another characteristic is that wicked problems have “no stopping rule”. This means that they are persistent, and those working with them must adjust their level of ambitions for solutions to what is “good enough” (196). Conklin (2006) used the same term when he developed “dialogue mapping”, a coherent system for approaching wicked problems in organisations with a high degree of social complexity (10). He emphasised that this classification does not represent a dichotomy but rather that problems have degrees of wickedness. From my experience as a physician, agitation very often complies to these characteristics.

Conklin’s description of wicked problems and the social complexity in which they often reveal themselves, rely heavily on the theories from complexity sciences. In this chapter I will introduce some of the main principles from complexity sciences and discuss how these theories can enhance our understanding of agitation. Concepts from complexity sciences have also been used in social sciences to analyse the social complexity of organisations and social systems. This complexity needs to be understood and accounted for when trying to implement new methods or working models (12, 197). Since the implementation of TIME in nursing homes is an example of such an implementation, these aspects of complexity will also be discussed.

Complex or complicated

Complexity theory, often used interchangeably with complexity sciences, can be regarded as a high-level theory or meta-theory, since it organises concepts of complexity and mid-range (local theories) into an overarching conceptual framework (122, 198). One of the pioneers in the field was chemist Ilya Prigogine, who won the Nobel Prize in 1977 for his study on the thermodynamics of nonequilibrium systems. Another pioneer in the field was philosopher Paul Cilliers. In his influential work “Complexity and Postmodernism” (1998), Cilliers started with drawing the distinction between the complicated and the complex (131). In a complicated system, the parts constituting the system, though always numerous, interact with each other in predictable ways, obeying known scientific laws. A complicated system can be understood by reducing the system in its parts, isolating and describing in detail its individual constituents, and by studying their individual interactions. Cars, computers and aeroplanes are examples of complicated systems. In a complex system the relationships between its components are not fixed; they are shifting and changing and, therefore, often unpredictable. Examples of complex systems, as mentioned by Paul Cilliers, are the brain, natural language and social systems. Studying complex systems by only reducing the systems into their basic constituents gives rise to a loss of essential information of the system. In essence, a complex system represents more than the sum of its parts (131). If it is assumed that a person with dementia and agitation constitutes a complex system, then the biopsychosocial model implies that the biological, psychological and social factors from this model interact in ways that are changing, shifting and often unpredictable. Furthermore, each of the components in the model belongs to its own systems, like the brain belongs to biological systems, the emotions and thoughts to psychological systems and the nursing home to social systems. According to Cilliers, these systems are not closed but open with no

sharp borders, interchanging and interacting with other systems. Nursing homes can be regarded as highly complex social systems because they consist of different stakeholders such as professionals, leaders, residents and their relatives in constant shifting interactions (11, 12, 199).

Complexity sciences as a framework of theories have a series of different concepts, including complex mathematical non-linear functional equations especially developed for the understanding of biological networks (198). These concepts are beyond the scope of this thesis. However, three important features from complexity sciences that could directly apply to agitation and the social world of nursing homes are the concepts of non-linearity, self-organisation and emergence (131, 198).

Non-linearity

It is a common clinical experience that the same treatment measures applied to a person with agitation, such as for example personalised music therapy, can have an impressive effect in reducing agitation one day, whilst the next day, applied in the same way, just increases the agitation even if the circumstances seemed quite similar. Introducing only subtle changes during meal-time for persons with dementia susceptible to develop agitation, could be the difference between a calm meal and no meal at all (200). These are examples of non-linearity. Non-linearity means that small inputs could have tremendous impact on systems creating a cascade of reactions, and vice versa, as large inputs sometime produce small results. Change does not have to be proportional to inputs (198). There may still be some causal relationships between inputs and outputs, but the inputs are remodelled by other interacting elements in the system, and outputs are seldom *determined* by the inputs (201). This implies that, in many cases with agitation, one must often experiment with a set of different treatment measures because there is no way to know in advance which measures are going to be successful and under what circumstances. This experimental aspect of treatment measures for agitation will be further developed in the Chapter 2.12 when presenting TIME.

Self-organisation

All biological and social systems are prone to changes in both the external environment and from within the systems themselves. To be able to adapt to these influences, the systems must change themselves continuously. The systems must be “plastic” and are, therefore, often labelled Complex Adaptive Systems (CAS) (198). This process of changing through adaption is the concept of self-organisation in complexity science (201). It is an ongoing process that cannot be completely controlled, only influenced. The process continuously changes the relationship between the elements of the systems, accounting for the systems’ unpredictability. Self-organisation explains why complex systems are never stable. Sometimes heavy internal or external influences push the systems towards extreme instability or even chaos (202). In the brain, one example of self-organisation is the plasticity of neuronal circuits to take over lost functions after strokes. Another example can be agitation as the expression of unmet needs when people with dementia are not properly understood because of reduced verbal communication abilities due to neural degeneration. Agitation due merely to breakdown and changes in neural circuits controlling behaviour and

emotions might explain some of the persistence of this symptom discussed in earlier chapters. Self-organisation is not necessarily logical, even though it is not random. It might not necessarily always serve the system to achieve a goal. As such, self-organisation is not a deliberate choice of the system, but rather an inevitable property of a non-linear adoption in all complex systems (198).

In social systems, self-organisation is usually defined as a construction where people in the system make sense of the tasks and orders they are told to fulfil and the way this construction changes and adapts to external and internal demands (11, 203). It represents the always changeable “inner life” of the organisation, which is often not perfectly in line with formal aims and visions of the same organisation. Philip Haynes (2011) described this process as “bottom-up” in his work *Managing Complexity in the Public Services* (11). According to Stacey (1996) and his work on complexity in organisations, self-organisation in social systems can be influenced (but not controlled) to fulfil the aims of an organisation mainly through three processes: 1. increasing information flow; 2. adding more connections amongst people and 3. promoting the development of more diversity in cognitive schemas by mutual systematic reflection (203). In a study using complexity science as a framework, Anderson and colleagues (2003) explored the relationship between management practices and resident outcomes (aggressive behaviour, restraint use, complications of immobility, and fractures) in 164 NH. They concluded that a relationship-oriented leadership, by allowing for greater communication openness and participation in decision making, contributed to better resident outcomes (13).

Emergence

When self-organisation leads to a high degree of instability, systems might abruptly develop unexpected trajectories or events, often perceived as random events. From the outside, these events occur without any apparent connection to prior events. In complexity sciences these events are called emergent phenomena (198). They are not random, but often unpredictable because of the extreme instability in a non-linear system. Returning to NPS in persons with dementia, extreme agitation and aggression, as part of what is perceived clinically as a situation out of control for both the person her/himself and the carer, could be interpreted as an example of emergence. Mismatch between the expectations from the carer and the ability of the person with dementia to process, interpret and respond adequately due to severe dementia could be a possible equivalent perspective in the biopsychosocial model (8, 128, 129). Emergence could also arise without demands from the outside as a result of extreme instability within neural systems as clinically observed in the fluctuating symptoms of dementia with Lewy bodies. Emergence in social systems is usually the results of abrupt changes in relations between people, in their way of thinking and in their shared understanding. It is a bottom-up process with unpredictable results (11).

Criticism of complexity sciences

Complexity theory as a meta-theory is a theoretical integration of knowledge. It represents an attempt to describe phenomena from different areas in the same way (130, 198). Being a meta-theory, it does not, however, replace other theoretical perspectives. A theoretically

holistic approach like complexity theory should not be promoted in opposition to, for example, a reductional approach as something “better” than the latter (130). It is rather a question of what kind of phenomenon is being faced and at what theoretical level should the phenomenon be examined and understood. Sometimes, it will even be fruitful to combine several theoretical approaches. Some of the core concepts, like non-linearity, self-organisation and emergence, have mathematical origins that even for mathematicians, can be qualified as very abstract and exotic (198). Although there have been several suggestions on how perspectives from complexity sciences could inform biological and psychological processes and the management of organisations, fewer have been developed on how these core concepts should inform research and clinical practice (10, 11, 198, 199, 203). As such, there is always a risk that so-called holistic theoretical approaches remain out of content, i.e. empty for practical equivalents (130).

To conclude the discussion on complexity in agitation and in NH, it can be argued in line with Cilliers (1998), that using the perspective of complexity sciences enable us to understand natural and social phenomena in a more a comprehensive way because this perspective is richer in information than a purely reductionistic one. It represents a shift from control and prediction of systems to understanding (131). Returning to the settings of this thesis of the NH, this view is consistent with accepting uncertainty when approaching NPS in persons with dementia. This is meant both for leaders and staff to promote a flexible and non-controlling approach towards organisational issues and the residents. This view places emphasis on our understanding of the person and of the context in which the person lives. These issues will be further developed in Chapter 2.12 when presenting TIME.

2.10.2 Implementation of complex interventions

Complex interventions or complex systems?

Effectiveness trials in hospitals, NH and municipalities, such as testing the effectiveness of a healthcare intervention, are evidently quite different from controlled experiments in a laboratory or even randomised controlled trials for drugs. An effectiveness trial is defined as a test of the effect of a programme or an intervention delivered under real-world conditions, whilst an efficacy trial tests the effects of the programme or the intervention when delivered under optimum conditions (155). Most of the challenges related to the complexity of the health care services, i.e. the social systems, were described in the previous chapter. The social systems differ in their characteristics, often change during the trial and affect not only the content of the intervention itself (i.e. standardisation) but also the implementation process (154). A randomised controlled trial of a complex intervention will never be completely *controlled* in the strict sense of the word. This process reflects the self-organisation and the non-linearity of a complex system as discussed earlier, i.e. the output is not proportional to the input. As stated by Hawe and colleagues (2004), it is instead a question of “How out of control can a randomised trial be?” (197). When it comes to the evaluation of an effectiveness trial, new questions arise. The components of a complex intervention are often interrelated and the delivery tends to be lengthy, so the complexity of the causal chains makes it difficult to determine what are usually called the “active

ingredients” of an intervention (154). Therefore, we face a triple set of complexity; the social system within which the intervention is supposed to be implemented, the intervention itself and, between them, the process of implementation. These are some of the issues to be discussed in this chapter.

Definition of complex interventions

Richards and Hallberg (2015) defined complex interventions as “Activities that include a number of component parts with the potential for interactions between them which, when applied to the intended target population, produce a range of possible and variable outcomes” (204). The Medical Research Council (MRC, 2013) guidance on developing and evaluating complex interventions applies a similar definition and states that few interventions are truly simple, and that it is more a question of the degree of complexity (205). This complexity depends on both the number of interacting components and the number of behaviours required by those delivering and receiving the interventions. It also depends on the number of groups or organisational levels targeted by the intervention.

Different phases in the development and evaluation of complex interventions

Campbell and colleagues (2000) divided the processes of developing and evaluating complex interventions into five phases that do not necessarily follow a linear process, but are often iterative (206). These phases are consistent with the framework advocated in the MRC’s new guidance on Developing and Evaluating Complex Interventions from 2016 (154).

These five phases are:

The preclinical phase: Identifying/developing the appropriate theory base for the intervention and identifying the relevant, existing evidence base on the subject.

Phase I: Modelling process and outcomes

Phase II: The feasibility and piloting phase (exploratory trial)

Phase III: Evaluating a complex intervention (e.g. definitive randomised controlled trial)

Phase IV: Long term implementation – putting evidence into practice

The preclinical phase is a theoretical phase where the research team should explore and decide what theoretical underpinnings the intervention could be based on. The questions to be asked are: What changes could be expected and based on what reasons? There can often be more than one theoretical approach to these questions, and previous studies on similar approaches could generally inform these questions. Theoretical assumptions could lead to changes in the intervention and to the implementation processes, by emphasising certain components.

In Phase I, the different components of the intervention should be tested in ordinary clinical settings in case studies and evaluated for relevant clinical outcomes. This could also be done by using qualitative methods through focus groups, stakeholder interviews or preliminary

surveys. The results should be used to remodel the intervention and prepare it for the next phase.

In Phase II, the intervention is tested in a pilot study for its feasibility and applicability, preferably in the settings where a future evaluation should take place. If the future evaluation is to be a randomised controlled study, randomisation in this phase could help to calculate an appropriate sample size. At this stage, a mixture of qualitative and quantitative methods could help to discover barriers and facilitators for the implementation as well as an estimation of possible effects. The results from a pilot study often lead to changes in the components of the intervention, the implementation process, the control condition, and the outcomes before a main evaluation trial. For example, in this phase it would be appropriate to determine the degree of standardisation of the intervention, the level of flexibility and the tailoring to the local context necessary in the next phases.

Phase III represents the main intervention trial. If this phase is supposed to assess effectiveness of the intervention one should always consider a controlled randomised trial if possible, because it is the most robust design to avoid selection bias. Since healthcare interventions often take place in group settings (e.g. NH, hospital wards, municipalities) where it can be difficult to avoid contamination of the intervention to the control group, cluster randomisation is an alternative. In cluster randomisation trials, the randomisation level is the setting, like the NH, and groups of residents from each setting are randomly allocated to the intervention condition or the control condition.

Finally, the last phase (Phase IV) concerns the dissemination of the intervention in real-world settings outside the context of the effectiveness trial. This usually implies long-term follow up and surveillance of implementation outcomes such as uptake and sustainability of the intervention (154, 206).

Efficacy (explanatory) or effectiveness trials (pragmatic) – why is the difference important?

From the very beginning of the planning of a complex intervention, researchers should address the question about where on the continuum between efficacy and an effectiveness a trial should be defined. The answer will have an impact on all aspects of a trial, such as deciding on the setting, type of recruitment, eligibility of participants, the delivery (by whom and with what degree of intensity) of the intervention, the degree of complexity of the intervention itself, frequency of follow-ups and the choice of outcomes (155, 156). Efficacy trials are characterised by strong control and a high degree of standardisation both at the programme level and at the intervention level. In contrast, to answer to the challenges that complex social systems offer regarding complex interventions, there is a need for interventions with a lower degree of standardisation (197, 207). This could be done at both the programme level and at the implementation level, allowing for flexibility and tailoring to the local context where the interventions are supposed to be implemented. Flexibility and adaptation to the context are characteristics of effectiveness trials. In general, the target population in efficacy trials in contrast to effectiveness trials, is narrowly defined to be more homogeneous using strict exclusion criteria. Table 5 (from Glasgow et al., 2003) summarises

the main characteristics of efficacy and effectiveness trials, using the RE-AIM evaluation framework (155). RE-AIM is an acronym for five evaluation dimensions: Reach (the number, proportion and characteristics of the target population that participated), Effectiveness or efficacy (the ability to change desired outcomes), Adoption (the number or proportion of settings that adopted the intervention), Implementation (how well the intervention was delivered as designed), and Maintenance (how well the programme effects are maintained and the continued use of the programme) (208-210). RE-AIM is an often-used evaluation framework for health care interventions that can be applied to inform all the phases of the development of a complex intervention.

Another important aspect of the difference between efficacy and effectiveness trials is the delivery of the interventions. If the research team performs the main parts of the interventions, including after an initial educational phase, then the trial is more consistent with an efficacy trial. In healthcare interventions, research staff usually bring in expertise to ensure that the interventions are consistently implemented, because the interventions are too complex for the stakeholders in the settings, or because they demand some formal qualifications to be delivered (156). Though this will result in enhanced internal validity, this will usually not be possible under normal non-trial conditions. Expert-led interventions, therefore, usually reduce the trial's external validity and the generalisability of the results (156).

Process evaluation of the implementation

Fixsen defined implementation as a set of specific activities combined in practice to introduce an activity or a programme with known components. Similar to an actual intervention (programme or model), the implementation includes a set of activities and a set of outcomes (211). It is this set of activities and outcomes that are to be evaluated in a study of a process evaluation. The MRC guidance (2016) advocates for the importance of performing a process evaluation nested within an effectiveness trial (154). This evaluation should be performed with the same high methodological standards as the trial for effectiveness. The main purposes of a process evaluation are to ease replication and future implementation by informing fidelity and quality of the implementation. A process evaluation could also clarify possible causal mechanisms of outcome results and inform health leaders and policymakers to what extent the intervention is flexible, easy to implement and can be adapted to the local context (154, 212).

In the document "Process evaluation of complex interventions", the MRC (2013) defined an overarching framework for the development and evaluation of complex interventions, emphasising the value of combining both quantitative and qualitative data in the process (212). A mixed-method design makes it possible to compare and interpret quantitative results from a survey or the outcomes of an RCT with findings from, for example, interviews exploring the perspectives of the stakeholders in health care services. This comparison may add to the validity of the results and to the value of the assumptions on possible causal

mechanisms of the effect of the intervention (213, 214). In the MRC guidance, the RE-AIM framework is described as a useful framework for assessing the overall implementation impact of interventions. Glasgow and colleagues (2003) proposed that the impact of an intervention can be conceptualised using the RE-AIM dimensions in the equation: Individual Impact (II) = Reach (R) × Effectiveness (E) × Implementation (I). At the organizational level the impact could be conceptualised as: Organisational Impact (OI) = Adoption (A) × Implementation (I) (155).

An effectiveness-implementation cluster randomised hybrid trial (215, 216) is a step further into the development of the design of effectiveness trials with the aim to shorten the time needed for translation from research results to dissemination in real-world settings. In a hybrid design, the research team develops a priori a plan for assessing both clinical effectiveness and the implementation process. Curran and colleagues (2012) proposed three different types of effectiveness-implementation hybrid design: (1) experimental testing of effectiveness of a clinical intervention on relevant outcomes whilst observing and collecting information on implementation; (2) experimental testing of both clinical outcomes and implementation interventions/strategies; and (3) experimental testing of an implementation strategy whilst observing and gathering information on the clinical intervention’s impact on relevant outcomes (215).

TABLE 5. Characteristics of Efficacy and Effectiveness Intervention Studies, using the RE-AIM¹ framework dimensions (from Glasgow et al., 2003) (155)

RE-AIM Issue	Efficacy Studies	Effectiveness Studies
Reach	Homogeneous, highly motivated sample; exclude those with complications and other comorbid problems	Broad, heterogeneous, representative sample; often use a defined population
Efficacy or Effectiveness	Intensive, specialised interventions that attempt to maximise effect size; very standardised; randomised designs	Brief, feasible interventions not requiring great expertise; adaptable to setting; randomised, time series, or quasi-experimental designs
Adoption	Usually 1 setting to reduce variability; settings with many resources and expert staff	Appeal to and work in multiple settings; able to be adapted to fit setting
Implementation	Implemented by research staff closely following specific protocol	Implemented by variety of different staff with competing demands, using adapted protocol
Maintenance	Few or no issues; focus on individual level.	Major issues; setting-level maintenance is as important as individual-level maintenance

Notes: ¹RE-AIM, Reach, Effectiveness, Adoption, Implementation, Maintenance

2.11 Learning and coping at work

Most of the care delivery-level interventions described in Chapter 2.8.2 aim at changing the staff's behaviours and actions towards residents by using educational programmes (25, 26). Therefore, although not always explicitly expressed, these interventions must be based on theories of learning, knowledge and coping strategies. As described earlier, NPS and the considerable extent of comorbidity amongst residents make heavy demands on the staff (217, 218). Both the staff's knowledge and their ability to understand and support the residents' needs and cope with complex ("wicked") problems will be challenged. Therefore, different theoretical aspects of knowledge, learning and coping will be discussed in this chapter.

2.11.1 Formal and situated learning

A pragmatic traditional definition of knowledge in the context of the NH could be the staff's knowingness about the residents' life story, dementia, and NPS as well as the residents' physical conditions. Knowledge also implies that the staff are able to translate and use this knowledge in their everyday interactions with the residents and with each other. External courses, as well as advice from specialists and experts are often used to improve staff knowledge defined this way. This view on knowledge can be regarded as the reproduction of already packaged knowledge delivered by others, either as generalised knowledge or as direct advice for referred residents (219, 220). One important question attached to this view on knowledge is how the staff can translate this abstract and generalised knowledge in their own context to a multitude of everyday, and infinitely new and changing complex, situations. Is this view on knowledge and learning consistent with the complexity of NH and NPS? As discussed earlier, agitation can be perceived as a "wicked" problem in which two of the main characteristics are that every problem is essentially a new one without any set of definite solutions. If this is correct, then there is a need to create a new type of knowledge in these situations for the staff in their approach to these problems.

These questions lead us to the notion of situated learning introduced by Lave and Wenger (221), to "reflection in action" by Schön (219), and to the notion of developmental learning by Ellström (222). Situated learning means that learning is essentially developed in the social situations and social systems that provide the context for the learning to take place. According to Lave and Wenger, learning is a process that takes place in a participation framework within practice in a group as a result of the sharing of different perspectives amongst the participants. The individual mind learns during this process, but the learning is mediated through a transformation and a learning process which affects the group as a whole.

Schön developed the notion of "reflection-in-action" in contrast to the notion of "knowing-in-action" (219). Knowing-in-action is knowledge that can be carried out spontaneously without reflection and even sometimes without any awareness on how the actions were

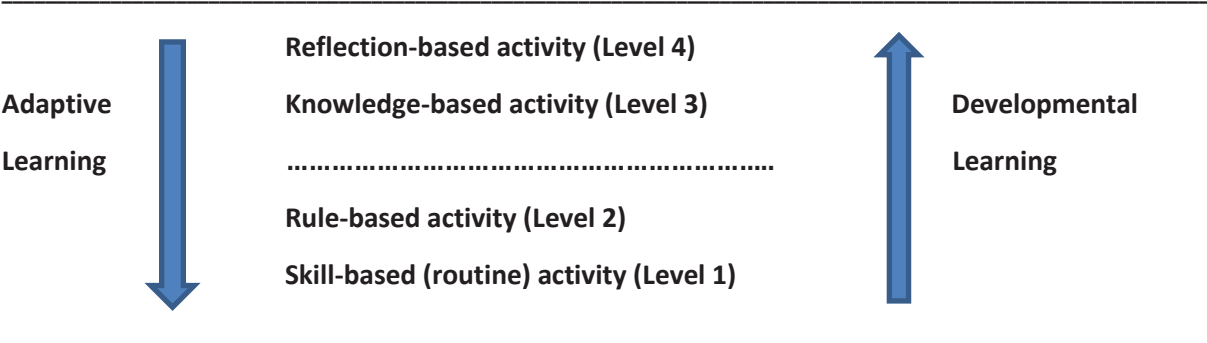
learned. To illustrate “reflection-in-action”, Schön used the example of how members of a good jazz band improvise together. In the bottom of the action lies a schema familiar to all the members. This means they all know the melody that brings in order, the basic knowledge of the melody. They also have basic general musical knowledge and skills and have a learned a repertoire of musical figures. However, jazz is about improvising. It is to create variations and to interact with the other musicians who, deliberately and consciously, act in different ways every time. They do not reflect with words, but with tones and rhythms. This example is not essentially different from reflecting with thoughts and words. In using the term “reflection-in-action” in discussing professional knowledge, Schön emphasised that this practice of reflection can last for minutes, hours, days or even months, depending on the problem or situation to be reflected upon. He stated that when dealing with divergent situations someone who reflects-in-action “becomes a researcher in the practice context”. The practitioners’ testing of possible actions to answer the question “What if?”, is a part of this reflection-in-action and is called an exploratory experiment. This experimental attitude towards reflection and action will be further developed when presenting the case conference in TIME.

Formal learning, or what Ellström (2001) calls adaptive learning, is a necessary learning activity but not sufficient in approaching complex problems (222). Formal learning can bring in new general knowledge, but there is also a need for what he describes as developmental learning. Developmental learning is based on systematic reflection both on actions and context. These conceptions of learning are closely related to the ideas and theories of situated learning introduced by Lave and Wenger (1991) and reflection-in-action by Schön (2008) (219, 221). Ellström (2006) has provided a typology in which activity in practice takes place at four different levels involving these two main different forms of learning (Figure 1) (220). These are: 1) skill-based (routine) activity; 2) rule-based activity; 3) knowledge-based activity; and 4) reflection-based activity. The daily routines in a NH involve activity at Levels 1 and 2, but if a resident’s NPS persist over a period, this will lead to a need for activity at Level 3 and often at Level 4. All the levels of activity specified here involve some degree of reflection, although mostly at Level 4. At Level 4, developmental learning can be focused and developed.

There are several conditions that need to be fulfilled to allow for developmental learning at work. One condition is what Ellström calls readiness to learn or a shared mental analytical model for interpreting experiences. To share this kind of knowledge, this mental model must be explicit, not tacit (219, 222). That is, to succeed in applying this form of learning activity, the staff must first “learn how to learn”. This means that they must adopt an awareness and a method of learning. Another important condition mentioned by Ellström is time. Time pressure tends to favour non-analytic decision-making processes, which in Ellström’s typology means favouring a skill-based level of action, meaning one performs as one usually does or in the same way as last time. This level of action is similar to Schön’s “knowing-in-action” and contrasts with the notion of “reflection-in-action”. Reflective activities require

time to observe what is going on before, stopping, thinking, and discussing and sharing ideas with others. In healthcare and in NH it also means to discuss and share ideas with the residents. However, it is equally important *how* time for reflection is used. The notion of “learn how to learn”, an analytical way of reflecting, must be shared collectively by all members of the organisation. This reflective learning process must be integrated into everyday activities at work. If not, the “shadow system”, or what from the perspective of complexity science can be labelled as self-organisation, will take over reflective activities, perhaps also outside the organisation and its goals (203).

Figure 1. Typology for adaptive and developmental learning according to Ellström (220)



2.11.2 Coping with complex problems

The ability to cope with complex everyday demands is crucial for the staff in their work in NH. Knowledge and learning as discussed in the previous paragraph are two important factors involved in coping strategies; however coping also involves other aspects (223). Psychologist Richard Lazarus (1991) has been one of the most influential contributors in research on stressors, coping and emotions (223). According to Lazarus, coping can be defined as cognitive and behavioural efforts to manage external and internal demands, including conflicts amongst them, when these demands are appraised as surpassing the person’s resources. In other words, coping is about the relationship between one’s thoughts (interpretations), emotions and behaviours and the context in which one lives (223). Lazarus further outlined two different coping strategies: problem-focused coping and emotion-focused strategies. The problem-focused coping process is based on actions to resolve problems, whilst emotion-based, also called cognitive-based coping, involves mainly new alternative interpretations of problems. The latter strategy usually takes place when the person interprets the situation as static and difficult to change. In the centre of both strategies is the person’s own appraisal and interpretation of the situation and the context. This appraisal and interpretation of the situation determine the emotional and the behavioural reaction to the situation. That is why the same situation can be perceived as stressful for one person and not stressful at all for another person. Both these coping strategies are deemed appropriate for the staff when approaching severe NPS in persons

with dementia. These coping strategies have much in common with principles from problem solving strategies used in cognitive behavioural therapy (CBT), which was one of the theoretical underpinnings for TIME when the model was first developed (28, 224).

2.12 The development and description of TIME

2.12.1 The development of TIME

The very first TIME

In 2007, when I was working as a part-time NH physician and as a general practitioner, a resident in our NH exhibited a behaviour that was perceived as extremely challenging by the staff. Only two or three of the staff seemed to be comfortable with the situation. The resident was continuously following the staff, asking the same repetitious questions that were not easily understood due to a progressive non-fluent aphasia. When he was not answered immediately, he would spit at them or try to hit or pinch them. This aggressive behaviour also took place during care situations such as washing, dressing, or assisting him to the toilet. It was evident that he was struggling, and he was often very anxious and sweating. There was a feeling of powerlessness in the staff. Any attempt they made to alleviate his distress it did not seem to work. They expressed that they had tried “everything”. Some of the staff were exhausted and started to feel reluctant to come to work. The situation in the ward was deemed chaotic. At that time, I was participating in a two-year continuing educational programme in cognitive behavioural therapy (CBT) for general practitioners. As a part of this training I had started practicing CBT for some of my patients in my general practice. I was struck by the effect of the structured approach from CBT in the consultations. Even in the most chaotic personal- and social situations, the problem solving method from CBT often helped the patient and I create a shared understanding of the situation and experiment with some rather simple solutions from consultation to consultation. It was not always a success, but often. Then, I asked the leading ward nurse at that time, Ann-Marit Tverå, if we could arrange for a meeting with most of the staff where we could use the same structuring techniques from CBT as I had done for individual consultations in my general practice. It turned out to have an amazing effect not only on the staff’s perception of the resident, but also on the resident’s agitation. Our immediate interpretation of this meeting was that we had managed to create a shared understanding amongst the staff of the situation and a common commitment on how to work with the resident in the weeks to come. In the following years, we used the same type of structured meetings, at that time called supervised meetings (case conferences), for many residents with NPS. In these first few years, the model was gradually refined and modelled by Tverå and me. In 2009, we began a collaboration with the Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, to further develop the model with the goal to test it scientifically.

National and international inspirations

In Norway, there was no official national guideline on NPS at the time of the development of TIME. Therefore, the development of TIME was mainly inspired by a nearly yearly attendance to the national dementia conference, “Demensdagene”, since the first conference in 1997 in Oslo, and by the pioneering work in the field of dementia in Norway by Knut Engedal and colleagues (47). We also relied on the international recommendations from the International Psychogeriatric association (IPA) on BPSD (143). However, the main reason for the elaboration of TIME was a perceived need in NH for a practical tool for the translation of existing recommendations for the assessment and treatment of NPS into the everyday clinical settings.

The two previous paragraphs describe what correspond to the preclinical phase (theoretical phase) of the development of complex interventions, according to Campbell and colleagues outlined in Chapter 2.10.2. In the next paragraph, the corresponding Phase I: Modelling process and outcomes, and the Phase II: The feasibility and piloting phase (exploratory trial) will be described (206).

The pilot study – and a remodelling of TIME

The first printed official version of the TIME manual was published in 2012, after a pilot-study in 2010-2011 conducted by the Centre for Old Age Psychiatric Research, Innlandet Hospital Trust. This study was an open non-controlled trial in nine NH over three months and included 30 persons with dementia and moderate to severe agitation. The main purpose of the pilot study was to test the feasibility of the intervention and the ability of the intervention to induce clinically meaningful change in outcome measures. The results showed that the residents’ agitation and mood symptoms and the staff’s distress were significantly reduced. It also showed that TIME was highly feasible but needed some modifications, mainly regarding the implementation process. The results from the pilot study were published as conference abstract in International Psychogeriatrics in 2011 and 2015 (29, 225).

The modifications of TIME were done after the pilot study and prior to the controlled randomised trial in 2016. The TIME manual was elaborated with more detailed instructions on how to perform the case conferences, and a second edition was published in 2015 (28). This was done based on the results from focus group interviews after the pilot study revealed that the TIME administrators asked for more instructions on this subject. In view of these demands, we also made available a web-accessible educational film illustrating the three phases of TIME, with an emphasis on how to conduct a case conference (226). We also expanded the educational programme given to the NH with two extra hours allowing for more exercises in the performance of case conferences. In 2015 a website was created as a support for the NH, www.tidmodell.no, with all the necessary information on how to use the model, as well as access to the TIME manual, the educational film, research projects and all

necessary assessments instruments. In 2018, this website was further developed as an interactive tool for the participants on the “train the trainer course in TIME”, an educational research project for the dissemination of the model on a larger scale in Norway (227). Part of the content of the website is available in English. TIME has also been implemented in psychiatric hospital wards using a modified educational programme for the staff (228).

2.12.2 The description of TIME

TIME represents a biopsychosocial approach and is a multicomponent interdisciplinary intervention for NH staff and physicians. TIME is based on the theoretical framework of CBT and PCC (125, 224, 229). The aim of TIME is to customise measures for the resident, building on a comprehensive assessment in accordance with the resident’s values, resources and preferences and a systematic group reflection.

The intervention with TIME consists of three overlapping phases (28):

- 1. A registration and assessment phase (Table 6)**
- 2. A guided reflection phase, including one or more case conferences (Table 7)**
- 3. An action and evaluation phase (Table 8)**

The division into phases is mainly done for educational purposes, since in practice one must often go back and forth between the phases. However, a case conference is usually more successful when a comprehensive assessment of the symptoms or behaviours at stake has been performed. Treatment actions should usually follow a systematic reflection in a case conference, but occasionally, actions must precede reflections and are to be reflected upon afterwards. Sometimes, a measure decided upon in a case conference is to perform a better assessment during the subsequent days because of a perceived lack of information. The phases are intertwined and the process is non-linear. These phases are consistent with reviews describing the “state-of-the-art” management of NPS (8, 15). The different components of TIME acting together thus provide an evidence-informed standardised approach to managing NPS.

The registration and assessment phase (Table 6)

In this phase, the staff gather personal background information with an emphasis on the persons preferences and resources, pain is assessed, NPS are registered in detailed 24-hour daily records, and NPS are assessed with established clinical instruments, including the NPI-NH. The NH physician performs an examination of the resident, and the resident’s previous medical records and medications are critically reviewed. The duration of this phase is not standardised and will vary from a few hours up to several weeks, depending on the nature and burden of the symptoms, how critical the situation is and the resources available in the NH.

The guided reflection phase (the case conferences) (Table 7)

In this phase, one or more case conferences are conducted for as many of the staff as possible, including the physician and the leading ward nurse. The goal of this guided reflection is to create a shared understanding of the actual NPS of the resident and to tailor a detailed treatment plan that will be tested in the upcoming weeks. The case conference has a fixed agenda, adapted from the agenda of individual consultations in CBT (230). The conference starts with the presentation of the resident's life story including resources and preferences followed by a short presentation of his or her mental and physical health. The participants of the case conference create a problem list, and they prioritise amongst the problems on the list. The case conference participants then reflect on the situation using the cognitive problem solving method, in which one problem is analysed at a time (231). This reflection is performed systematically using a five-column sheet technique on a whiteboard or on a shared display from a projector (230). The following five aspects for each problem are reviewed: assessed facts, interpretation, emotions, actions to take and evaluation. The theoretical underpinnings for the column technique will be explained in Chapter 2.12.3. In general, a case conference will last between 60-90 minutes. The time frame and the agenda for the case conferences are outlined in Table 7. The frequency of the case conferences is not standardised and will depend on the organisational routines and the resources available in the wards, but it is recommended that the NH incorporate a case conference as a part of the routines in the wards once or twice a month, in addition to on demand.

Table 6. Registration and assessment phase (28)

Checklist for the registration and assessment phase of TIME			
Activity	Target symptoms: Agree on the primary challenges for the resident using the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) to define precise target symptoms for the assessment		Responsible
	Observation of the target symptoms using a 24-hour observation form	Staff	
	NPI-NH ¹ to assess other neuropsychiatric symptoms	Staff	
	CSDD ² or another scale to assess possible symptoms of depression	Staff	
	Physical examination	Nursing home physician	
	Review of medication	Nursing home physician	
	MOBID-2 ³ or another assessment scale to assess possible pain	Staff Nursing home physician	
	CDR ⁴ and/or the MMSE ⁵ to assess the dementia stage	Staff Nursing home physician	
	PSMS ⁶ or another assessment scale to assess activities in daily life	Staff	
	Collection of resident life history, including preferences and resources, using an optional questionnaire	Staff interview the resident (if possible) and/or the next of kin	
	Make an appointment, i.e., set the date, time and place for the case conference	Staff/TIME administrator	

Notes: ¹Neuropsychiatric Inventory Nursing Home version (NPI-NH) (7); ²Cornell Scale of Depression in Dementia (CSDD) (232, 233), ³Mobilisation-Observation-Behavior-Intensity-Dementia Scale (MOBID-2) (234), ⁴Clinical dementia Rating Scale (CDR)(235); ⁵Mini-Mental State Examination (MMSE) (236), ⁶Physical Self-Maintenance Scale (PSMS) (237)

Table 7. Agenda and timeframe for the TIME case conference (28)

Agenda for the TIME case conference 60-90 minutes				
Activity	Preparation: Convene a meeting and prepare a meeting room with a blackboard or similar facilities (projector, if available). Check that a flip pad and markers are available	TIME administrators: One is the chairman for the meeting. One takes notes on the whiteboard One writes the minutes on the 5-column sheet		Responsible
	1. Status Report: Personal history and main points from the resident’s medical record are presented	10-15 min	Decide in advance who should prepare and present the resident’s personal history and the main points from the medical record	
	2. Create a problem list	10 min	Staff (as many as possible should attend the conference) The leading registered nurse and the nursing home physician should preferably attend the conference	
	3. Prioritise problems from the list			
	4. Draw a 5-column sheet on the whiteboard: facts – interpretations (thoughts) - emotions – actions – evaluation	60 min		
	5. Describe facts from the registration and assessment phase: one problem at a time			
	6. Suggest interpretations – guided discovery – discuss and reflect on them			
	7. Describe any emotions experienced by the staff – with interpretations by the staff			
	8. Suggest SMART¹ actions – based on the interpretations – decide how and when to perform an evaluation of the actions			
9. Summarise interpretations and actions – close the meeting	5-10 min	TIME-administrator (chairman)		

Notes: ¹SMART, Specific, Measurable, Actual, Realistic, Time-framed) (238)

The action and evaluation phase

As the actions and treatment measures are supposed to be tailored to each resident, they will display great variations. In this way, TIME serves as a guide for the staff to create actions and treatment measures that are customised to the resident’s resources and preferences, the NPS and the context in the NH. The list of potential actions is endless: music therapy, reminiscence therapy, increased physical activity, baking, facilitating ADL, aromatherapy, shielding (protecting), setting boundaries, validation therapy, reality orientation, initiatives to increase the involvement of the resident’s relatives, detailed procedures and advice for communication during care routines, agreeing on the distribution of responsibilities amongst the staff, etc. Actions to take can range from changes that affect the whole ward to ones that are targeted for the specific resident. Pharmacological actions may also be deemed necessary, but non-pharmacological options should be tested first whenever possible. The actions should then be registered in the daily/weekly plans, nursing plans, treatment plans, etc. (239). The minutes from the case conferences are supposed to use the same column technique as used on the blackboard and will serve as an immediate report created during the conference. Using a shared display with a projector and a computer will facilitate this task. The minutes serve as a long-term memory for the group (10).

To ensure that actions decided upon in the case conference are put into practice, they are to be described as SMART, an acronym commonly used in CBT. SMART stands for Specific, Measurable, Actual (or Achievable), Realistic and Time-framed (238). The evaluation of these actions is performed using the same clinical scales and observation forms as described in the first phase of TIME. To help the staff in performing a precise evaluation, five questions have been developed as a guide in the TIME-manual, see Table 8. A more detailed description of TIME can be found in the TIME manual, available in Norwegian and English, at www.tidmodell.no (28).

Table 8. Guiding questions for the evaluation of actions from the case conference (28)

An evaluation involves discussing these five points for every action or group of actions:

1.	Have the actions been carried out as planned?
2.	If the actions have not been carried out as planned, why? Do they need to be adjusted or can hindrances be removed?
3.	Have they had the desired effects on the target symptoms?
4.	Have they had undesirable effects or side effects that require a change or discontinuation of the programme?
5.	Should the actions be continued? In which case, for how long? When and how should the next evaluation be executed?

2.12.3 Educational programmes for TIME

Two educational programmes have been developed for the implementation of TIME in NH or other care settings: the TIME basic course and the Train the Trainer in TIME course.

The TIME basic course

The staff is first given a two hour lecture covering different aspects of dementia and NPS. Apart from in the TIME trial, this is made optional depending on the knowledge level in the staff on these themes, and the content of the lectures can also be adapted to the perceived knowledge needs. After this session, the staff is given a three hour training programme following the steps in the TIME manual, including an introduction to CBT. There will also be a role play in performing the case conferences. It is strongly recommended that all staff members attend the basic course to ensure a high degree of reach to facilitate implementation (fidelity) and ensure effectiveness (145, 209). To ensure interdisciplinarity and leader support for the implementation process, it is also recommended that the leading ward nurse and the NH physician attend the course (145, 240). In each ward, three nurses called TIME administrators, and who are selected by the leading ward nurse, are given the

main responsibility to implement TIME in the ward (i.e. implementation champions). They are given three additional hours of lectures and roleplay with special emphasis on the use of assessments instruments and instructions about leading a case conference. This session is to be adapted in its content to the knowledge of the TIME administrators in each ward. One specialist registered nurse from the education and training team attends and supervises the TIME administrators' first case conference in their NH. After having completed the educational programme the staff in the NH are supposed to be able to use TIME independently of the research and educational team.

The Train the Trainer in TIME course

The purpose of the Train the Trainer in TIME course is to promote dissemination of TIME. In this course, the participants are supposed to learn how to use TIME, as in the basic course, but also to learn how to arrange the TIME basic course in their municipality. To attend this course, one must be a registered nurse or have an equivalent or higher educational level in health or social care. The participants are given a two day course that consists of face-to face training sessions, including lectures and role play in performing case conferences. The main themes for the lectures are an update on dementia and NPS, an introduction to CBT, information about translating principles from person-centred care into practice, the components of TIME and instructions on how to arrange the TIME basic course. To be certified as a trainer in TIME, one must have attended the train the trainer course, arranged one TIME basic course, supervised one case conference for the TIME administrators at a ward and sent a written report of their experiences to the educational and training team. A research project with the aim to perform a process evaluation of this way of disseminating TIME was started in Mars 2018 as a collaboration between the Centre for Old Age Psychiatric Research, Innlandet Hospital Trust and The Joint Action Dementia II Project (Work package 6, Quality in Residential Care), funded by The European Union's Health Programme (227).

The participants of both courses have access to the TIME website, www.tidmodell.no, where they can find a detailed description of TIME, handouts, the TIME manual, an educational film, assessment instruments and other support for their performance of TIME. All the participants are given a printed version of the TIME manual. The TIME administrators and the trainers are given a ring binder each with all the necessary educational and implementation materials. The trainers will have an exclusive access to all educational materials, lectures and handouts they need for conducting lectures and training sessions for their operation of the TIME basic course. This website can also be used for the trainers as a communication channel for discussions, and for asking questions to the research leaders and educational group.

2.12.4 Principles from cognitive behavioural therapy (CBT) adapted to TIME

The problem solving method in TIME is adapted from CBT (224). In addition, in the development of TIME, a selection of principles from CBT were included in the model. Most

of the principles in CBT are easy to understand without being a professional or cognitive therapist. In individual therapy with CBT the ideal is collaborative empiricism, which means that the patient and the therapist are exploring the patient's world together from different perspectives but from the same level (241). Together, they use guided discovery, meaning the therapist uses the Socratic dialogue, to help and learn the patient to reflect upon and elucidate the challenges (241, 242). In the Socratic dialogue reflection is performed by using open-ended questions which are exploratory and promote logical thinking (242). Psychoeducation is essential, and the patient usually learns the ABC method as an analytic and learning tool for working with his or her symptoms. The ABC method will be further explained below. In TIME, the performance of the case conferences is inspired by collaborative empiricism where the staff, the TIME administrators, the leading ward nurse, and the NH physician explore the world of the resident from different perspectives, but in a non-hierarchical way. Guided discovery is the base for the reflections, as the TIME administrators who lead the case conferences are trained in Socratic dialogue. The whole staff have received training in the ABC method and its visualisation by the column technique as a part of the TIME basic course.

Structure form CBT as a means for enhancing coping for the staff

Individual consultations in CBT use nearly the same agenda each time with the purpose of creating a structure during the consultation to be more effective. A secondary effect is the reassuring and learning effect of structure itself for the patient when problems seem overwhelming and chaotic and the patient feels powerless and exhausted (230). Structure gives a direction for how to approach complex problems. That is why we have adapted this agenda to the case conference in TIME in the approach to complex (wicked) problems. The use of structure in TIME is presumed to enhance coping amongst the staff.

The ABC method and the column technique as an analytical and learning tool for NPS

In the column technique in CBT, every situation or problem is analysed in detail with columns for the situation (activating event or facts), thoughts (interpretations), emotions and behaviours, sometimes with a fifth column for alternative thoughts and behaviours (230). This represents a visualization of the ABC method, a method in CBT where A stands for the activating event, B for beliefs (thoughts) and C for consequences, including emotions and behaviours (224, 229). In cognitive therapy, the main idea is that our beliefs or interpretations (B) of the activating event (A), determine our behaviours and emotions (C). Following this, our emotions and behaviours will change if we change our beliefs. This is, of course, a simplistic presentation of the theories underpinning CBT, but it provides a simple and rather intuitive model for people to start analysing their own unhelpful and inappropriate thoughts. The five columns in TIME represent the facts concerning the NPS and the situation (A), the thoughts (i.e. the staff's interpretations) (B), the emotions (staff's emotional reactions) (C), the treatment actions (C) and the evaluation measures. An example of the use of this column technique in a case conference is presented in Table 9. One of the

main tasks in the educational programme in TIME is to train the staff in the ABC method and teach them to differentiate between facts (what we can observe or measure), interpretations, and emotions. Staff are taught that thoughts and interpretations are not facts and are liable to be changed by reflection.

An important point is that the column technique used as an analytical tool for NPS will be repeated many times. In this way, the staff are given the possibility to learn how to methodically relate to NPS in the same way every time, including outside the case conferences. This analytical learning approach is the same for every resident, but the action and treatment measures that are finally adopted are individual, based on flexibility and customised to the individual resident. The goal is to give the staff a feeling of security and coping, which can also have a beneficial effect on the environment in the ward for all residents.

Table 9 An example of a five-column sheet from a case conference (28)

Facts	Interpretations, thoughts, understanding	Feelings and emotional reactions (from staff)	What to do? Actions and treatments	Evaluation - how and when
<p>Aggression At bedtime, hits and kicks the staff when receiving care</p> <p>Anger and swearing when staff change over</p> <p>Every day</p>	<p>“He does it deliberately?” He has frontal lobe involvement, resulting in reduced control and options</p> <p>Dementia is advanced, he doesn’t understand</p> <p>We are unsafe, can be injured? No one has been injured so far, he is not strong, little danger.</p> <p>We have too few people on shift? We have tried utilising more, it didn’t help</p> <p>Side effects of haloperidol and oxazepam: weakened cognition</p> <p>At shift changeover - busy and little contact with staff; sundowning; overburdening during the day, increased confusion</p>	<p>Irritation and anger</p> <p>Anxiety</p>	<p>Acceptance of the behaviour as a part of his disease, leaving him no choice</p> <p>Training, techniques to avoid blows</p> <p>Split day between staff – see list</p> <p>Avoid leaving him alone at shift changeover</p> <p>Reality orientation before confusion builds up</p> <p>Shield in own room if possible after dinner, rest, use music he likes</p> <p>Preventive: go for walk just before dinner</p> <p>Check music preferences – obtain CD – speak with relatives</p> <p>Stop haloperidol first, then stop oxazepam. After one week, consider giving donepezil 5 mg, increasing to 10 mg after 4 weeks</p>	<p>Continue behaviour registration, brief review at physician’s visit: 2 weeks</p>

Treatment measures perceived as experiments

In CBT, behavioural experiments are an important tool as a source of information for the treatment, especially if the patient has an affective disorder (231, 242). The patient agrees with the therapist to do something new or something she has avoided doing, just as an experiment, and then note how she manages to perform the task, symptoms that arise etc. The purpose is often to disprove dysfunctional thoughts that the patient had in advance about the task, and to encourage for more variation in the patient behavioural repertoire. Denoting the task as an *experiment* makes it changeable, not eternal, and requires an evaluation. It opens up more creativity in the choice of possible tasks. In TIME, the treatment measures are to be perceived by the staff as experiments to not only enhance creativity in the choice of measures, but also to ensure that they are properly evaluated. The notion of experiments in the approach to complex problems is in line with theories from complexity sciences because of the unpredictability and non-linear characteristics of complex problems, as discussed in Chapter 2.10.1. Furthermore, in his concept of reflection-in-action, Schön

introduced what he called the exploratory experiment as an important tool for learning in practice (219) (See Chapter 2.11.1).

Understanding the interrelation aspect of behaviour

In TIME, as in CBT, human behaviour is understood as being subject to biological, psychological, and social factors (231). This usually demands an extensive assessment of NPS, as seen in the registration and assessment phase of TIME. Behaviour is often relational, and mutually influenced by interacting with others, which is why challenging behaviour in residents is often seen when they are interacting with other residents or staff, for example, at mealtimes or during personal care (8, 200). According to cognitive psychology, the way one interprets a person's behaviour influences and shapes one's own behaviour towards the person; in this way, one can maintain, reinforce, or change the behaviour of the person. By reassessing unhelpful thoughts and interpretations, our emotions and behaviour in a given situation can be changed (230, 242). Cognitive behavioural therapy recognises that humans are, to a large extent, influenced by their surroundings. However, one can contribute to the way one feels by changing unhelpful interpretations and behaviour, even though the surroundings cannot be changed (230, 242). Sometimes, for example, in the case of advanced dementia, the residents' behaviour cannot be changed, no matter what measures are taken; however, practitioners and staff can change their interpretation of the residents' behaviour. If they are successful in changing their mindset, it may be easier to endure the period they are caring for the resident and thereby provide her with good quality care.

2.12.5 Person-centred care in TIME

Including person-centred care and the VIPS framework in TIME

One of the theoretical underpinnings for TIME are principles derived from person-centred care (125). There are many common traits in the understanding of NPS between CBT and person-centred care. Both emphasise the relational aspect in the understanding of behaviour, and recognise that an approach should combine biological, social and psychological factors. Both state that it is mainly the interaction between these factors that produces the symptom complexity in the individual resident (125, 231). Both emphasise that treatment actions must be customised for the individual resident if they are to have any effect. When Tom Kitwood introduced the concept of person-centred care (PCC) in the 1990s, he defined what he called personhood as "a standing or status that is bestowed upon one human being, by others, in the context of relationships and social being. It implies recognition, respect and trust"(125). To arrive at this definition he relied on discourses of transcendence stating that "being-in-itself is sacred", on ethical discourses stating that "each person has absolute value", and from social psychology that the person's self-esteem is linked to given roles and the person's place in a social setting (125). Kitwood's philosophy on person-centred care has been summarised through the VIPS framework (172, 173, 243). VIPS is an acronym for the following dimensions:

- Valuing persons with dementia

- Individualised care
- the Perspective of the person with dementia
- Social inclusion

A list of 24 indicators were developed to concretise the four dimensions above and are meant to guide the staff in their service to provide PCC for persons with dementia (173) . The VIPS framework states that a person has an independent value irrespective of the disease and level of functioning. Treatment and care for the person must be based on the person's individual life story, preferences, resources and abilities. To understand the individual's symptoms and behaviour, one must always strive to understand the situation from his or her perspective. In addition, there must be an emphasis on the social environment where the person lives. An effort should be done to preserve existing social relationships and to establish new ones. The challenges of person-centred care have been to transfer the complex theoretical set of ideas to the field of practice. This has, for example, been done by introducing the VIPS Practice Model and Dementia Care Mapping (DCM) (151, 243).

In TIME, the three phases make use of all the principles from person-centred care and the VIPS-framework (28). In the registration and assessment phase, the resident's personal history, values, resources and preferences are central when gathering information from the residents themselves and their families. This information is then used in the case conferences, where one of the main questions the participants reflect upon is precisely what they think are the resident's own thoughts behind his or her behaviour and symptoms, i.e. the resident's perspective. The actions to agree upon in the case conference and to be tested in the action and evaluation phase, are to be personalised to the individual resident based on all available information. In summary, the treatment actions must be customised for the resident based on a rigorous assessment of social, psychological, and biological factors.

Staff's feelings

Kitwood's ideas on person-centred care were not only restrained to the personhood of the person with dementia, but he also wrote about the personhood of the care staff. In the book "The New Culture of Dementia Care" from 1995, which he edited along with Sue Benson, he claimed that staff cannot give person-centred care to others if their own personhood is not acknowledged (244). One of the key components in this process, according to Kitwood, is not for the staff to hide behind a professional mask, but to allow them to be in touch with their feelings and vulnerabilities. During the TIME case conference, there is time dedicated to revealing and discussing their feelings such as sadness, helplessness, fear, anger, and irritability. The purpose is to help the staff to realise that such feelings are normal, but that they can affect their interactions with the resident. By accepting this, they can discuss how to manage such feelings and help themselves to understand the feelings by using the ABC method from CBT. Strong and unpleasant feelings can then be reduced once a more realistic understanding and interpretation of the situation has been reached (28).

3.0 The present thesis

Although TIME was developed in 2007-2009 by the author of this thesis, and later revised after a pilot study in 2010 (29), the work with the thesis started in 2015 at the Centre of Old Age Psychiatric Research, Innlandet Hospital Trust, with the planning of the TIME-study.

3.1 Aims

The overarching aim of this thesis is to describe the development and the evaluation of a Norwegian interdisciplinary model for the evaluation and treatment of NPS, TIME. Chapter 2.12 gives a description of the different components of TIME and the development of TIME from the conception of the idea of the model to a fully developed testable mode. The evaluation of TIME was performed by addressing these three aims:

1. To test if TIME reduces agitation in nursing homes residents with dementia.
2. To explore the staff's experiences with TIME and how the model meets the challenges when dealing with the complexity of NPS.
3. To perform a process evaluation of the intervention of TIME to ease replication and future implementation and clarify possible causal mechanisms of effectiveness at the resident level.

3.2 Design

To address the aims of the study we conducted three substudies using an effectiveness-implementation hybrid, type 2 design. In this design, experimental testing of both clinical outcomes and implementation interventions/strategies are planned a priori and executed during one overarching study (215, 216).

Paper 1 reports from the protocol of the TIME study with the study design for all three substudies.

In Sub-Study 1 (Paper 2), we used an experimental design by conducting a three month cluster randomised controlled trial, where we tested the hypothesis that TIME could reduce agitation in residents with dementia living in NH.

In Sub-Study 2 (Paper 3), we used a qualitative explorative design with focus group interviews to explore the staff's experiences with TIME.

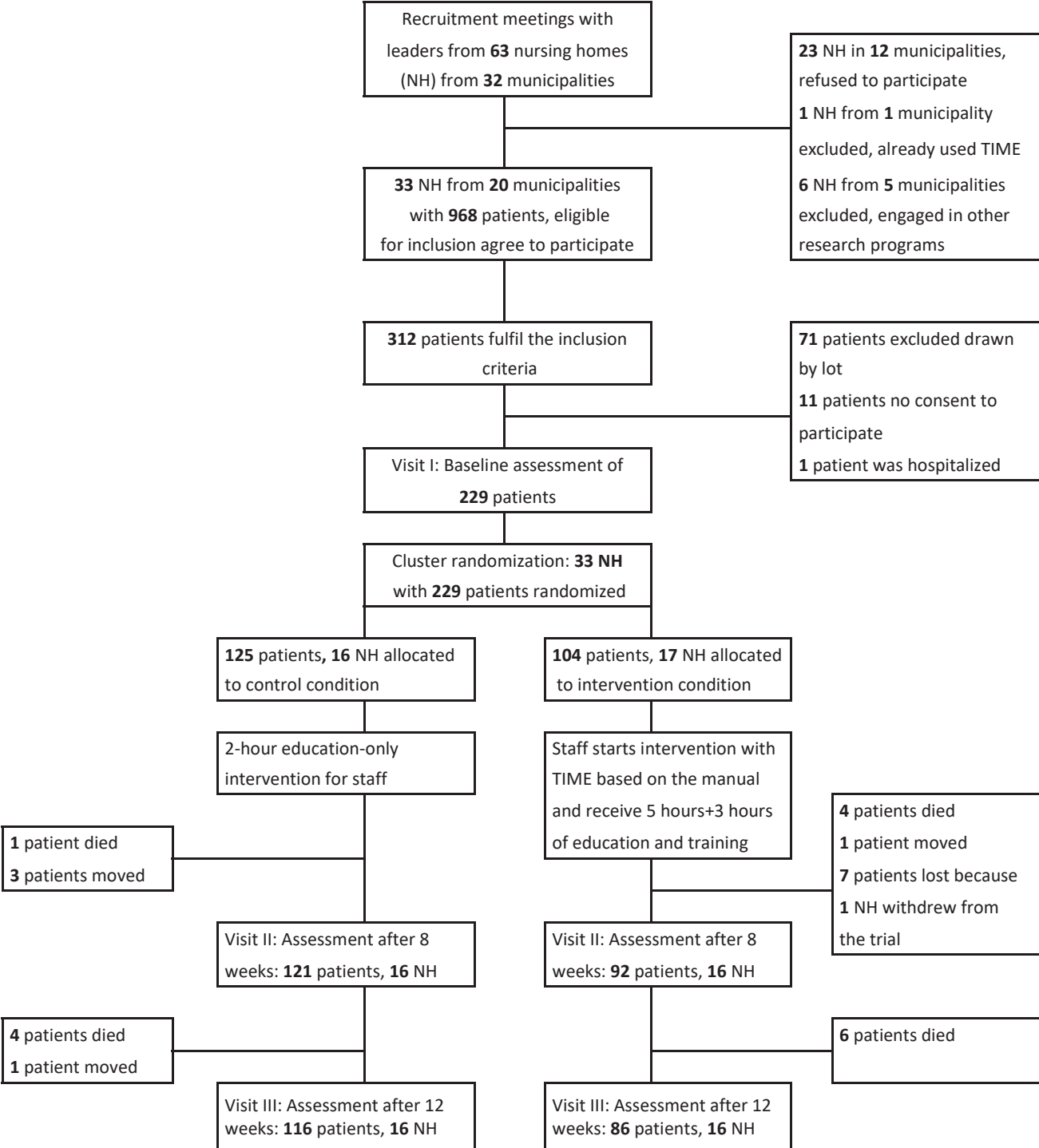
In Sub-Study 3 (Paper 4), to perform a process evaluation, we conducted a 12-month mixed method study with a quasi-experimental (pre-test/post-test, control group) design with questionnaires and a qualitative exploratory design with focus groups interviews and document analysis.

3.3 Methods

3.3.1 Settings

Sixty-three municipalities with a total of 130 NH located in the north, middle and south-eastern parts of Norway were invited to take part in the study. The approach was effectuated by an e-mail invitation to the manager of the elderly care department of each municipality. NH already using TIME, NH engaged in other research projects and NH that primarily offered short-term care were not invited. The research team arranged information meetings for managers and physicians from NH in 32 municipalities that responded positively to the invitation. In these municipalities there were 63 NH. Finally, 33 NH in 20 municipalities agreed to take part in the trial (Figure 2).

Figure 2. Flowchart of the clusters and individuals throughout the phases of trial



3.3.2 Participants

Residents

All residents in the wards in participating NH were considered eligible for inclusion in the trial and were assessed against our inclusion criteria. Inclusion criteria were:

1. probable dementia, defined as a Clinical Dementia Rating scale (CDR) (235) score of 1 or higher
2. a moderate to high degree of agitation, defined as a score of at least 6 on the single agitation/aggression item of the Neuropsychiatric Inventory Nursing Home Version (NPI-NH) (7)
3. being a long-term resident, residing in the NH for at least two weeks before inclusion

Exclusion criterion was:

1. life expectancy of less than six weeks.

Staff

In the process evaluation of the trial, all staff members both regular and temporary staff members, were invited to participate in the survey by receiving questionnaires at baseline, including 797 staff members and 22 leading ward nurses from INH and 889 staff members and 24 leading ward nurses from CNH.

The five focus groups consisted of 32 staff members from 11 of the 17 INH, 10 registered nurses, 12 auxiliary nurses, seven leading ward nurses and three NH physicians. We used purposeful sampling of the participants, with homogenous groups (245). To ensure information-rich participants, the leading ward nurse in each NH designated the staff members to attend the focus groups (246). The leaders were instructed to select participants that were familiar with TIME and whom they judged would be able to promote views in a group context, disregarding profession. To minimise selection bias in selecting the NH to be represented in the groups, we selected them randomly from the pool of 17 NH that had received the TIME intervention (247).

3.3.3 Cluster randomisation

We performed cluster randomisation, using the NH as the cluster, because of the risk of transmitting all or parts of the intervention model to the control units or individual control residents at the same NH (248). NH were first stratified by size into three blocks to ensure approximately equal numbers of residents in the two trial arms. Block size was fixed, depending on the number of residents fulfilling the inclusion criteria in each cluster: Block 1 had 1-5 residents, Block 2 had 6-9 residents, and Block 3 had 10 or more residents. Within each block, NH were randomly assigned 1:1 to either the intervention group or the control group. A researcher performed the randomisation procedure independently of the project management team and the NH. The project management team then provided the NH with the randomisation and allocation results immediately after this procedure.

3.3.4 Interventions

Similar educational sessions for the staff in CNH and INH—CNH continue practice as usual

Three nurses in each unit in both the INH and CNH were given a special responsibility in the trial. Before randomisation, these nurses completed a three-hour training session in the procedures for the trial. Their main task was to facilitate the interviews for the assessments at baseline, and after eight and 12 weeks. These nurses were selected by the leading ward nurse based on the following criteria: nurses who work on a nearly full-time basis, have shown interest in professional development and have gained legitimacy with the rest of the staff. Thus, these nurses could be selected amongst registered nurses, auxiliary nurses, nursing aides or members of other professional groups in the NH.

After randomisation, the entire staff in the INH and the CNH were given a two-hour lecture about dementia, person-centred care and NPS. This lecture represented the education-only intervention administered to the staff in the CNH. These staff members then continued practice as usual for the residents throughout the remainder of the trial.

Exclusive education and training of staff in the INH—intervention utilising TIME in the INH

In addition to the two-hour lecture about dementia and NPS, the staff in the INH completed three hours of lectures, training and roleplay related to TIME. The education and training team responsible for conducting the education and training sessions consisted of the project management team (a physician with special competence in NH medicine and two specialist registered nurses in geriatrics) and four specialist registered nurses in old age psychiatry, all of whom were familiar with TIME. Training sessions were always performed by a group consisting of two persons from the team, and the INH were evenly distributed amongst the team members. The lectures were standardised according to the steps listed in the TIME manual. The leading ward nurse of each ward in the INH was supposed to attend these lectures to ensure that this leading nurse provided support to the staff during the trial. We encouraged the NH physicians to participate. The staff were also given access to an educational film about TIME and a website to support the intervention. The three nurses in each unit in the INH who participated in the common three-hour training session in the procedures for the trial for both INH and CNH described above, held a special responsibility for putting the model into practice based on the manual. These nurses, therefore, received three additional hours of education, training and role play related to the different components of TIME and the implementation of the intervention. These lessons were adapted to their knowledge and skill levels after a brief oral assessment by the educational team. In the trial, they were referred to as the TIME administrators.

Immediately after randomisation and allocation, the project management team contacted the TIME administrators via telephone and instructed them to begin to implement the intervention according to the steps in TIME manual for the residents included in the trial (See Chapter 2.12.2 for the description of TIME). Elapsed time between baseline assessment and intervention initiation varied from one to six days. The TIME manual was available online.

One specialist registered nurse from the education and training team attended and supervised the TIME administrators' first case conference about their first resident in the

NH. For the remainder of the TIME intervention, and for the other residents included in the trial, the TIME administrators and the staff carried out the intervention independently.

3.3.5 Data collection and measurements of quantitative data (Papers 2 and 4)

For the RCT (Paper 2), before randomisation, specially trained project nurses not affiliated with the NH assessed the residents' baseline characteristics via telephone by interviewing the staff members who best knew the residents. The same assessors also assessed the effects of interventions eight and twelve weeks later using the same procedures. The assessors were blinded to the randomisation. All 10 assessors were nurses with substantial experience and formal training on the use of the assessment scales. They attended a one-day course on the use of the assessment scales before the start of the trial.

In the process evaluation study (Paper 4), questionnaires were distributed to the staff and the leaders through their work e-mail. An overview of the questionnaires in this study, their timeframe, the target population (i.e. staff members or leadership in INH or CNH) and their relation to the RE-AIM dimensions are presented in Table 10. The complete set of questionnaires is presented in Appendix 1 (Questionnaires for the staff) to Paper 4 at the end of this thesis (Original papers).

Primary and secondary outcomes in the RCT (Paper 2)

The primary outcome was the difference in the change between the intervention and control group in agitation/aggression at eight weeks from baseline, as measured by the single item agitation/aggression of the NPI-NH. The secondary outcomes were the difference in change between the two groups in agitation/aggression from baseline to 12 weeks as well as the changes from baseline to eight and to 12 weeks in all other single NPI-NH items, NPI-10 sum, NPI-subsyndromal agitation score, NPI-subsyndromal psychosis score, NPI-subsyndromal affective symptoms and NPI-Sum of caregiver disruptiveness. Similarly, the differences in change between the two groups from baseline to eight and to 12 weeks in agitation measured by the Cohen-Mansfield Agitation Inventory (CMAI)(95), symptoms of depression measured by the Cornell Scale for Depression in Dementia (CSDD) (232, 233), quality of life measured the Quality of Life in Late-Stage Dementia (QUALID) Scale (249, 250) and use of psychotropic and analgesic medications given regularly, coded and grouped according to the Anatomical Therapeutic Chemical index were also defined as secondary outcomes (251) .

As a post-hoc analysis not included in the published paper or the protocol for the RCT, we decided to evaluate as an outcome the percentage reduction in the single item NPI-NH agitation/aggression scores from baseline to eight and 12 weeks and the proportion of residents achieving standard thresholds of response. We defined these thresholds of response as a reduction in the single item agitation/aggression of 30% (clinically meaningful

response) and 50% (marked reduction). The NPI manual suggests that a 30% decrease in scores is generally clinically meaningful (162).

Neuropsychiatric Inventory - Nursing Home Version (NPI-NH)

The Norwegian version of the NPI-NH has shown high inter-rater reliability and validity (250). The NPI-NH assesses the frequency (0-4) and the severity (0-3) of 12 psychological and behavioural symptoms. An item score is generated by multiplying frequency by severity, giving a range of 0-12, where higher scores indicate more frequent and severe NPS. The NPI-NH sum score represents the sum of all 12 items, with a range of 0-144. The NPI-NH 10 sum score (range, 0-120) represents the sum of all NPI-NH items except the last two, night-time behaviour and appetite disturbance/eating change, which primarily capture vegetative symptoms. The NPI-subsyndromal agitation score is the sum of the aggression/agitation, disinhibition and irritability items, with a range of 0-36. The NPI-subsyndromal psychosis score (range 0-24) is the sum of the delusions and hallucinations items, and the NPI-subsyndromal affective score (range 0-24) is the sum of the depression and anxiety items. These subsyndromes are based on data from a previous principal component analysis amongst NH residents with dementia (65). In the NPI-sum of occupational disruptiveness, the caregiver rates the disruptiveness of each behaviour or symptom on a five-point scale, resulting in a range of 0-60, where higher scores indicate more disruptive behaviour.

Cohen-Mansfield Agitation Inventory (CMAI) (95), Cornell Scale for Depression in Dementia (CSDD) (232, 233) and Quality of Life in Late-stage Dementia (QUALID) Scale (249, 250)

The CMAI measures 29 types of agitation symptoms and the frequency at which they occur. Each item is scored between 1-7, where higher scores indicate more frequent agitation. The range for the total score is 29-203. The CSDD assesses symptoms of depression, and higher scores indicate greater severity (range 0-38). The QUALID assesses quality of life by rating 11 behaviours on a five-point Likert scale, where lower scores indicate higher quality of life (range, 11-55).

Covariates in the RCT

Measured covariates in the RCT were: level of dementia, as assessed by the CDR (235); level of functioning in daily activities, as measured by the Physical Self-Maintenance Scale (PSMS)(237) and physical health, as measured by the General Medical Health Rating Scale (GMHR)(252). The CDR is a six-item instrument where the total score is produced using an algorithm giving precedence to memory. Scores of 0, 0.5, 1, 2 and 3 indicate no dementia, questionable dementia, mild dementia, moderate dementia, and severe dementia, respectively. The PSMS is a six-item scale that produces a sum score with a range of 6-30, where higher scores denote more severe functional impairment. The GMHR is a one-item global rating scale with categories of good, fairly good, poor and very poor.

Residents demographic and clinical characteristics

The following data from residents' medical records were collected: age, gender, marital status, type of ward (regular somatic ward, special care units for residents with dementia or other types), known diagnoses (chronic diseases) and known dementia diagnosis.

Ward and staff characteristics

The questionnaires distributed to the staff at baseline collected demographic information from the staff, such as age, employment relationship, percentage of full-time engagement, number of years of experience in health-related jobs and number of years of health-related and relevant continuing education. Organisational and structural factors of the NH wards were obtained at baseline from the leading ward nurses: type of ward (special care unit, regular ward or other type of ward), the ward size (number of residents and the number of staff working full-time), the number of staff working per resident during the day time, and the number of hours the NH physician was worked per resident per week.

Questionnaires for the staff and leaders

The following three questionnaires were administered to the staff before the start of the intervention (i.e. before randomisation of the NH), and six and 12 months later, in both INH and CNH (name or acronym of questionnaires, RE-AIM dimensions): the Approach to Dementia Questionnaire (ADQ, Effectiveness at staff level) (253, 254), the General Nordic Questionnaire for Psychological and Social Factors at Work regarding mastery and social interaction (QPS-Nordic, Effectiveness at staff level) (255), and a brief self-developed questionnaire assessing perceived competence for individual staff members regarding NPS (Competence Questionnaire, Effectiveness at staff level). Only the staff members who answered a questionnaire at baseline received a follow-up questionnaire at six months, and only those who answered at six months received a follow-up questionnaire at 12 months.

ADQ (253, 254)

The ADQ assesses general attitudes to dementia, and has been validated (254) and translated to a Norwegian version (253). The questionnaire consists of 19 statements, and respondents indicated on a five-point Likert scale from 1 (strongly agree) to 5 (strongly disagree), the extent to which each statement was in accordance with their attitudes. The total sum score has a range of 19-95, with higher scores signifying more positive attitudes. A factor analysis resulted in two domains: the "hope" attitude (8 items, range 8-40) and the "person-centred" attitude (11 items, range 11-55) (254).

QPS-Nordic (255)

The QPS-Nordic has been validated in a Norwegian version, and consists of 13 subscales, covering essential social and psychological factors at work (255). The two subscales labelled Perception of Mastery and Perception of Social Interaction were used. Respondents indicated how appropriate each statement on the scales was for their situation on a five-point Likert scale from 1 (very seldom or never) to 5 (very often or always). Each subscale consists of six items, giving a subscale score with a range of 6-30.

Competence Questionnaire

The Competence Questionnaire consisted of five statements. The respondents indicated how appropriate each statement was for their situation on a seven-point Likert scale from 1 (very low competence) to 7 (very high competence), giving a total sum score between 7-35. Competence was defined in the questionnaire as a composition of the concepts “knowledge” and “skills” (256).

Fidelity Questionnaire (Implementation)

This was a questionnaire constructed for this study to assess the performance of the main 10 components of the TIME was addressed by a brief telephone interview with one of the TIME administrators in the INH for each included resident, up to three times during the trial with an interval of three to four weeks. Each component was given a score of 1 if it was performed except for the performance of the case conference, which was given a score of 8, and the evaluation procedure which was given a score of 4. The weighting of the score was based on the presumed time to perform each component. The sum score of the questionnaire thus had a score between 0-20, where a higher score indicates a higher level of fidelity to the model. A score of 20 for a resident, means that 100% of the components for the resident were performed.

Current Practice Questionnaire (Adoption and Maintenance)

This was a questionnaire developed for the assessment and the treatment routines of NPS at the ward level, which was distributed to the leading ward nurses before the start of the intervention, and six and 12 months later, in both the INH and CNH. This questionnaire was developed by the research team based on the TIME manual and evidence-informed best practices (8, 28, 148). Respondents indicated how appropriate each statement was for their situation on a five-point Likert scale, from 1 (very seldom or never) to 5 (very often or always). The questionnaire consists of 13 items, giving a sum score of 13-65 where a higher score indicates better practices for the assessment and treatment of NPS.

Participation of staff, leaders, and physicians (Reach)

A registration form to assess the participation of staff, leaders and physicians in education and training sessions was used. The Reach fraction for the attendance to the training sessions was calculated by the number of participants per ward who attended the training sessions divided by the number of potential participants (i.e. the total number of regular and temporary staff in the ward) (209).

Table 10. Overview of questionnaires distributed to the staff and the leading ward nurses, timeframe and their relation to the RE-AIM-framework¹

What is assessed	Questionnaires	Corresponding dimension of the RE-AIM framework	Time frame	Respondents in the nursing homes (NH)
Proportion of staff members participating in education and training sessions	A registration form	Reach: proportion of staff in INH that actually participated in the intervention during the trial	At the start of the intervention during education sessions	All staff members in intervention nursing homes (INH)
Attitudes towards persons with dementia, mastery, social interaction, job satisfaction and self-assessment of competence with neuropsychiatric symptoms (NPS)	ADQ ² , QPS-Nordic ³ and The Competence Questionnaire (a self-developed questionnaire for assessment of competence with NPS)	Efficacy: outcomes regarding knowledge, skills and/or attitudes of the staff in NH	1 month before (baseline), and 6 and 12 months after the start of the intervention	All staff members in control nursing homes (CNH) and in INH
Clinical routines in place in NH, i.e., questions assessing daily routines of practice for assessment and treatment of NPS at the ward level	The Current Practice Questionnaire (a self-developed questionnaire based on evidence-informed best practice for the assessment and treatment of NPS)	Adoption: proportion of wards that will adopt the intervention Maintenance: extent to which the model is sustained over time	1 month before (baseline) and 6 and 12 months after the start of the intervention	Leading ward nurse in INH and CNH
Fidelity to the main components in the model	The Fidelity Questionnaire: (Interview of TIME administrators by telephone using a checklist based on the components in the TIME manual)	Implementation: extent to which the intervention is implemented	3 brief interviews, the first one 3 weeks after the start of the intervention and then at 1-month intervals	TIME administrators in INH
Organisational structure in the nursing homes: size of wards, type of unit, number of staff, etc.	A registration form	Implementation: possibility to assess and analyse implementation barriers and facilitators	At the start of the intervention	Leading ward nurse in INH and CNH

¹RE-AIM Reach Effectiveness Adoption Implementation Maintenance (208); ²ADQ The Approach to the Dementia Questionnaire (253); ³QPS-Nordic The General Nordic Questionnaire for Psychological and Social Factors at Work (255).

3.3.6 Data collection of qualitative data (Papers 3 and 4)

Focus groups

Five focus groups were composed as follows: two staff groups with eight and six informants consisting of staff members, registered nurses and auxiliary nurses (where two staff members together in each group came from the same NH); one TIME-administrator group with eight registered nurses and auxiliary nurses; one leader group with seven leading ward nurses and one physician group with three NH physicians (one participant from each NH in these last three groups). All five focus interviews took place in a meeting room at a hotel. Each group met once for a 90-minute interview. The moderators were the authors of this thesis for three of the interviews and the second author of Paper 3, JM, for two of the interviews. They were both present either as moderator or facilitator for all five interviews. The third author of the second paper, AG, participated in three interviews, and served as a co-facilitator. She posed follow-up questions towards the end of each interview. The interviews were based on a semi-structured interview guide where the informants were asked to reflect on two main themes (257): 1) coping and learning experiences in working with residents with dementia and NPS and 2) implementation and sustainability of the intervention (Table 11). These main themes were followed up with open-ended and exploratory questions whenever necessary. When other key themes spontaneously emerged during the interviews, time was allotted to elaborate these themes. At the end of each interview, the facilitator summarised the main explicit content and key findings of the interview and asked the participants to verify or amend the summary. The interview guide was the same for all five groups. The interviews were recorded and transcribed verbatim by the first and second author and cross-checked by listening to the recorded interviews.

Minutes from the case conferences

To further assess implementation we collected the minutes from 84 of the 85 case conferences conducted in INH (258, 259). The minutes were all written by one staff member from each ward during the case conference using the five-column sheet for problem analysis from the TIME manual (28). The use of the five-column sheet for problem analysis was part of the training sessions for the staff in the intervention NH. The main purpose of writing minutes during the case conferences was to create a written documentation to be integrated in the residents' care plans.

Table 11 The interview guide used in the focus groups interviews

Themes	Questions used in the interviews
1. Coping and learning in working with residents with dementia and NPS	<p>What are your thoughts/views about your own knowledge in your work with residents with dementia and neuropsychiatric symptoms? Same question was posed for attitudes, skills, and coping.</p> <p>Same questions as above, but now about their thoughts/views concerning the rest of the staff.</p> <p>Has using TIME affected your own knowledge in your work with residents with dementia and neuropsychiatric symptoms? If so, in what way? Same question was posed for attitudes, skills, and coping.</p> <p>Same questions as above: but now their thoughts/views concerning the rest of the staff.</p>
2. Implementation and sustainability of the intervention ¹	<p>What conditions are of significance to adopt a model like TIME in your ward?</p> <p>What promotes and inhibits the adoption of such a model?</p> <p>Conditions in the ward?</p> <p>Conditions concerning the education and training programme for the model?</p> <p>Conditions concerning the model itself?</p> <p>What conditions are of significance to continue to use a model like TIME in your ward?</p> <p>Conditions in the ward?</p> <p>Conditions concerning the education and training programme for the model?</p> <p>Conditions concerning the model itself?</p>

Notes: ¹The results from theme 2 in this interview guide were reported in Paper 4 as a part of the process evaluation of the TIME intervention.

3.3.7 Analysis

Statistical analysis for the cluster RCT (Paper 2)

A power calculation was performed based on the following assumptions. A previous non-controlled pilot study of TIME showed that the intervention reduced the NPI-NH agitation item score by an average of 2.8 (SD 3.1)(260). We assumed that the education-only intervention would have some effect on the control group, but less than that of the TIME intervention in the intervention group. We then assumed a mean difference in change between the groups would be 1.5 with an SD 3.1, as measured by the NPI-NH agitation item. Based on this, we estimated that 65 participants were needed in each group to observe a statistically significant difference with a power of 80% and a significance level of 5%. Because of the possible cluster effect within NH, we assumed an intra-class correlation coefficient (ICC) of 0.05. We assumed a relatively small ICC since we expected a small number of included residents in the clusters. Adjusted power calculations suggested that at least 78 participants were needed in each of the intervention and control groups, totalling 156. According to the pilot study, approximately 12% of the residents in NH had dementia and the necessary NPI-NH agitation item score, our main criterion for inclusion. Previous studies have shown that we can anticipate a 30% loss to follow-up per year (resulting from mortality, relocation, or withdrawal from the study), or 7.5% loss in three months. With

these two assumptions, we aimed to include a total of at least 168 residents, implying that approximately 1400 NH residents would be needed for screening against our inclusion criteria.

All primary analyses for the cluster RCT were performed by a statistician who was not affiliated with the research centre and who was blinded to the randomisation. Analyses were performed as intention-to-treat analyses. Differences in the outcomes between the intervention group and the control group were assessed by a linear mixed model with fixed effects for the time and group components as well as the interaction between the two. A significant interaction implies differences between the groups. Random effects for residents nested within NH were included in the model. Individual time-point contrasts were derived within each group at each time point with the corresponding 95% CI. Linear mixed models correctly adjust estimates for intra-cluster correlations as well as for intra-individual correlations due to repeated measurements in time. The model also addresses unbalanced data by allowing inclusion of all available information, including information from drop-outs. Standardised mean differences (SMD) were calculated by re-running the mixed models with the outcome variables divided by the standard deviation. The intra-class correlation coefficient assessing the level of clustering within NH was calculated from a random effects model. Statistical analyses were performed using R version 3.2.0, lme4 version 1.1-12 and SAS version 9.4. All tests were two-sided, and results with P-values below 0.05 were considered statistically significant.

As an additional analysis, not part of the predetermined analysis plan, the difference between the groups in reduction in agitation was assessed by logistic regression model for hierarchical data. The model contained fixed effects for groups and random intercepts for NH. The results from these analyses are presented as additional results in Chapter 3.5.3.

Statistical analysis for the quasi-experimental controlled trial (Paper 4)

Data were presented as means and standard deviations (SD) or frequencies and percentages, as appropriate. Differences between the two groups in the sum scores for items from the questionnaires were assessed by a linear mixed model with random effects for wards, controlling for possible intra-ward correlations. Fixed effects for time, group allocation and the interaction between these two were included in the model. A significant interaction implies differences between the groups throughout the study period. The results were presented as means and 95% confidence intervals estimated at each time point within the groups with p-values quantifying the between- and within-groups differences.

Qualitative analysis for the focus groups interviews (Papers 3 and 4)

For the analysis of the data for the focus groups, thematic content analysis was used. In thematic content analysis the purpose is to identify, analyse and reveal themes in qualitative data (261, 262). Both the manifest and latent content of the data are systematically described, and new concepts and understanding of phenomena are developed. This analysis was performed in four steps: (1) An overview of the content was obtained from multiple readings of the transcribed text. (2) Meaning units were identified using coding, and these meaning units were then condensed. Coding was done by labelling related text elements,

derived from the original text, and then meaning units were reassembled in a new document. (3) These units were then abstracted and grouped into subthemes and the sub-themes that were related; and (4) these sub-themes and themes were discussed in the context of our research questions, existing theories or new theoretical formulations, if necessary (261). This approach to the coding process was mainly inductive, and we, therefore, coded the entire data set (261).

The primary analysis was performed by the author of this thesis and the second author, JM, of Paper 3. A third researcher, AG, who participated in the interviews and was the third author of Paper 3, did the primary analysis alone before discussing her results with the rest of the authors. Preliminary analyses were conducted after each group, and when no obvious new meaning units or new sub-themes occurred in the last interview, we considered have met saturation of the data (245).

Qualitative analysis of the minutes from the case conferences (Paper 4)

The documentary analysis of the minutes from 84 case conferences was performed by using structuring documentary content analysis (258, 259). This analysis looks for types or formal structures in the data and uses preformed categories as codes to analyse frequencies and different degrees of quality in a category. This approach to the coding process is deductive, and therefore does not analyse the documents for other content, patterns, or themes.

According to one of our research questions that concerns the fidelity (implementation in the RE-AIM framework) to the model, our categories were the main structuring components of the case conferences used in TIME (28). For the components: use of a problem list, selection of a prioritised problem, the overall understanding and use of the five columns, and actions described as SMART were classified as being executed not. For the descriptions of the components: prioritised problem and evaluation procedures of the treatment actions were classified by the degree of details in the description (adequately, partly or not described). The author of this thesis and the second author of Paper 4, JM, separately evaluated each minute according to this procedure and met to achieve a consensus. Frequency analyses of the minutes were then performed based on these categories.

Mixed Methods analysis (Paper 4)

In Paper 4 we used mixed methods of the convergent parallel type according to Creswell and Clark (214). In this type of mixed-method, qualitative and quantitative data are collected in the same study and with equal priority. The data are analysed separately but integrated in the overall interpretation of the results.

3.4 Ethical considerations

The Norwegian Centre for Research Data (NSD) and the Regional Committee for Medical and Health Research Ethics in Eastern Norway (REC South East) approved the trial on 19 October 2015 (Project No.: 2015/1549). The trial was registered 6 January 2016 in ClinicalTrials.gov., registration number, NCT02655003. The trial was funded by a grant to the author of this thesis from the Innlandet Hospital Trust (Grant No.: 150333).

Residents with the capacity to provide consent were asked to give written consent. For those who lacked the capacity to provide consent, the next of kin were informed of the study and asked to give consent on behalf of the residents. We assumed that most of the residents would have moderate to severe dementia and would therefore probably lack capacity to consent. To ensure that the trial was designed according to Norwegian law requirements of research and international ethical standards (World Medical Association Declaration of Helsinki, 1964) it was important to clarify that the included residents would probably profit from the intervention, and that the risk of harm for these residents and the other residents in the NH was minimal (263, 264). All assessments scales used in the study were based on interviewing the caregiver and were part of routine clinical practice, and the burden on the participating residents was, therefore, judged to be minimal. It was likely that all included residents would benefit from the intervention in the study, due to more attention given to them. The residents in the CNH were assumed to profit from the brief educational intervention given to their staff. The interventions in both INH and CNH were assumed to have a positive effect on the rest of the residents, beyond the included residents in the NH, due to the training and education effect for staff in their entirety. NH residents in general will benefit from increased knowledge on the treatment of neuropsychiatric symptoms derived from the study. Finally, all the CNH were given the option to receive the same intervention with TIME as the INH, once the trial period and the survey for the staff had been completed.

All the participants from the staff were provided with written information about the study and the possibility to withdraw from the study at any time. They gave written consent to conduct interviews and online consent to participate in the surveys.

The main advantage of this hybrid design in an RCT is that it can accelerate the translation of research findings into routine practice. The intervention was designed with the purpose to not rely on continuous extra resources or expert inputs. This is in accordance with the ethical linkage norms of utility, fruitfulness and relevance of research towards society (265). When publishing the protocol for the effectiveness-implementation cluster randomised hybrid trial we followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013 Statement) (266). Our report from the RCT followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines and the CONSORT 2010 Statement: extension to cluster randomised trials (267). We also applied the Medical Research Council (MRC, 2013) overarching framework for development and evaluation of complex interventions emphasising the value of combining both quantitative and qualitative data in Sub-Study 3, the process evaluation (212). Finally, for the report from Sub-Study 2 on the staff experiences with TIME (Paper 3), we followed the Consolidated Criteria For Reporting Qualitative Research (COREQ, 2007) (268). All these efforts contribute to the application of ethical internal norms of science: truth seeking, testability, consistency, coherence and simplicity (265).

3.5 Results - Abstracts of the four papers and additional results

3.5.1 Paper 1: TIME – Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms: Protocol for an effectiveness-implementation cluster randomised hybrid trial

Nearly all persons with dementia will experience neuropsychiatric symptoms (NPS) during the course of their disease. Clinicians and researchers emphasise the need for an evidence-informed standardised approach to managing NPS that integrates pharmacological and nonpharmacological treatments for real-world implementation. The Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) represents such an approach and is a multicomponent intervention based on the theoretical framework of cognitive behavioural therapy.

The trial is a three-month cluster randomised controlled trial conducted in 30 NH including 168 participants with dementia and a high level of agitation. Each NH defined as a cluster will be randomised to receive either the TIME intervention (the intervention group) or an education-only intervention regarding dementia and NPS (the control group). TIME is a manual-based, multicomponent programme that includes a rigorous assessment, one or more case conferences and the treatment and evaluation of NPS. Resident-level measurements are taken at baseline (prior to randomisation) and eight and 12 weeks later. The primary outcome measure is the between-group difference in the change in agitation, as defined by the Neuropsychiatric Inventory-NH Version at eight weeks from baseline. Secondary outcome measures include the between-group difference in the change in agitation at 12 weeks from baseline and the change from baseline at eight and 12 weeks in other NPS, quality of life, and the use of psychotropic and analgesic medications. Mixed methods will be used to measure and explore the implementation process and the effect of the intervention at the staff level and the organisational level. Combining measurements of clinical effectiveness and implementation outcomes define this trial as an effectiveness-implementation hybrid trial.

Conclusion: Measuring the implementation and effect of complex interventions aimed at reducing NPS in NH is challenging. In this study protocol, we describe a multicomponent programme, TIME, and discuss how an effectiveness-implementation cluster randomised hybrid trial can meet these challenges.

3.5.2 Paper 2: TIME - Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms – a cluster randomised controlled trial

Background: There is conflicting evidence about the effectiveness of nonpharmacological interventions for agitation in dementia. Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) is a biopsychosocial intervention based on the theoretical framework of cognitive behavioural therapy and person-centred care. The model consists of a comprehensive assessment of the resident and one or more case conferences with the goal to create, and put into action, a tailored treatment plan.

Aim: To determine the effectiveness of TIME, for treatment of agitation in people with dementia living in nursing homes.

Methods: In 2016, we conducted a cluster randomised controlled trial in 33 nursing homes (clusters) in Norway. 229 residents with dementia and a moderate to severe degree of agitation were included. A total of 104 residents in 17 nursing homes and 125 residents in 16 nursing homes were randomised to the intervention group and the control group, respectively. The intervention group received TIME and the control group received a brief education-only intervention. The residents were assessed before randomisation (baseline), at eight and at 12 weeks. The primary outcome was the between-group difference in change at the agitation/aggression item of the Neuropsychiatric Inventory, Nursing Home Version (NPI-NH), between baseline and eight weeks. Secondary outcomes were the between-group difference in change in the agitation/aggression item of the NPI-NH between baseline and 12 weeks, and in other neuropsychiatric symptoms, quality of life and use of psychotropic and analgesic medications between baseline and eight weeks and baseline and 12 weeks.

Results: A significant between-group difference in reduction of agitation at both eight weeks (1.1; 95% CI, 0.1 to 2.1; P=0.03) and 12 weeks (1.6; 95% CI, 0.6 to 2.7; P=0.002) in favour of the TIME intervention was found. Symptoms of delusions at eight weeks, and depression, disinhibition, and quality of life at 12 weeks, showed significant between-group differences in favour of the TIME intervention

Conclusion: The implementation of TIME resulted in a significant reduction of agitation amongst nursing homes residents with dementia. These results should inform training programmes for care staff in Norway and internationally.

3.5.3 Additional results from TIME - a cluster randomised controlled trial

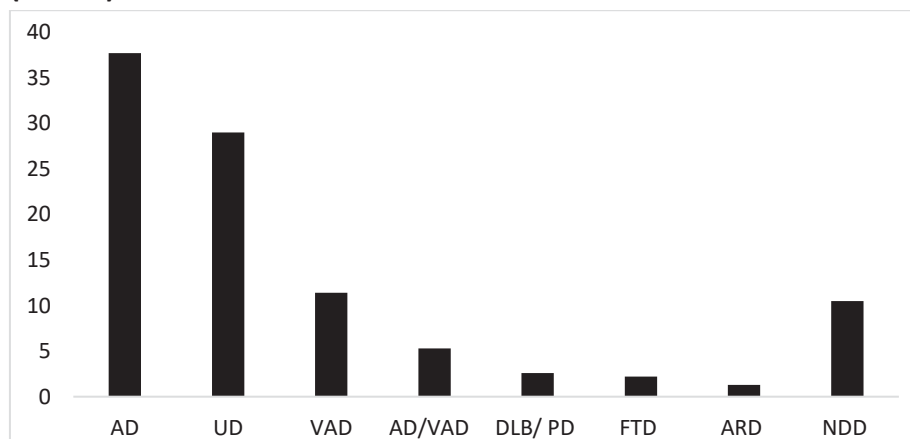
Settings

Fifty percent of the included NH came from large municipalities ($\geq 20,000$ inhabitants), 45% from medium municipalities (5,000 – 19,999 inhabitants) and 5% from small municipalities ($< 5,000$ inhabitants). Eighty-two percent of the included residents lived in a SCU, and 18% in a regular ward.

Dementia disorders for the included residents according to medical records

One of the inclusion criteria for the RCT was a probable dementia diagnosis defined as a score on the CDR of 1 or higher. In 89% of the residents (N=228, 1 missing) a diagnosis of dementia was recorded in their medical records (Table 12). The most frequent diagnosis was AD with 37% and VAD with 11%. In 29% of the residents unspecified dementia (UD) was recorded.

Tabell 12. Frequency of dementia disorders according to the residents' medical records, (N=228)

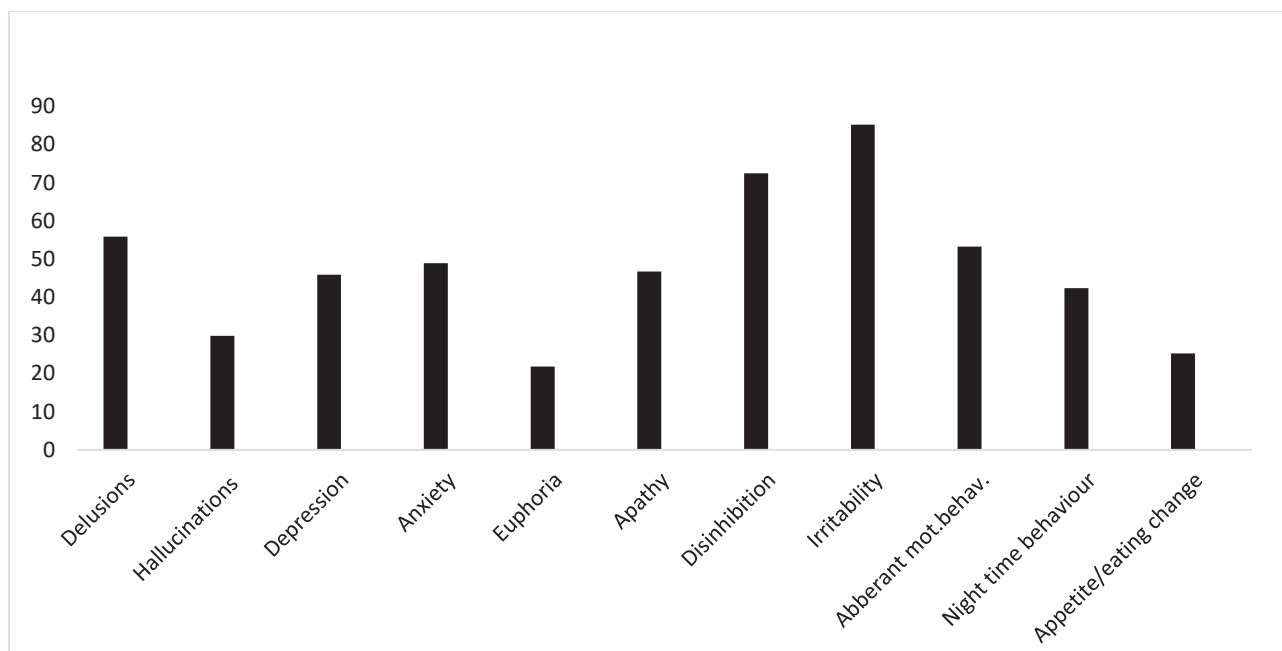


Notes: AD, dementia due to Alzheimer disease; UD, unspecified dementia; VAD, vascular dementia; AD/VAD, mixed AD VAD dementia; DLB/PD, dementia with Lewy-bodies or Parkinson disease dementia; ARD, alcohol related dementia; NDD, no dementia diagnosis in the medical records

Frequency of concurrent NPS to agitation/aggression

One of the inclusion criteria was a score of 6 or higher on the single-item NPI-NH agitation-aggression, signifying moderate to severe agitation. The residents were likely to exhibit many other clinically significant NPS at baseline as measured by the NPI-NH (Table 13). Except for hallucinations, euphoria, and appetite/eating changes, each NPI-NH item was present in more than 40% of the residents concurrently with moderate or severe agitation. The most prevalent of these concurrent clinically significant symptoms were irritability and disinhibition, which were present in approximately 85% and 73% of the residents, respectively. Interestingly, nearly half of the residents (47%) also displayed concurrent clinically significant apathy, a symptom phenotypically opposite to agitation.

Tabell 13. Frequency (%) of clinically significant NPS¹ concurrent with moderate to severe agitation/aggression as measured by NPI-NH² in nursing home residents. Baseline values.



Notes: ¹Clinically significant NPS: each item of the ²NPI-NH (Neuropsychiatric Inventory-Nursing Home Version) has a score ≥ 4

Percentage reduction in the NPI-NH agitation/aggression score (post-hoc analysis)

Percentage reduction in the single item NPI-NH agitation/aggression scores from baseline to eight and 12 weeks and the proportion of residents achieving standard thresholds of response can be used to further analyse the clinical response. The difference in the proportion of residents in INH versus CNH who had a 30% reduction in the NPI-NH agitation/aggression single item at eight weeks was non-significant ($P= 0.101$). However, the proportion of residents who achieved a reduction in this symptom score defined as a 50% decrease was significantly larger in the INH, 30.4%, versus 18.2% in the CNH at this time point ($P=0.040$) (Table 14). The difference in the proportion of residents in INH versus CNH who had a 30% reduction in the NPI-NH agitation/aggression single item was significantly larger at 12 weeks, with a proportion of 53.5% in the INH and 35.3% in the CNH ($P=0.013$). The difference in the proportion of residents between the two groups achieving a 50% reduction in this item score was not significant at 12 weeks ($P=0.256$) (Table 15).

Table 14. Percentage reduction in the NPI-NH¹ agitation/aggression single item score from baseline to 8 weeks and proportion of residents achieving standard thresholds of response

	Intervention Nursing Homes (INH)	Control Nursing Homes (CNH)	P-value
	N (%)	N (%)	
$\leq 30\%$ reduction	49 (53.3)	78 (64.5)	0.101
$>30\%$ reduction	43 (46.7)	43 (35.5)	
$\leq 50\%$ reduction	64 (69.6)	99 (81.8)	0.040
$>50\%$ reduction	28 (30.4)	22 (18.2)	

Notes: ¹NPI-NH: Neuropsychiatric Inventory-Nursing Home Version, Range 0-12 for each single item

Table 15. Percentage reduction in the NPI-NH¹ agitation/aggression single item score from baseline to 12 weeks and proportion of residents achieving standard thresholds of response

	Intervention Nursing Homes (INH)	Control Nursing Homes (INH)	P-value
	N (%)	N (%)	
<=30% reduction	40 (46.5)	75 (64.7)	
>30% reduction	46 (53.5)	41 (35.3)	0.013
<=50% reduction	62 (72.1)	93 (80.2)	
>50% reduction	24 (27.9)	23 (19.8)	0.256

Notes: ¹NPI-NH: Neuropsychiatric Inventory-Nursing Home Version, Range 0-12 for each single item.

3.5.4 Paper 3: Experiences of nursing home staff using the Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) – a qualitative study

Background/Aims: Neuropsychiatric symptoms (NPS) in dementia pose great challenges for residents and staff in nursing homes. The Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) has in a randomised controlled trial demonstrated reductions in NPS. We explored the participating staff’s experiences with the model and how it met the challenges when dealing with the complexity of NPS.

Methods: Three to six months after the end of the intervention, we interviewed 32 of the caregivers, leaders and physicians participating in the trial in five focus groups. We used thematic content analysis.

Results: The analysis yielded two main themes: (1) a systematic reflection method enhanced learning at work; (2) the structure of the approach helped staff to cope with NPS in residents with dementia.

Conclusion: TIME shifts the way of learning for the staff from traditional to more innovative and reflection-based through a process of learning how to learn at work. This made translation of knowledge into action easier. The staff experienced increased coping in their approach to complex problems. Our results emphasise the importance of a structured and biopsychosocial approach to NPS in clinical practice. Future research should explore models for integrating situated learning in daily routines in nursing homes.

3.5.5 Paper 4: TIME to reduce agitation in dementia in persons with dementia in nursing homes. A RE-AIM based process evaluation of a complex intervention

Background: The Targeted Intervention Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) has been shown to reduce agitation in NH residents with dementia. To ease replication and future implementation, and to clarify possible causal mechanisms, we report from a process evaluation of this intervention based on the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, Maintenance).

Methods: An exploratory and quasi-experimental design with mixed methods was used. The RE-AIM dimensions were explored by questionnaires to 807 staff members and 46 leaders in both the intervention NH (INH) and the control NH (CNH), distributed before the start of the intervention (baseline) and after six and 12 months. To assess implementation, we used a checklist for performance of the main components in TIME and analysed the minutes from 84 case conferences in the INH. To explore adoption and maintenance, five focus group interviews with 32 participants from the staff in the INH were conducted three to six months after the intervention.

Results: Reach: On average 61% (SD 22) of the staff in each ward in the INH attended the training sessions. Effectiveness at staff level: There were no between-group differences throughout the study period for attitudes towards dementia, perceived competence or perception of mastery and social interaction. Adoption: In total, 16 of the 17 INH completed the intervention. The INH and the CNH did not differ throughout the study period regarding adherence to recommended clinical practice for the assessment and treatment of NPS. Implementation: Overall, 75% or more of the components of TIME were performed for 91% of the included residents. Maintenance: Most of the nursing homes used TIME three to six months after the end of the intervention. An easy-to-grasp model and an engaged and present leadership facilitated the intervention and its sustainability.

Conclusions: A high degree of reach, adoption, implementation and maintenance might have contributed to the effectiveness of TIME at the resident level. Another causal assumption of the effectiveness of TIME is the development in the staff of a new, shared and situated knowledge about each individual resident, which is not reflected by measurements in general knowledge and attitudes. Future research should explore methods for assessing how general knowledge and attitudes are translated into an everyday approach for each individual resident.

4.0 Discussion

The results from the papers will be discussed by first setting the results of effectiveness at the resident level from the RCT (Paper 2) in context with other research projects aiming at reducing agitation in dementia. Both Paper 3 and 4 represent different aspects of a process evaluation of a complex evaluation clarifying, the “How does it work?” and “Why does it work?” questions of the intervention with TIME (212). The results from these two papers, exploring the experiences of the staff using TIME and the process evaluation using the RE-AIM framework, will be discussed in the light of theories from complexity sciences and learning theories (11-13, 208, 209, 220-222). The discussion in Chapter 4.1.3. on possible causal assumptions of the effectiveness of TIME at the resident level will include results from both these two papers. Finally, the results will be brought together and visualised in a diagrammatic presentation by constructing a logic model for the intervention with TIME (213, 269). Methodological issues for the three sub-studies will be discussed separately at the end of this chapter.

4.1 The main findings

In the cluster RCT (Sub-Study 1, Paper 2), we found a significant between-group difference in the reduction of agitation at both eight weeks (primary outcome) and 12 weeks (secondary outcome) in favour of the TIME intervention. In addition, agitation measured by the CMAI at eight and 12 weeks, symptoms of delusions at eight weeks, and depression, disinhibition and quality of life at 12 weeks, showed significant between-group differences in favour of the TIME intervention (secondary outcomes).

In the explorative, qualitative study on the staff's experiences with TIME (Sub-Study 2, Paper 3) one main finding was that TIME shifts the way of learning for the staff from traditional to more innovative and reflection-based through a process of learning how to learn at work. The staff's experienced increased coping in their approach to complex problems.

The process evaluation of the intervention (Sub-Study 3, Paper 4) revealed a high degree of reach, adoption, implementation and maintenance. Regarding effectiveness at the staff level, there were no differences between staff at the INH and staff at the CNH throughout the 12-month study period for attitudes towards dementia, perceived competence or perception of mastery and social interaction. At the ward level, the INH and the CNH did not differ throughout the study period for adherence to recommended clinical practice for the assessment and treatment of NPS. An easy-to-grasp model and an engaged and present leadership facilitated the intervention and its sustainability. Conversely, lack of support from the leading ward nurse and not integrating the case conferences as a part of the routines in the wards were perceived as the main barriers to implementation and maintenance.

4.1.1 Effectiveness of TIME for reducing agitation (Paper 2)

Comparison of the results with previous studies

This single-blinded cluster randomised controlled trial showed that TIME compared to an education-only intervention, reduced agitation after eight and 12 weeks in nursing homes residents with dementia and moderate to severe of agitation. These findings were strengthened by the significant results in the secondary outcomes both at eight and 12 weeks using another instrument that measures agitation (i.e. CMAI). As pointed out in a published commentary to our paper, a major strength of the study is that significant benefits were achieved within a clinically meaningful period (270). When the purpose is to treat moderate to severe agitation and aggression, it is of importance both for residents and staff to achieve clinically meaningful results as soon as possible. To compare the effect size in randomised trials, the SMD between treatment groups is commonly used (164). The SMD for our primary outcome was estimated at 0.32 and 0.47 at eight weeks and 12 weeks, respectively. This implies a small to moderate effect size, which is higher compared to what has been reported from most pharmacological trials (22, 182) and comparable with most non-pharmacological trials that have demonstrated effects in the treatment of agitation as the primary outcome (25, 26). The Chenoweth study testing the effectiveness of DCM and PCC compared with usual care (three arms) showed an SMD of 0.34 and 0.44 in favour of DCM and PCC, respectively, for the reduction of agitation as measured by CMAI at four months' follow-up, but with no significant difference between the change in the groups directly after the four month intervention (26, 158) (Table 4). The care delivery study by Rapp et al. comparing usual care with a staff educational programme for individualised activities, demonstrated at 10 months' follow-up a significantly change in the CMAI score in favour of the intervention with an SMD of 0.54 (Table 4) (26, 177). Zwijsen et al. found a significant but modest between-group difference in reduction in agitation as measured by the CMAI at eight months (Table 4). The SMD was not reported in the paper and it was not possible to calculate the SMD because of insufficient data (26, 176). The SMD must not be confused with clinical importance of the results (164). Even a small, but statistically significant between-group difference in an outcome in which the variation in changes within the groups is small (i.e. a low pooled SD for the changes in the groups) will give a rise to a high figure for the SMD. As discussed in Chapter 2.8, the percentage reduction in the outcome from baseline and the MCID are both measures that may be used to better define what can be judged as clinically meaningful changes.

Clinically meaningful changes

Both the residents in the intervention group and the control group showed significant reductions in agitation from baseline to eight weeks and from baseline to 12 weeks. For the intervention group the reduction in the single NPI-NH item agitation/aggression from baseline to eight weeks and 12 weeks was 2.6 (30%) and 3.0 (34%), respectively. A 30% decrease in the NPI-NH scores from baseline is usually judged as clinically meaningful (162, 163). For the control group, the reductions from baseline to eight weeks and 12 weeks was 19% and 17% respectively. These reductions in the agitation item in the intervention group, mean that, on average, there was a decrease in the frequency of agitation from several times a week to once a week for a symptom of severe degree or a decrease in the degree of

severity from severe to moderate for agitation occurring several times a week. As discussed in Chapter 2.8, a common threshold used to determine MCID is 0.4 times the SD of the change in score from baseline (160, 161). The MCID in our trial for the changes in both groups from baseline to eight and 12 weeks was 1.4. Thus, the changes observed within the control group just reached this threshold, whilst the changes observed in the TIME intervention group were far above it. The possible explanations for the reductions of agitation in the control group are discussed in Chapter 4.2.3 on data collection and measurements.

The post-hoc analysis showed that the difference in the proportion of residents achieving a marked reduction (50% reduction) on the single item NPI-NH agitation/aggression was significantly larger in the INH compared to the CNH at eight weeks from baseline, but with no differences between the groups for a moderate, but still clinically meaningful reduction (30% reduction) (Table 14) (162). Conversely, at 12 weeks from baseline, there were no significant difference between the groups in the proportion of residents achieving a marked reduction at this item, but rather a significant difference between the groups achieving a moderate reduction in favour of the INH (Table 15). The results showed that 53.5% of the residents in the INH had a moderate or marked reduction in agitation from baseline to 12 weeks versus 35.3% in the CNH ($P=0.01$). As for the results based on the between-group difference in the change of the means of the single item NPI-HH agitation/aggression, the results showed that the effectiveness of TIME to produce a clinically meaningful reduction in agitation is more pronounced at 12 weeks than at eight weeks. The observed significant difference in the change in means for agitation between the two groups at eight weeks, can to a large extent, be explained by the significantly larger proportion of residents in the INH compared with the CNH displaying a marked reduction in agitation at eight weeks. Although this way of presenting results could be easier to interpret clinically than the difference in the changes in means between groups, it should, however, be considered with caution. These are post-hoc analyses, and the calculation of the power of the study was not based on a predetermined dichotomous outcome of the difference in the proportion of residents achieving a predefined threshold of reduction of agitation. Fedorov et al. demonstrated that the transformation of a continuous outcome (response) to a binary outcome in a trial could lead to a loss of power equivalent to a study with two thirds of the data (271).

Duration of the trial and the use of psychotropics

The short duration of the trial might in part explain why the use of psychotropic drugs did not change, despite the reduction in NPS. The most prominent reductions in the NPS were seen after 12 weeks from baseline, consistent with the fact that the intervention starts with a comprehensive assessment of the residents. The average number of weeks that elapsed from the intervention initiation to the performance of case conferences where decisions on customised treatment actions are made was 5.0 (SD 1.8). We believe that reductions in psychotropics will only take place when symptoms are perceived as stable by the staff and the physician. The duration of the trial is also a limitation, since it makes drawing conclusions about long-term effectiveness difficult. The intervention was not designed to particularly reduce the use of psychotropics, though one component of the registration and assessment phase in TIME is a critical review of the resident's medication by the NH physician. This was

also part of the one-day educational programme for the staff, leaders, and physicians in the INH. From the process evaluation (Paper 4) we know that 41% of the NH physicians participated in these educational programmes and they attended 32% of the case conferences. The INH physicians performed or tried to perform a physical examination on 92% of the residents, but we did not gather information about whether this examination also included a review of their medication as intended in the TIME manual (Paper 4).

Efficacy or effectiveness interventions – comparing interventions

As discussed in detail in Chapter 2.10.2, the main difference between an efficacy and an effectiveness trial is that an efficacy trial is conducted under more idealised, highly controlled conditions, often with the use of external resources and, to large extent, implemented by the researchers, whilst an effectiveness trial is conducted in real-world settings with less control and minimal extra resources available (155, 156). The continuum between an efficacy and an effectiveness trial also depends on the characteristics of the samples, eligibility, relevant outcomes in terms of clinical relevance and timeframe, settings, flexibility of delivery, etc. (156). The intervention with TIME can be regarded as an effectiveness trial due to relevant clinical inclusion criteria and the primary outcome measure, the low involvement of the researchers in the implementation process, the rather modest time allocated for educational purposes and the moderate degree of flexibility for adaption of the intervention to the context of the nursing homes. Table 4 in Chapter 2.8.2 displays the main results and characteristics regarding the interventions of some care delivery interventions aiming to reduce agitation in nursing homes. All these interventions were conducted in nursing homes and with usual care as the comparison except for the Rokstad study, where the staff in the control nursing homes were also given five DVDs containing 30-minute lectures on dementia (151). The exact use of these DVDs was not reported but was assumed to be modest in the paper. Amongst these studies, the first reported significant difference in the reduction in agitation between INH and CNH was eight months after baseline (i.e. intervention initiation) in two of these interventions (158, 176). For the treatment of moderate or severe agitation, this is a long period without knowing if the intervention has any effect and reduces the results' applicability for these groups of residents. A long-term effect, however, is important for the prevention of agitation and the sustainability of the intervention (26). The studies by Chenoweth et al. (2009) and Fossey (2006) et al. were both highly intensive in terms of involvement from the researchers, for the implementation of both DCM and the PCC programmes (158, 174). The duration of the interventions lasted four months and ten months, respectively. DCM in the Chenoweth study was performed by the researchers in collaboration with staff members trained in DCM procedures. Follow-up was intense, with regular telephone support in the Chenoweth study and weekly supervision of the staff in the Fossey study. The physicians in the INH in the Fossey study worked with a psychiatrist two days a week during the 10-month trial with the aim of reducing the use of psychotropics. These features of rather intensive involvement from the researchers place these studies in the direction of efficacy studies. In the study by Rokstad et al. (2013), the DCM study arm had some resemblance to the DCM study arm in

the Chenoweth study, but with less intense frequency of supervision of the staff from the researchers. Also, in the Rokstad study the DCM observations were carried out by the researchers in collaboration with internal DCM-certified staff. In addition, in the PCC arm of the Rokstad study, the leading ward nurse, an auxiliary nurse and a registered nurse from each ward attended a three-day basic course before implementing the VIPS practice model (VPM) in each ward. These three nurses were labelled VPM coaches, and they conducted a three-hour introduction course to the rest of the staff. The main element of VPM was the weekly 45-60 minutes consensus meeting in the NH ward led by the VPM coaches. The involvement of the researchers was considerably less in this study arm than in the other above-mentioned studies. The report from the study does not include information about the flexibility allowed for the performance of the components in the VPM programme. The intervention in the PCC arm in the Rokstad study and the intervention by Zwijsen et al. (2014) have some similarities with the intervention of TIME regarding the low intensity of involvement of researchers and modest time allocated for educational purposes (102, 151, 176). Training of the staff in the study by Rapp et al. (2013) to support activity therapy interventions consisted of two four-hour educational sessions during a single day (177). The core of the intervention was individual treatment sessions provided by activity and occupational therapists twice a week for 45 minutes. In addition, group activities once a week continued as usual. Prescribing psychiatrists were trained in individual sessions for four hours each. The number of psychiatrists attending sessions is not mentioned in the report. It is not clear from the report how many activity or occupational therapists were involved in the intervention, whether they were already part of the staff in the NH or if they had been given any additional training. It is, therefore, difficult to place this trial on the efficacy-effectiveness continuum.

4.1.2 The learning and coping experiences of the staff (Paper 3)

Our findings show that TIME is a feasible model that can enhance learning at work, problem solving and coping in the approach to NPS in nursing homes. The overall impression is that these coping experiences the staff refer to are mainly based on what Lazarus labelled the problem-focused coping process (223). As discussed in more detail in Chapter 2.11.2, it is the person's own appraisal and interpretation of the situation and the context that lies at the centre of one's coping strategies (223). These findings relate to the two main factors involved in coping strategies according to Lazarus, namely knowledge and learning. Before discussing our findings in relation to learning theories we will discuss how concepts from complexity science could contribute as an overarching theory for our findings.

NPS and nursing homes - A dual complexity

The complexity of NPS and the need for a biopsychosocial approach, were clearly expressed in our findings. The participants emphasised that TIME integrated learning about biopsychosocial factors and contextual factors such as the resident's personal history. In a similar study using case conferences for the analysis and management of NPS, Holle D et al. also highlighted the importance of considering the biographical knowledge about the

residents (272). In addition to the complexity of the symptoms, there is a dual complexity because nursing homes can be regarded as complex systems as they consist of different stakeholders, such as professionals, leaders, residents and their relatives in constant interactions (11-13). Complex systems are instable and there is a constant need for work to be done to maintain a certain order and reduce instability (202). In our context, this means that complex problems like NPS can pose great strain on the staff and the organisation in an already complex system like a nursing home. The participants highlighted that TIME both gave them a new approach for learning about NPS and a method for problem solving for the individual resident. In addition, the structure in this approach was regarded as important for their shared understanding and coping with these symptoms. In view of the complexity theory, these two findings can be regarded as added attractors to the system, i.e. norms of behaviour or logics of operation (11, 273). Attractors contribute to a more stable system, facilitate more order, and make the organisation more able to fulfil their goals. How they contribute as attractors will be discussed below.

Systematic reflection and learning how to learn at work

The participants in our study found the principles for analysing NPS from CBT easy to adopt and to learn. They highlighted the column technique from CBT based on the ABC method as an easy and simple way to understand and analyse NPS. They added that they also used the ABC method outside the case conferences, in the daily interactions with the residents. It is possible that this method for analysis, visualised by the column technique, made a considerable contribution to what Ellström (2001) called readiness to learn or a mental model for interpreting experiences (222). As discussed in Chapter 2.11.1 on Formal and situated learning, this mental model must be explicit, not tacit (219, 222). During the case conferences the staff participated in a learning activity where they learned a mental method for learning. They learned how to learn. A mental mode for learning is essential for developmental learning which is based on systematic reflection both on actions and context. According to Ellström's typology of learning activities, we can infer that knowledge-based activity (level 3) and reflection-based activity (level 4) are given dedicated space and time in the case conferences (See Fig. 1, Chapter 2.11.1) (220). This is where developmental learning can be focused and developed. Developmental learning shares essentially the same characteristics as the concept of situated learning introduced by Lave and Wenger, and the concept of reflection-in-action by Schön (219, 221). The use of a shared display, using a projector or a whiteboard, made the analysis method visible for the participants of the case conferences and enhanced the sharing of interpretations and decisions about the resident and the NPS. Conklin (2006) described the use of a shared interactive display as an essential condition to achieve a shared understanding and commitment in meetings when working with complex problems (10).

However, to bring in new generalised knowledge to the organisation and to learn skills in performing procedures, what Ellström called adaptive learning, is also a necessary learning activity (222). The participants stressed that lack of formal education made it difficult to

apply tailored measures for the residents. This was particularly difficult during summer and weekends when the number of temporary staff without formal health or social care education was higher. TIME did not in itself, after the initial educational program for the staff was completed, include a system for bringing new generalised knowledge from the outside into the organisation. Instead, TIME helped to share this type of knowledge amongst the staff and translate it to the context of the individual residents and the varied complex situations in the NH. Furthermore, from our experience, bringing into the case conference new generalised knowledge for example about the characteristics of the actual resident's dementia disorder, is an excellent way of combining both adaptive and developmental learning during the case conference. When the case conference is interdisciplinary it is possible to bring in and share new perspectives from different disciplines. This is how generalised knowledge becomes shared, contextualised and situated. So, both adaptive and developmental learning are necessary and complementary activities in an organisation. They are involved depending on the requirements of the activities (i.e. the typology of the four activity levels according to Ellström, see Figure 1, Chapter 2.11.1) (220). Reflection without the input of new and updated generalised knowledge risks to be reduced to self-reflection, even at group level, and may only maintain existing ways of thinking and acting, instead of contributing to changes and development within the organisation (274).

Structure in the approach: an attractor that reduces instability by increased coping

The structure in TIME was regarded as a factor that created security and coping for the staff in their work. Severe NPS in residents with dementia sometimes created a sense of hopelessness and a feeling of being powerless amongst the staff. Therefore, leaning on a structure that is adopted in the organisation could have contributed to a sense of coping. This effect of structure at the organisational level corresponds to the same effect as when using CBT at an individual level for problem solving (224). The structure permeates the model and the way of working and can be regarded as an attractor in an unstable, complex system both at an individual level and at the organisational level. Structure may also facilitate creativity. Developmental learning, as discussed in the section above, is supposed to increase creativity in problem solving and is, therefore, also labelled creative or innovative learning (220). Problem solving in CBT favours the importance of discussing alternative and more appropriate interpretations and solutions (224). It is possible that the sense of security felt and expressed by the staff also increased their creativity. Structure and creativity might intuitively be perceived as contradictory concepts. However, evidence shows that organisations that find the balance between too much and too little structure also are more open to innovation and change (203, 275). To summarise, TIME seems to contribute to several attractors to the complex systems in the nursing homes (e.g. NPS, residents, and different stakeholders). These attractors (i.e. the structure and a new developmental learning process) have the potential for reducing the inherent instability in these complex systems (11, 273).

4.1.3 The process evaluation (integrating results from Papers 3 and 4)

Few studies of complex interventions in nursing homes report from the implementation process and to what degree the interventions were adopted and sustained over time (272, 276-280). A common conclusion in these reports is that management support, organisational factors and properties within the intervention programme are the main issues in the implementation process. One important question for health leaders and policy makers is to what extent the intervention is flexible, easy to implement and can be adapted to the local context. Furthermore, a process evaluation is important to guide projects that aim to reproduce the intervention. And finally, a process evaluation could shed light on possible causal mechanisms (155, 213).

Reach, adoption and implementation

The importance of aiming to train and include most staff in the intervention (i.e. high degree of reach) was highlighted by Rapaport et al. (2017) in a systematic review on the effective components of psychosocial interventions (145). In this review, staff perceived difficulties sharing new approaches with those who had not attended training sessions. Appelhof et al. (2018) conducted a process evaluation for an intervention to reduce NPS in SCU for residents with young-onset dementia (280). They concluded that the low participation rates in the educational programme were likely to have reduced the effectiveness of the intervention. The importance of including the entire staff in all the phases of TIME model was also underpinning the sub-theme “shared understanding and commitment” in our qualitative study of the staff experiences with TIME as reported in Paper 3 (281). The staff believed that including as many individuals as possible in the case conferences led to more loyalty and commitment towards the agreed upon treatment measures (281). According to Stacey and his work on complexity in organisations, this means affecting the system’s (i.e. the NH’s) self-organisation through increasing the information flow, adding more connections amongst people and promoting the development of more diversity in cognitive schemas by mutual systematic reflection (203). This is the “bottom up” process in decision making in complex systems and is considered an effective way for an organisation to fulfil its aims (11, 13).

A high degree of adoption and implementation in our study can to some extent be explained by the finding that TIME was perceived by the staff as an easy-to-grasp model. In addition, to achieve acceptable adoption and implementation, several studies have supported the importance of interventions to be simple, appreciated by the staff, and not too overly complex (276-278). This flexibility of a complex intervention has been emphasised as an important factor to improve the effectiveness of the interventions by increasing their applicability (197, 204, 212, 280). According to Hawe et al., it is the function and processes of the intervention that should be standardised, not the components themselves. Adaption should be performed both at the programme level and at the implementation level (197). In this regard, TIME was developed as a “road map” for the staff, helping them to create treatment measures for the residents that are not standardised but tailored and person-centred. At the implementation level we adapted the content of the educational sessions for

the TIME administrators after a brief assessment of their knowledge level. The results showed that TIME was used with some variation between the study sites. The variation in the time the staff needed to perform the assessment of each resident and organise a case conference, as well as the number of staff from each ward that attended the case conferences, may, in part, be explained by organisational conditions. Allowing for some adaptation of complex interventions to the organisational context of the settings is in line with viewing organisations (e.g. nursing homes) as complex systems (197, 212).

Effectiveness

There were no between-group differences in any measurements of effectiveness at the individual staff level throughout the study period. As will be further discussed in Chapter 4.2 on design, data collection and measurements, there are some major limitations regarding these results. The results are nevertheless consistent with the qualitative results in our Paper 3 exploring the staff's experiences with TIME. Here, the staff expressed that their formal knowledge on dementia and NPS was sufficient and good (281). The results are in line with two recent systematic reviews on the impact of staff training on staff outcomes (208, 279). In the same reviews, some studies found increased staff knowledge and self-efficacy, but these findings were not consistently maintained over time. Although there might not be any measurable change in generalised knowledge, the results from the focus groups interviews (Paper 3) showed that the staff perceived an increase in specific knowledge and coping related to each individual resident (281). These changes were interpreted in the analysis as a consequence of a new innovative learning process that took place during the interdisciplinary case conferences. This learning process seems to create new and shared situated knowledge about the resident and made it easier to customise the approach towards the individual residents. Most questionnaires assessed mainly general attitudes and general knowledge about dementia (282). These general attitudes and knowledge do not necessarily reflect the staff's capability to translate this general competence into their real-world approach to an individual resident with, for example, severe agitation that they confront on an everyday basis.

Maintenance - facilitators and inhibitors to the implementation process

Our results indicate that most of the nursing homes were still using TIME three to six months after the end of the intervention. Adherence to recommended clinical practice increased from baseline to six and 12 months, though there were no significant difference between the two groups throughout the study. A supporting leadership consisting of both the leading ward nurse and the TIME administrators was considered to be important both as a maintenance factor and as a facilitator for the adoption of the intervention. Several reports from process evaluations of complex interventions in nursing homes have stressed the importance of management support to achieve both adoption and sustainability (145, 208, 240, 276-279). In a systematic review, Rapaport et al. (2017) claimed that the leadership attending training sessions and meetings, and allocating space and time for the staff to

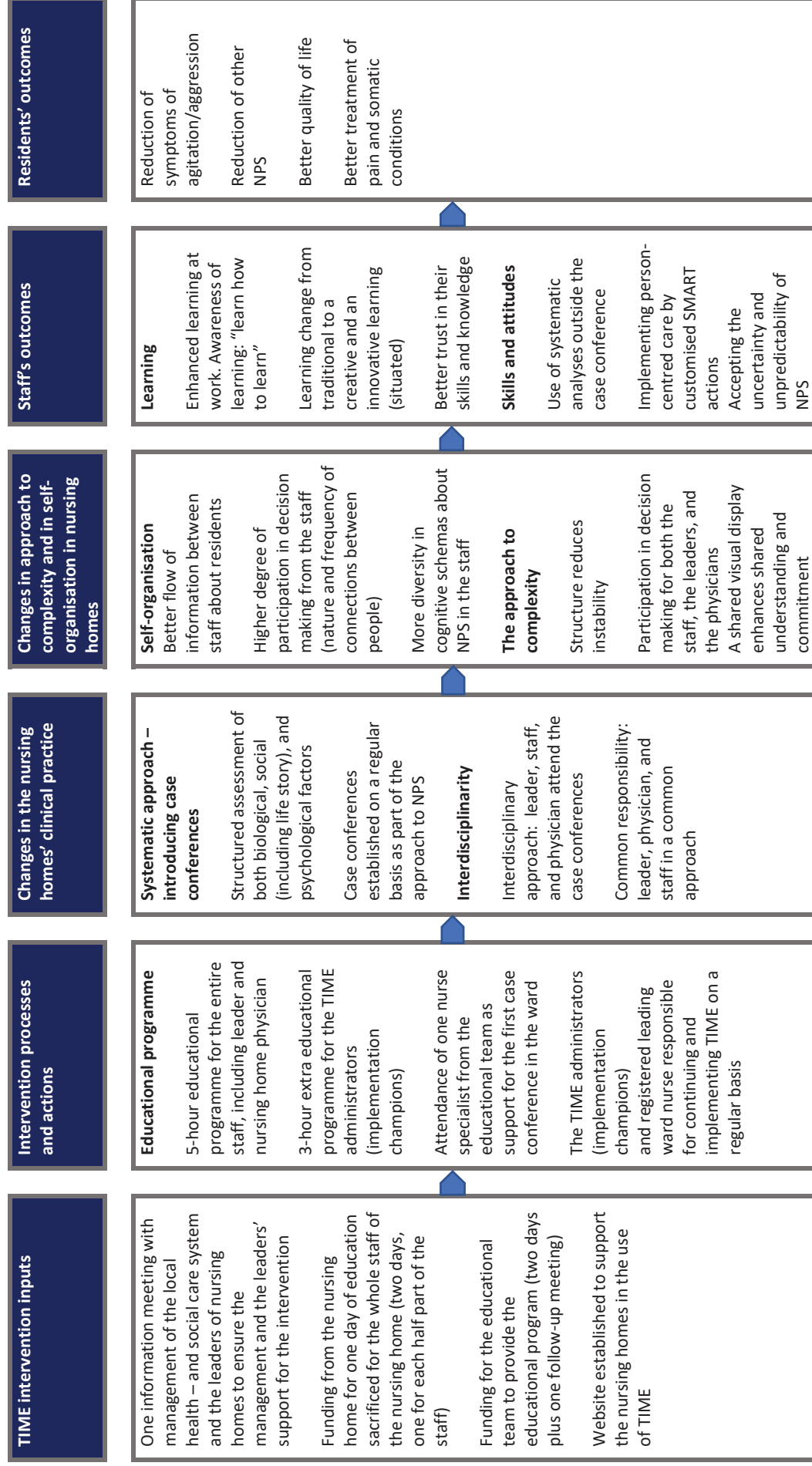
engage in the intervention, were some of the most important facilitators for a sustainable implementation (145). Conversely, lack of support from the leading ward nurse and not integrating the case conferences as a part of the routines in the wards were perceived as the main barriers to implementation and maintenance. Most of the leading registered nurses in the TIME trial attended the same educational training sessions as the rest of the staff, and they also attended nearly half of the case conferences. In line with other studies, we found that the TIME administrators were important for the implementation process and acted as implementation leaders (283, 284). These implementation leaders were labelled “change champions” by Scalzi et al. (2006) and were regarded as one of the most important enablers for culture change (284). Assigning three nurses per ward as TIME administrators was conceived important by the staff to create a team of change champions. Appelhof et al. (2018) espoused the same view and stated that with only one champion per ward, the implementation was less resistant towards sick-leaves and absence for other reasons (280). The staff emphasised that the feature of TIME as an easy-to-grasp model also had an impact on the sustainability of the model. The TIME administrators in cooperation with the leading ward nurse were shortly after the educational programme, able to carry out the intervention independently of the research team. This makes it easier to adapt the model to the context of the nursing homes and the settings’ self-organisation processes (13, 202). The leadership possessing contextual knowledge of their settings, can adapt the intervention with flexibility to influence self-organisation in the nursing home in a direction that facilitates implementation (197, 203). This will also increase the probability of maintenance of the intervention, reduce the cost for implementation and ease the proliferation of the model.

4.1.4 Bringing the results together - A logic model for TIME

A complex intervention consists of multiple interacting components, participants at different levels of the intervention and a diversity of outcomes (204). It might, therefore, be difficult for others not directly involved in development of the intervention and the implementation process to grasp, “What is really going on?” The Medical Research Council (2013) has emphasised the importance of constructing a logic model to give other researchers, decision-makers and clinicians a quick but comprehensive overview of the complex intervention and the possible causal assumptions (212). A logic model is a diagrammatic representation of an intervention, describing delivery mechanisms (resources applied to ensure implementation), intervention components (what is to be implemented, e.g. TIME), mechanisms of impact (presumed or proved) and intended outcomes (presumed or proved) (213, 269). However, it should be emphasised that this representation merely gives an illusion of a linear process with the aim only to simplify it. In fact, as described earlier in the section on complexity, the intervention, the implementation, and the context interact with each other as complex systems. The phases of the implementation may, to some extent, overlap and there is no one-way direction between the components. The process of implementation is non-linear with often unpredictable outcomes, due to the self-organisation processes in the context (i.e. the NH and the residents) (154). In Figure 3, representing the logic model for TIME, all the main concepts and the outcomes used in the

representation have been described and discussed in the previous chapters of this thesis. In this way, the logic model represents a diagrammatic summary of the thesis.

Figure 3. A logic model for TIME with presumed or proved mechanisms of impact and outcomes



4.2 Methodological issues

4.2.1 Design

According to accepted definitions, TIME can be classified as a complex intervention (See Chapter 2.10.2) (154, 204). For the evaluation of a complex intervention it is recommended to use different research designs adapted to multiple research questions addressing the components of a complex intervention (154). This is why we chose the overarching design of an effectiveness-implementation hybrid trial, which can also accelerate the translation of research findings into routine practice (215, 216). Limitations and strengths regarding study samples, data collection and measurements for all three substudies are discussed in Chapters 4.2.2 and 4.2.3.

Experimental design with a cluster randomised controlled trial

Our trial had several strengths. The experimental design with a cluster randomised RCT was chosen for testing the effectiveness of the TIME intervention at the resident level. No other design for an experimental trial reduces selection bias to the same extent as an RCT. To avoid the risk of transmitting all or parts of the intervention model to the control units or individual control residents at the same NH we chose to use a *cluster* randomised RCT (248). We tested an intervention where all the components of the intervention were described in detail in a web-accessible manual and in the published protocol for the project (28, 285). This will ease the reproduction of the trial for other research groups and the translation of the trial results into everyday clinical practice (154). Randomisation was performed after baseline measurements were conducted, and the randomisation procedure was performed by a researcher independent of the project management team and the nursing homes. Baseline demographics and ward and clinical characteristics for the included residents did not differ between the INH and CNH, ensuring a low risk of selection bias. There is a very low risk of attrition bias, since 88.2% of the participants fulfilled the trial and all losses to follow-up were addressed. A statistician not affiliated with the research centre performed all primary analyses blinded for the randomisation status of the two groups.

There are some major limitations with an experimental design using an RCT for complex interventions in health care services. In the NH, the social systems will differ in their characteristics, sometimes changing during the trial, and they will affect both the content of the intervention itself (i.e. standardisation) and the implementation process (154). These processes reflect the self-organisation and the non-linearity of a complex system discussed earlier in Chapter 2.10. To address these challenges in complex systems and improve the adoption of interventions, Hawe et al. (2004) recommended allowing for a certain degree of flexibility and the adaption of the intervention to the local context. The results from the process evaluation of the intervention with TIME, discussed in Chapter 4.1.3, illustrate how a process evaluation can address and clarify these limitations of the RCT design for complex interventions.

The explorative design with qualitative methods (Papers 3 and 4)

A qualitative explorative design with focus group interviews was used to answer the research questions in Sub-Study 3 on the staff experiences with TIME, and as a part of the design in Sub-Study 4 on the process evaluation of the intervention. One of the advantages of using qualitative methods alongside an RCT is that the results from the qualitative study contribute to in-depth knowledge, making it possible to explain some of the results from the prior randomised controlled trial (212).

The quasi-experimental and exploratory design using mixed methods

During the process evaluation, we used a quasi-experimental design that gave us the same quantitative data from the CNH as from the INH. Another strength is that we used a mixed-method design, which allows us to compare and interpret quantitative results from the survey with findings from the qualitative analysis of the perspectives of the staff, leaders, and physicians derived from the focus groups. This comparison adds to the validity of our results and to the value of our assumptions on the possible causal mechanisms of the effect of TIME at the resident level (213, 214). The main strength of this process evaluation is the rigorous use of a well-established and recommended framework for evaluation of complex interventions (209, 212). The only interference during the randomised controlled trial was the use of the checklist for assessing performance of the main components of the intervention to explore the implementation (the fidelity questionnaire). This checklist could possibly have served as a reminder for the TIME administrators and, thereby, increased fidelity towards the components of TIME during the trial. The participants in the survey for the process evaluation (i.e. staff and leaders) were anonymous during the survey, restricting the possibility to evaluate the individual changes between baseline and follow-ups, thus restricting the study to changes at a group level. Therefore, we could only compare the group's means for the outcomes at each time point and not between-group differences in changes in the outcomes. This is a limitation affecting the analysis of the effectiveness of the intervention at the staff level. One important limitation is that we do not know to which extent the model became a stable enduring part of the clinical routines of the NH beyond the six months after the end of the intervention. Another limitation is that this process evaluation was executed by the same research team as the team responsible for the trial (212). The focus groups interviews were executed before the results from the RCT were known, but the analyses of the data for the process evaluation, inclusive the data from the focus groups, were performed afterwards. These phenomena could have created some bias in the analysis of the data. However, the data collection for the process evaluation was planned in advanced, published in a protocol, and collected independently of the trial (285). Furthermore, integrating the process and outcome evaluation with the same team may limit the risk of one data collection disturbing another.

4.2.2 Samples

The nursing homes in the study

The NH included in the study represent a convenience sample recruited by sending an e-mail invitation to the health and social authorities in neighbouring municipalities in the north, middle, and south-eastern parts of Norway (286). This choice was made because of resource

reasons to minimise travel time and costs for the research and educational group and, at the same time, strive for a representative sample of NH. Since one of the inclusion criteria for the residents was moderate to severe agitation, small municipalities were expected to have fewer residents fulfilling the criteria and, therefore, few small-sized municipalities were invited. We succeeded to recruit NH from an equal number of large and medium-sized municipalities but with only a few small-sized municipalities (5%) as intended due to budget reasons. This inclusion criterion also contributes to the explanation of why the interest to participate in the trial mainly came from NH with SCU. Participation for the NH in the study, as is the rule for most other RCTs, was voluntary (286). It is, therefore, possible that the staff and leaders in the NH that accepted to participate in the study had a more positive view towards new methods and ways of working and had more resources than those that declined. In implementation science, this phenomenon is referred to as the concept of readiness to change (287). This could have affected their willingness to implement TIME, thus easing the implementation process in the INH. It should, however, be noted that this situation mimics real-world implementation processes for NH where proposed clinical programmes or models are not made mandatory in national clinical guidelines, and the NH are free to implement them or not according to their preferences (62). However, we did not gather data describing the characteristics of the NH that refused to participate in the trial. This limits our ability to compare these NH with those that agreed to participate. As explained below, staff and residential characteristics in our trial did not differ substantially compared to trials conducted in Norwegian NH. Therefore, we assume that the 33 NH in the trial are representative of Norwegian NH.

The residents included in the RCT

One main strength of our trial is the relatively large size of both the number of NH and number of residents included, contributing to increasing generalisability (286). Wide inclusion criteria with only one exclusion criteria for the residents, life expectancy less than six weeks, added to the applicability of the results in NH settings (286). An inclusion criterion of 6 or higher on the single item agitation/aggression of the NPI-NH is probably comparable to clinical settings where treatment for agitation is mainly deemed necessary when symptoms are perceived as moderate or severe (62, 178). This is in accordance with the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions to balance inclusion criteria between narrow and broad criteria to include relevant clinical participants (288). The concept of applicability concerns the similarity between the characteristics of participants and settings in the study and the population where the results are supposed to be applied. Murad et al. emphasised that a high degree of applicability includes not only a high degree of similarity, but also a feasible and realistic intervention and outcome measures relevant to patients and healthcare providers (286). We did not require a precise diagnosis of dementia but included residents with probable dementia, defined as a CDR of 1 or higher. Nevertheless, we confirmed a diagnosis of dementia from the residents' medical records in 89% of the participants. This is a higher proportion of confirmed diagnoses for dementia in medical records than found in another published study about Norwegian NH by Røen et al. (2017). In this study only 56% of the 84% of the residents who

had dementia, according to all available data collected in the study, had a dementia diagnosis according to their medical records (138). The assessments for a dementia diagnosis in this study were performed at admission to the NH. In our study, 82% of the included residents lived in SCU compared to 33% in the study by Røen et al. Usually, only residents with a known dementia diagnosis are accepted as residents in the SCU. The distribution of types of dementia diagnosis were, however, comparable between our study and the study by Røen et al., if the large proportion of unspecified dementia in our study was considered as mainly due to AD.

To test the representativeness of the material, we compared our data with a study including two large cross-sectional samples of Norwegian NH (N=3021) (76). Amongst those with a CDR score of 1 or higher and an NPI-NH item-score agitation/aggression of six or higher, the mean age (SD), proportion of women and PSMS (SD) score were 82.5 (7.4), 68%, and 20.12 (5.4), respectively (personal communication with GS, one of the authors). Apart from the proportion of women, which was 60% in our study, the figures are similar to our sample of NH residents. Therefore, we have reasons to assume that the residents in the 33 NH in the study are representative of Norwegian NH.

The staff in the study

To ensure a high degree of generalisability and internal validity, we invited all the staff in the included NH from the RCT, including both regular and temporary staff members, to participate in the survey for the process evaluation. The relatively low response rate (approximately 48% at baseline) for the questionnaires, ADQ, QPS-Nordic, and the Competence questionnaire assessing effectiveness at staff level for the process evaluation (Paper 4) limits the generalisability of the results from these questions. However, a response rate of this magnitude is common in surveys. A meta-analysis of 308 surveys in 18 studies from the field of counselling and clinical psychology reported of an average response rate of 49.6% (289). In contrast, the questionnaires for organisational factors and clinical routines regarding NPS, sent to the leading ward nurses, had a response rate between 91% to 100% throughout the study, with no differences between the INH and CNH. Furthermore, the fidelity questionnaire for the TIME administrators was completed by 100% of the wards. We sent the questionnaires in the survey to the staff members' and leaders' working e-mail addresses except for the fidelity questionnaire which was based on interviews by telephone. One of the reasons for the low response rate in the survey for the process evaluation is probably that the NH staff did not regularly use their e-mail account at work. We sent three reminders with one to two weeks intervals for the questionnaires. Since we wanted to assess possible changes in the groups from baseline to six and to 12 months, in attitudes, competence, social and psychological factors at work, we only sent follow-up questionnaires to the staff members who had answered a previous questionnaire. This also contributes to a low response rate. We do not have data on the part of the staff who did not participate in the survey. This limits our possibilities to compare these staff members with those that agreed to participate and limits the internal validity of the results to some extent. However,

the response rates were similar in both INH and CNH throughout the study period. Assuming that the characteristics of the staff that did not participate in the survey and their reasons for not participating are equally distributed in the two groups, the comparison between the two groups should, however, be judged as valid.

A recently published study described staff characteristics in special care units and regular units in Norway (N=1161) (144). The authors reported similar staff characteristics regarding age distribution, years of health-related education, relevant continuing education and staff having at least a 75% working engagement, as in our sample (144). The two samples only differed by the years of working experience for the staff, with more years of working experience for the staff in our trial, and by the number of hours per resident per week for the NH physician, with a slightly lower number in our trial. Therefore, we assume that the staff in the 33 NH in the trial are representative of staff in Norwegian NH.

Our purposeful sample in the qualitative focus group study consisted of five homogenous groups of leaders, auxiliary nurses, registered nurses and physicians selected from a random sample of 11 of the 17 NH, in total 32 participants (246). Although random selection normally is not used for participants in a study using qualitative methods, random selection of *sites or settings* from which information-rich participants are recruited is encouraged by Krueger and Casey (2015) to minimise selection bias of settings that would be represented in the groups (247). This gave us rich data on the experiences and challenges perceived by informants from all the professional groups in the INH. Therefore, we believe that our study findings have a high degree of transferability to staff in other NH approaching NPS in residents with dementia.

4.2.3 Data collection and measurements

Choice of primary outcome in the cluster RCT

All assessments instruments used in the cluster RCT (Paper 2) are well-established clinical instruments with known psychometric properties and Norwegian versions, and they have been widely used in similar studies. We used the single-item agitation/aggression of the NPI-NH as the primary outcome measure for three main reasons. Firstly, in the pilot-study this outcome measure was used as the primary outcome and proved to be sensitive for change in agitation. Secondly, this NPI-NH item tends to measure a narrower spectrum of agitation symptoms with an emphasis on aggressive behaviour compared to, for example, CMAI, which covers a range of different forms of agitation and might not be as sensitive to changes as the NPI-NH single items (101). Thirdly, as discussed in Chapter 2.6.4 about the concept of agitation, it is clinically meaningful to differentiate between agitation with and without aggression, since many forms of mild to moderate non-aggressive agitation can be left untreated if the resident is not suffering from the symptom (26). Finally, as discussed before, choosing a clinically meaningful primary outcome adds to the applicability of the results.

Proxy-based data collection

The collection of data on NPS (NPI-NH, CMAI and CSDD), severity of dementia (CDR), activities of daily life (PSMS), physical status (GMHR) and quality of life (QUALID) relied on only proxy-based information from the staff who best knew the residents. This is a common procedure in trials with people with moderate to severe dementia (101). Although the assessors who interviewed the staff by telephone were blinded for the randomisation status of the residents, the use of proxy-based information is a limitation in the study. Proxy-based information relies on the observer's ability to observe behaviour and symptoms and on the observer's conception of the behaviours and symptoms at stake. Various reports have suggested that the informants' observations of behaviour and symptoms are influenced by their own mood and distress (101, 290). In addition, different measurements, as discussed in detail in Chapter 2.6.5, do not rely on a shared definition of agitation, and there is no sharp distinction when normal behaviour like, for example, restlessness, irritability and stubbornness becomes an agitation *symptom*. Therefore, there is a risk for variability between observers. Normally, these variabilities would be equally distributed between groups when the trial is large enough and should not give rise to systematic errors (286). In addition, all 10 assessors in the trial were nurses with many years of experiences in the use of the assessment instruments, and they were not affiliated with the nursing homes. They were instructed to check for the informants understanding of the measurements whenever in doubt. The assessors had attended a one-day course with training in the actual measurements for the trial. Approximately 70% of the residents in both groups had severe dementia, and the mean agitation level was severe as measured by both NPI-NH and CMAI. It would probably have been difficult to interview the residents themselves because of these features. We did not consider interviewing the residents' next of kin or relatives for these measurements, since most of them only observe the resident in the nursing home less than two hours a week (41).

Possible bias in data collection in single blinded RCTs

In single-blinded non-pharmacological RCTs it is not possible to completely reduce the risk of observer bias. Observer bias may occur when the outcomes measures are dependent on subjective judgement and there is a systematic tendency to reduce or exaggerate observations (291). In our trial, there was a risk that the informants in the INH were influenced by their own efforts to implement TIME and, therefore, could be reporting fewer and less intense symptoms for the residents during follow-up. The most important strategy we used to reduce the risk of this bias was the blinding of the assessors and performing baseline assessments before randomisation (291). Secondly, three nurses from each ward in the INH and CNH completed a three-hour training session in the procedures for the trial and how to understand the assessment instruments (291). To further reduce the observer bias impact on the comparison between the INH and INH, we also gave the staff in the CNH a brief, face-to-face educational intervention with lectures on assessments instruments, dementia, and treatment of NPS. The purpose was to give the staff in the CNH a sense of

being part of an intervention. Participants in a research project could be affected by the so-called Hawthorne effect, meaning that the participants change their behaviours only because they are monitored in a study (292). However, this phenomenon should affect both the staff in the INH and CNH equally and, therefore, not influence the difference in the outcome effects between the groups. The phenomenon regression to the mean could have an effect, but since the baseline values did not differ between the groups, this effect should have had an equal impact on both groups (293).

Questionnaires in the explorative quasi-experimental study (Paper 4)

The ADQ (253, 254) and the QPS-Nordic (255) are questionnaires with known psychometrics values that have been translated to Norwegian. The Fidelity Questionnaire, the Competence Questionnaire and the Current Practice Questionnaire are all short questionnaires for the evaluation of the implementation process inherent to TIME and were, therefore, developed by the research team. They were not validated, and their psychometric properties are not known. The two latter of these questionnaires are self-report questionnaires based on the participants' own subjective evaluation of their own competence and practice. This is an important limitation in this process evaluation study. The Fidelity Questionnaire is mainly a check-list for the performance of the main components in TIME, conducted by interviewing the TIME administrators by telephone, and is, therefore, less prone to self-reporting bias. The documentary analysis of the meetings from the case conferences also contributed to a more valid judgement of the implementation (fidelity) dimension of the RE-AIM framework (209).

Data collection of qualitative data (Paper 3 and 4)

We chose focus groups as our data collection method because they are suitable for exploring experiences and views on health programmes and interventions (257, 268). The advantage of focus groups is that they can generate useful group dynamics displaying information that would not be available in one-to-one interviews (294). However, one important limitation of data collection by focus groups is that focus groups tend to develop consensus. We observed a vivid discussion and believe that different views were freely expressed without the domination of some participants.

The collection of the minutes from all the case conferences for documentary analysis gave us data without risk of selection bias. These data contain indirect information on staff's use and understanding of the structuring concepts of the case conferences but does not reveal data on the interactions and the performance of the case conferences. One important limitation is that the minutes were not written for research purposes but rather for the use in the participants' everyday clinical work. This means that some of the data collected may not provide sufficient details to answer research questions (258).

Addressing reflexivity in research

The researchers' gender, professional background and experiences and relationship with the participants might influence both the data collection and analyses. In exploring health interventions, the researchers' preconceptions and involvement in the intervention might create a bias in the research process (245, 295). Addressing these features in all steps of the

research process, is what Malterud (2001) describes as the concept of reflexivity (245). All research processes have an element of subjectivity, and the idea of a complete neutral observer is an illusion (245). The two main interviewers in the focus groups, the author of this thesis and JM (co-author of Paper 3 and 4), are a physician and a nurse, respectively, as well as researchers. Both took part in the teaching and training of the staff at the start of the intervention for one third of the participating nursing homes. The author of the thesis was the primary developer of the intervention. Both have worked several years in nursing homes, but none of these nursing homes took part in the trial. The close involvement with the intervention and the context has both advantages and disadvantages. We could discover a variety of aspects of the participants' experiences by posing in-depth follow-up questions that might not have been possible without this detailed knowledge of both the intervention and the context. However, our involvement might have influenced the participants to display a more positive view about the intervention. To counterbalance this possible bias, another co-author of Paper 3, AG, participated in three of the five interviews and did the primary analysis alone before discussing her results with the rest of the authors. She did not have any involvement with the intervention or with the participating nursing homes. She posed follow-up questions towards the end of the interviews. Finally, her analyses did not differ substantially from the analyses done by BL and JM. At the end of each interview, the facilitator summarised the manifest content and findings of the interview and asked the participants to verify or amend the summary. This procedure adds to the validity of the data (295).

5.0 Conclusions

Agitation is common in NH residents with dementia and causes profound suffering for the residents, their relatives, and their caregivers. Since psychotropic drugs only have modest efficacy and are associated with serious side effects, non-pharmacological interventions are recommended as a first-line approach for agitation. There is however conflicting evidence about the effectiveness of non-pharmacological interventions for agitation in dementia. In this thesis, we have demonstrated that TIME, a multicomponent biopsychosocial approach, significantly reduced agitation in residents with dementia living in NH, with a possible reduction in other NPS and a possible improvement in quality of life. This study infers that since agitation in dementia often represents complex problems with multifactorial causes, multicomponent interventions with a comprehensive biopsychosocial approach should be recommended. Due to the inherent complexity properties of the NH, interventions should allow for adaption and flexibility to the settings to ensure implementation. TIME seems to address the complexity of NPS and NH by including as many of the staff as possible in an interdisciplinary decision process, by contributing to structure in problem solving and increasing coping amongst the staff. The effectiveness of the intervention with TIME at the residential level is probably due to a high degree of reach, implementation and maintenance. In addition, TIME shifts the way of learning for the staff from traditional to more innovative and reflection-based through a process of learning how to learn at work. This seems to make translation of knowledge into action easier. Therefore, another causal assumption of the effectiveness of TIME is the development in the staff of a new, shared and situated knowledge about each individual resident, which, through systematic group reflexion, leads towards person-centred treatment actions. An easy-to-grasp model and an engaged and present leadership facilitated the intervention and its sustainability. Conversely, lack of support from the leading ward nurse by not integrating the components of the intervention as part of the ward's clinical routines was perceived as the main barrier to implementation and maintenance.

6.0 Clinical implications and future research

National and international guidelines recommend non-pharmacological approaches based on PCC as the core of dementia care. TIME is an example of a model in which principles from person-centred care can be integrated in an interdisciplinary evidence-based approach towards NPS in NH. Although the results from the TIME-trial need to be replicated, they are unique and convincing and should inform training programmes for care staff in Norway and internationally. Since TIME represents a new non-pharmacological approach towards NPS that is highly feasible without continuous extra resources or expert inputs, dissemination on a large scale should be considered. A pilot study testing TIME as a method for problem solving for the staff in an old age psychiatric ward with patients with affective disorders without dementia has been conducted with promising results (228). Further development of TIME to be adapted to other complex conditions and settings beyond the NH represents an opportunity to be pursued.

There is a need for the development of new clinical assessment instruments for neuropsychiatric symptoms in dementia that take into account new understanding and knowledge of NPS in dementia based on PCC and the complexity of these symptoms. For agitation, this means that instruments need to be able to distinguish between agitation with and without aggression and not confuse resistance or disobedience towards care with aggression. Most existing clinical instruments aiming at measuring caregivers' competence are developed for assessing only *general* attitudes, knowledge and skills that are decontextualised from the caregivers' clinical practice. They do not shed light on what happens to the caregivers' interpretations, attitudes and actions in real-world care situations when they are confronted with challenging or complex situations. Qualitative methods like participant observation are used for this purpose but have some major limitations regarding generalisation and the methods' impact on the intervention itself. Future research should, therefore, explore new methods for assessing how general knowledge, attitudes and skills are translated into an every-day approach towards each individual resident.

This thesis emphasises the importance of situated learning to develop PCC. Future research should explore models for integrating situated learning in daily routines in nursing homes. There is still a gap between research and practice because of the difficulties in the translation of evidence-based knowledge to the field of practice. TIME was first developed within the practice field of nursing homes. More active involvement of the local settings in developing and adapting both the elements of an intervention and the implementation process, seems to promote implementation and dissemination of research results. Participatory action research approaches could achieve this aim. The research team, in collaboration with the practice field, would then have a better starting point for the exploration of the complexity in the local setting and the factors that facilitate or inhibit implementation.

7.0 References

1. Statistisk Sentralbyrå. Omsorgstenester (2017) [updated 15.06.2018. Available from: <https://www.ssb.no/helse/statistikker/pleie>.
2. Nygaard HA, Naik M, Ruths S, Straand J. Nursing-home residents and their drug use: a comparison between mentally intact and mentally impaired residents. The Bergen district nursing home (BEDNURS) study. *Eur J Clin Pharmacol*. 2003;59(5-6):463-9.
3. Helvik AS, Engedal K, Benth JS, Selbaek G. Prevalence and Severity of Dementia in Nursing Home Residents. *Dement Geriatr Cogn Disord*. 2015;40(3-4):166-77.
4. Selbaek G, Kirkevold O, Engedal K. The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *Int J Geriatr Psychiatry*. 2007;22(9):843-9.
5. Selbaek G, Engedal K, Benth JS, Bergh S. The course of neuropsychiatric symptoms in nursing-home patients with dementia over a 53-month follow-up period. *Int Psychogeriatr*. 2014;26(1):81-91.
6. Wetzels RB, Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Course of neuropsychiatric symptoms in residents with dementia in nursing homes over 2-year period. *Am J Geriatr Psychiatry*. 2010;18(12):1054-65.
7. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*. 1997;48(5 Suppl 6):S10-6.
8. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.
9. Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry*. 2009;194(3):212-9.
10. Conklin J. *Dialogue Mapping - Building Shared Understanding of Wicked Problems*. West Sussex: John Wiley & Sons, Ltd; 2006.
11. Haynes P. *Managing complexity in the public services*. London: Routledge; 2015. p. 24-50.
12. Shiell A, Hawe P, Gold L. Complex interventions or complex systems? Implications for health economic evaluation. *BMJ*. 2008;336(7656):1281-3.
13. Anderson RA, Issel LM, McDaniel Jr RR. Nursing homes as complex adaptive systems: relationship between management practice and resident outcomes. *Nurs Res*. 2003;52(1):12-21.
14. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977;196(4286):129-36.
15. Kales HC, Gitlin LN, Lyketsos CG. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc*. 2014;62(4):762-9.
16. Kales HC, Lyketsos CG, Miller EM, Ballard C. Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus. *Int Psychogeriatr*. 2018:1-8.
17. Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *Int Psychogeriatr*. 2015;27(1):7-17.
18. Brodaty H, Connors MH, Xu J, Woodward M, Ames D. Predictors of institutionalization in dementia: a three year longitudinal study. *J Alzheimers Dis*. 2014;40(1):221-6.
19. Peters ME, Schwartz S, Han D, Rabins PV, Steinberg M, Tschanz JT, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. *Am J Psychiatry*. 2015;172(5):460-5.
20. van Kooten J, van der Wouden JC, Sikkes SAM, Smalbrugge M, Hertogh C, Stek ML. Pain, Neuropsychiatric Symptoms, and Quality of Life of Nursing Home Residents With Advanced Dementia in The Netherlands: A Cross-sectional Study. *Alzheimer Dis Assoc Disord*. 2017;31(4):315-21.

21. Zeller A, Hahn S, Needham I, Kok G, Dassen T, Halfens RJ. Aggressive behavior of nursing home residents toward caregivers: a systematic literature review. *Geriatr Nurs*. 2009;30(3):174-87.
22. Wang J, Yu JT, Wang HF, Meng XF, Wang C, Tan CC, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2015;86(1):101-9.
23. Selbaek G, Janus SIM, Bergh S, Engedal K, Ruths S, Helvik AS, et al. Change in psychotropic drug use in Norwegian nursing homes between 2004 and 2011. *Int Psychogeriatr*. 2018;30(3):385-94.
24. Janus SI, van Manen JG, MJ IJ, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *Int Psychogeriatr*. 2016;28(11):1775-90.
25. Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, Patel N, et al. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. *Health Technology Assessment (Winchester, England)*. 2014;18(39):1-226, v-vi.
26. Brasure M, Jutkowitz E, Fuchs E, Nelson VA, Kane RA, Shippee T, et al. *AHRQ Comparative Effectiveness Reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.
27. Seitz DP, Brisbin S, Herrmann N, Rapoport MJ, Wilson K, Gill SS, et al. Efficacy and feasibility of nonpharmacological interventions for neuropsychiatric symptoms of dementia in long term care: a systematic review. *J Am Med Dir Assoc*. 2012;13(6):503-6.e2.
28. Lichtwarck B, Tverå AM, Røen I. *TIME - Targeted Interdisciplinary Model for Evaluation and treatment of neuropsychiatric symptoms - Manual 2nd Edition*. 2015 [30.04.2017]. Available from: www.tidmodell.no.
29. Lichtwarck B, Roen I, Selbaek G. Multidisciplinary Intervention for challenging behavior in Nursing home patients with Dementia. *International Psychogeriatric Association: Int Psychogeriatrics*; 2011. p. S137.
30. Gale SA, Acar D, Daffner KR. Dementia. *The American Journal of Medicine*. 2018;131(10):1161-9.
31. WHO. *International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)*: WHO; 2016 [Available from: <http://apps.who.int/classifications/icd10/browse/2016/en>].
32. APA. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* Washington D.C.: American Psychiatric Association; 2013 [Available from: <https://www.psychiatry.org/psychiatrists/practice/dsm>].
33. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(3):126-35.
34. WHO. *ICD-11 for Mortality and Morbidity Statistics (ICD-11 MMS) 2018 version*: WHO; 2018 [Available from: <https://icd.who.int/browse11/l-m/en>].
35. Stevens T, Livingston G, Kitchen G, Manela M, Walker Z, Katona C. Islington study of dementia subtypes in the community. *Br J Psychiatry*. 2002;180:270-6.
36. Aarsland D, Rongve A, Nore SP, Skogseth R, Skulstad S, Ehrt U, et al. Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. *Dement Geriatr Cogn Disord*. 2008;26(5):445-52.
37. Engedal K, Haugen PK. *Demens - sykdommer, diagnostikk og behandling*. Oslo: Forlaget Aldring og Helse; 2018.
38. Ridley NJ, Draper B, Withall A. Alcohol-related dementia: an update of the evidence. *Alzheimers Res Ther*. 2013;5(1):3-8.
39. Draper B, Karmel R, Gibson D, Peut A, Anderson P. Alcohol-related cognitive impairment in New South Wales hospital patients aged 50 years and over. *Aust N Z J Psychiatry*. 2011;45(11):985-92.

40. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International (ADI); 2015.
41. Vossius C, Selbaek G, Ydstebø AE, Benth JS, Godager G, Lurås H, et al. Resource Use and Disease Course in Dementia (REDIC). Ottestad: Sykehuset Innlandet; 2015.
42. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. *N Engl J Med*. 2016;374(6):523-32.
43. Matthews FE, Stephan BC, Robinson L, Jagger C, Barnes LE, Arthur A, et al. A two decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II. *Nature communications*. 2016;7:1-8.
44. Kingston A, Robinson L, Booth H, Knapp M, Jagger C. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age Ageing*. 2018;47(3):374-80.
45. Prince M, Herrera A, Knapp M, Guerchet M, Karagiannidou M. World Alzheimer Report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future. London; 2016.
46. The Academy of Medical Sciences. Multimorbidity: a priority for global health research. London: The Academy of Medical Sciences; 2018.
47. Engedal K, Haugen PK. Demens - fakta og utfordringer (Dementia - Facts and Challenges). 5 ed: Aldring og Helse; 2009.
48. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. *BMJ*. 2013;347:1-9.
49. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(Pt 9):2456-77.
50. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*. 2017;89(1):88-100.
51. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22(12):1689-707.
52. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-734.
53. Jellinger KA, Attems J. Prevalence and pathology of dementia with Lewy bodies in the oldest old: a comparison with other dementing disorders. *Dement Geriatr Cogn Disord*. 2011;31(4):309-16.
54. Gale SA, Acar D, Daffner KR. Dementia. *THE AMERICAN JOURNAL of MEDICINE*. 2018 (In Press).
55. Erkinjuntti T, Pantoni L, Melkas S. What is vascular cognitive impairment ? In: Ames D, O'Brien JT, Burns A, editors. *Dementia*. 5 ed. Boca Raton U.S.: Taylor & Francis Group; 2017. p. 630-42.
56. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. *The Lancet*. 2015;386(10004):1683-97.
57. McKeith IG. Dementia with Lewy bodies: A clinical overview. In: Ames D, O'Brien JT, Burns A, editors. *Dementia*. 5 ed. Boca Raton U.S.: Taylor & Francis Group; 2017. p. 703-13.
58. Hodges J. Pick's disease: It's relationship to progressive aphasia, semantic dementia and frontotemporal dementia. In: Ames D, O'Brien JT, Burns A, editors. *Dementia*. 5 ed. Boca Raton U.S.: Taylor & Francis Group; 2017. p. 759-70.
59. Wilson K, Afghan S, Bowden-Jones H, Faruqui RA, Feeney A, Gerada C, et al. Alcohol and brain damage in adults - With reference to high-risk groups. London: Royal College of Psychiatrists; 2014.
60. Niu H, Alvarez-Alvarez I, Guillen-Grima F, Aguinaga-Ontoso I. Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurologia*. 2017;32(8):523-32.
61. Freudenberg-Hua Y, Li W, Davies P. The Role of Genetics in Advancing Precision Medicine for Alzheimer's Disease-A Narrative Review. *Frontiers in medicine*. 2018;5:108.

62. Helsedirektoratet. Nasjonal faglig retningslinje om demens (Norwegian National Guideline on Dementia) Oslo: Helsedirektoratet (The Norwegian Directorate of Health); 2017 [Available from: <https://helsedirektoratet.no/retningslinjer/nasjonal-faglig-retningslinje-om-demens>].
63. Young JJ, Lavakumar M, Tampi D, Balachandran S, Tampi RR. Frontotemporal dementia: latest evidence and clinical implications. *Therapeutic advances in psychopharmacology*. 2018;8(1):33-48.
64. Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr*. 1996;8 Suppl 3:497-500.
65. Selbaek G, Engedal K. Stability of the factor structure of the Neuropsychiatric Inventory in a 31-month follow-up study of a large sample of nursing-home patients with dementia. *Int Psychogeriatr*. 2012;24(1):62-73.
66. Aalten P, Verhey FR, Boziki M, Brugnolo A, Bullock R, Byrne EJ, et al. Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II. *Dement Geriatr Cogn Disord*. 2008;25(1):1-8.
67. Frederiksen KS, Waldemar G. Aggression, Agitation, Hyperactivity and Irritability. In: Verdelho A, Goncalves-Pereira M, editors. *Neuropsychiatric Symptoms of Cognitive Impairment and Dementia. Neuropsychiatric Symptom of Neurological Disease*. Switzerland: Springer International Publishing AG; 2017. p. 199-236.
68. Bergh S, Holmen J, Saltvedt I, Tambs K, Selbaek G. Dementia and neuropsychiatric symptoms in nursing-home patients in Nord-Trøndelag County. *Tidsskr Nor Lægeforen*. 2012;132(17):1956-9.
69. Aalten P, de Vugt ME, Jaspers N, Jolles J, Verhey FR. The course of neuropsychiatric symptoms in dementia. Part II: relationships among behavioural sub-syndromes and the influence of clinical variables. *Int J Geriatr Psychiatry*. 2005;20(6):531-6.
70. Kolanowski A, Boltz M, Galik E, Gitlin LN, Kales HC, Resnick B, et al. Determinants of behavioral and psychological symptoms of dementia: A scoping review of the evidence. *Nurs Outlook*. 2017;65(5):515-29.
71. Selbaek G, Engedal K, Bergh S. The prevalence and course of neuropsychiatric symptoms in nursing home patients with dementia: a systematic review. *J Am Med Dir Assoc*. 2013;14(3):161-9.
72. Robert P, Onyike CU, Leentjens AF, Dujardin K, Aalten P, Starkstein S, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24(2):98-104.
73. Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement*. 2011;7(5):532-9.
74. Reyes S, Viswanathan A, Godin O, Dufouil C, Benisty S, Hernandez K, et al. Apathy: a major symptom in CADASIL. *Neurology*. 2009;72(10):905-10.
75. Saxena S, Lawley D. Delirium in the elderly: a clinical review. *Postgrad Med J*. 2009;85(1006):405-13.
76. Helvik AS, Engedal K, Wu B, Benth JS, Corazzini K, Roen I, et al. Severity of Neuropsychiatric Symptoms in Nursing Home Residents. *Dementia and geriatric cognitive disorders extra*. 2016;6(1):28-42.
77. Goyal AR, Bergh S, Engedal K, Kirkevold M, Kirkevold O. Anxiety, Anxiety Symptoms, and Their Correlates in Persons with Dementia in Norwegian Nursing Homes: A Cause for Concern. *Dement Geriatr Cogn Disord*. 2017;43(5-6):294-305.
78. Orgeta V, Qazi A, Spector A, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *Br J Psychiatry*. 2015;207(4):293-8.
79. Goyal AR, Bergh S, Engedal K, Kirkevold M, Kirkevold O. The course of anxiety in persons with dementia in Norwegian nursing homes: A 12-month follow-up study. *J Affect Disord*. 2018;235:117-23.

80. Goyal AR, Bergh S, Engedal K, Kirkevold M, Kirkevold O. Norwegian version of the rating anxiety in dementia scale (RAID-N): a validity and reliability study. *Aging Ment Health*. 2017;21(12):1256-61.
81. Teri L, Ferretti LE, Gibbons LE, Logsdon RG, McCurry SM, Kukull WA, et al. Anxiety of Alzheimer's disease: prevalence, and comorbidity. *J Gerontol A Biol Sci Med Sci*. 1999;54(7):M348-52.
82. Olin JT, Katz IR, Meyers BS, Schneider LS, Lebowitz BD. Provisional diagnostic criteria for depression of Alzheimer disease: rationale and background. *Am J Geriatr Psychiatry*. 2002;10(2):129-41.
83. Borza T, Engedal K, Bergh S, Barca ML, Benth JS, Selbaek G. The course of depressive symptoms as measured by the Cornell scale for depression in dementia over 74 months in 1158 nursing home residents. *J Affect Disord*. 2015;175:209-16.
84. Prado-Jean A, Couratier P, Druet-Cabanac M, Nubukpo P, Bernard-Bourzeix L, Thomas P, et al. Specific psychological and behavioral symptoms of depression in patients with dementia. *Int J Geriatr Psychiatry*. 2010;25(10):1065-72.
85. Selbæk G. Psychosis in Dementia. In: Verdelho A, Goncalves-Pereira M, editors. *Neuropsychiatric Symptoms of Cognitive Impairment and Dementia. Neuropsychiatric Symptoms of Neurological Disease*. Switzerland: Springer International Publishing AG; 2017. p. 237-50.
86. Steinberg M, Tschanz JT, Corcoran C, Steffens DC, Norton MC, Lyketsos CG, et al. The persistence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry*. 2004;19(1):19-26.
87. Vilalta-Franch J, Lopez-Pousa S, Calvo-Perxas L, Garre-Olmo J. Psychosis of Alzheimer disease: prevalence, incidence, persistence, risk factors, and mortality. *Am J Geriatr Psychiatry*. 2013;21(11):1135-43.
88. Cohen-Mansfield J. Nonpharmacologic interventions for psychotic symptoms in dementia. *J Geriatr Psychiatry Neurol*. 2003;16(4):219-24.
89. Cohen-Mansfield J, Golander H, Cohen R. Rethinking Psychosis in Dementia: An Analysis of Antecedents and Explanations. *Am J Alzheimers Dis Other Demen*. 2017;32(5):265-71.
90. Cohen-Mansfield J, Cohen R, Golander H, Heinik J. The impact of psychotic symptoms on the persons with dementia experiencing them. *Am J Geriatr Psychiatry*. 2016;24(3):213-20.
91. Shah C, DeMichele-Sweet MA, Sweet RA. Genetics of psychosis of Alzheimer disease. *Am J Med Genet B Neuropsychiatr Genet*. 2017;174(1):27-35.
92. Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. *Biol Psychiatry*. 2014;75(7):542-52.
93. Whitfield DR, Francis PT, Ballard C, Williams G. Associations between ZnT3, tau pathology, agitation, and delusions in dementia. *Int J Geriatr Psychiatry*. 2018;33(8):1146-52.
94. Cohen-Mansfield J, Billig N. Agitated behaviors in the elderly. I. A conceptual review. *J Am Geriatr Soc*. 1986;34(10):711-21.
95. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol*. 1989;44(3):M77-84.
96. Jutkowitz E, Brasure M, Fuchs E, Shippee T, Kane RA, Fink HA, et al. Care-Delivery Interventions to Manage Agitation and Aggression in Dementia Nursing Home and Assisted Living Residents: A Systematic Review and Meta-analysis. *J Am Geriatr Soc*. 2016;64(3):477-88.
97. Maust DT, Kim HM, Seyfried LS, Chiang C, Kavanagh J, Schneider LS, et al. Antipsychotics, other psychotropics, and the risk of death in patients with dementia: number needed to harm. *JAMA Psychiatry*. 2015;72(5):438-45.
98. Reus VI, Fochtmann LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, et al. The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia. *Am J Psychiatry*. 2016;173(5):543-6.
99. Zuidema SU, Johansson A, Selbaek G, Murray M, Burns A, Ballard C, et al. A consensus guideline for antipsychotic drug use for dementia in care homes. Bridging the gap between scientific evidence and clinical practice. *Int Psychogeriatr*. 2015;27(11):1849-59.

100. Volicer L. Toward better terminology of behavioral symptoms of dementia. *J Am Med Dir Assoc.* 2012;13(1):3-4.
101. Gitlin LN, Marx KA, Stanley IH, Hansen BR, Van Haitsma KS. Assessing neuropsychiatric symptoms in people with dementia: a systematic review of measures. *Int Psychogeriatr.* 2014;26(11):1805-48.
102. Lichtwarck B, Selbaek G, Kirkevold Ø, Rokstad AM, Benth JS, Lindstrøm JC, et al. Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms: A Cluster Randomized Controlled Trial. *The American Journal of Geriatric Psychiatry.* 2018;26(1):25-38.
103. Volicer L. What is NPI item "agitation/aggression" really measuring? *Am J Geriatr Psychiatry.* 2011;19(12):1046; author reply -7.
104. Selbaek G, Kirkevold O, Engedal K. Psychiatric and behavioural symptoms and the use of psychotropic medication in Special Care Units and Regular Units in Norwegian nursing homes. *Scand J Caring Sci.* 2008;22(4):568-73.
105. Bergh S, Engedal K, Roen I, Selbaek G. The course of neuropsychiatric symptoms in patients with dementia in Norwegian nursing homes. *Int Psychogeriatr.* 2011;23(8):1231-9.
106. Livingston G, Barber J, Marston L, Rapaport P, Livingston D, Cousins S, et al. Prevalence of and associations with agitation in residents with dementia living in care homes: MARQUE cross-sectional study. *BJPsych open.* 2017;3(4):171-8.
107. Wetzels RB, Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Determinants of quality of life in nursing home residents with dementia. *Dement Geriatr Cogn Disord.* 2010;29(3):189-97.
108. Mjorud M, Kirkevold M, Rosvik J, Selbaek G, Engedal K. Variables associated to quality of life among nursing home patients with dementia. *Aging Ment Health.* 2014;18(8):1013-21.
109. Cohen-Mansfield J. Agitated behavior in persons with dementia: the relationship between type of behavior, its frequency, and its disruptiveness. *J Psychiatr Res.* 2008;43(1):64-9.
110. Trzepacz PT, Yu P, Bhamidipati PK, Willis B, Forrester T, Tabas L, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement.* 2013;9(5 Suppl):S95-S104.e1.
111. Hollingworth P, Hamshere ML, Moskvina V, Dowzell K, Moore PJ, Foy C, et al. Four components describe behavioral symptoms in 1,120 individuals with late-onset Alzheimer's disease. *J Am Geriatr Soc.* 2006;54(9):1348-54.
112. Kiely DK, Morris JN, Algase DL. Resident characteristics associated with wandering in nursing homes. *Int J Geriatr Psychiatry.* 2000;15(11):1013-20.
113. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. *JAMA.* 2017;318(12):1161-74.
114. Abengana J, Chong MS, Tay L. Delirium superimposed on dementia: phenomenological differences between patients with and without behavioral and psychological symptoms of dementia in a specialized delirium unit. *Int Psychogeriatr.* 2017;29(3):485-95.
115. Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ.* 2011;343:d4065.
116. Patel V, Hope RA. Aggressive behaviour in elderly psychiatric inpatients. *Acta Psychiatr Scand.* 1992;85(2):131-5.
117. Perlman CM, Hirdes JP. The aggressive behavior scale: a new scale to measure aggression based on the minimum data set. *J Am Geriatr Soc.* 2008;56(12):2298-303.
118. Wood S, Cummings JL, Hsu MA, Barclay T, Wheatley MV, Yarema KT, et al. The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *Am J Geriatr Psychiatry.* 2000;8(1):75-83.
119. de Medeiros K, Robert P, Gauthier S, Stella F, Politis A, Leoutsakos J, et al. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. *Int Psychogeriatr.* 2010;22(6):984-94.
120. Melander C, Savenstedt S, Olsson M, Walivaara BM. Assessing BPSD with the support of the NPI-NH: a discourse analysis of clinical reasoning. *Int Psychogeriatr.* 2018;30(4):581-9.

121. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. *JAMA*. 2012;308(19):2020-9.
122. Laksov KB, Dornan T, Teunissen PW. Making theory explicit - An analysis of how medical education research(ers) describe how they connect to theory. *BMC Med Educ*. 2017;17(1):18.
123. Verdelho A, Goncalves-Pereira M. Neuropsychiatric Symptoms in Cognitive Impairment and Dementia: A Brief Introductory Overview. In: Verdelho A, Goncalves-Pereira M, editors. *Neuropsychiatric Symptoms of Cognitive Impairment and Dementia*. Neuropsychiatric Symptoms of Neurological Disease. Switzerland: Springer International Publishing AF; 2017. p. 1-7.
124. Kitwood T. Towards a theory of dementia care: the interpersonal process. *Ageing & Society*. 1993;13(1):51-67.
125. Kitwood T. *Dementia Reconsidered - the person comes first*. Birmingham: Open University Press; 1997.
126. Geda YE, Schneider LS, Gitlin LN, Miller DS, Smith GS, Bell J, et al. Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *Alzheimers Dement*. 2013;9(5):602-8.
127. Algase DL, Beck C, Kolanowski A, Whall A, Berent S, Richards K, et al. Need-driven dementia-compromised behavior: An alternative view of disruptive behavior. *American Journal of Alzheimer's Disease*. 2016;11(6):10-9.
128. Zwijsen SA, van der Ploeg E, Hertogh CM. Understanding the world of dementia. How do people with dementia experience the world? *Int Psychogeriatr*. 2016;28(7):1067-77.
129. Spector A, Orrell M. Using a biopsychosocial model of dementia as a tool to guide clinical practice. *Int Psychogeriatr*. 2010;22(6):957-65.
130. Nortvedt P, Grimen H. *Sensibilitet og refleksjon. Filosofi og vitenskapsteori for helsefag*. Oslo: Gyldendal Akademisk; 2004.
131. Cilliers P. *Complexity and Postmodernism*. London: Routledge; 1998.
132. Helse-og omsorgsdepartementet. *Egenbetaling for kommunale tjenester i og utenfor institusjon 2014* [updated 18.12.2014].
133. Helse og omsorgsdepartementet. *Forskrift for sykehjem og boform for heldøgns omsorg og pleie 1998* [updated 21.06.2013. Available from: <https://lovdata.no/dokument/SF/forskrift/1988-11-14-932>].
134. Høyland K, Kirkevold Ø, Woods R, Haugan G. *Er smått alltid godt i demensomsorgen? Om bo - og tjenestetilbud for personer med demens*. Oslo: SINTEF; 2015. Report No.: 33.
135. Gjøra L, Ek A, Kirkevold Ø. *Nasjonal kartlegging av tilbudet til personer med demens 2014 (National survey for the assessment of health and social services for persons with dementia 2014)*. Oslo: Nasjonal kompetansetjeneste for aldring og helse (Norwegian National Advisory Unit on Ageing and Health); 2015.
136. Den norske legeforening. *Godkjente i kompetanseområdet i alders- og sykehjemsmedisin 2018* [updated 21.06.2018. Available from: <https://beta.legeforeningen.no/utdanning/kompetanseomrader/alders-og-sykehjemsmedisin/godkjente-i-kompetanseområdet-i-alders-og-sykehjemsmedisin/>].
137. Gautun H, Hermansen Å. *Eldreomsorg under press - Kommunenes helse-og omsorgstilbud til eldre (Elderly care under pressure - Municipal health and care services for the elderly)* Oslo: Fafo Institute for Labour and Social Research; 2011.
138. Roen I, Selbaek G, Kirkevold O, Engedal K, Testad I, Bergh S. Resource Use and Disease Course in dementia - Nursing Home (REDIC-NH), a longitudinal cohort study; design and patient characteristics at admission to Norwegian nursing homes. *BMC Health Serv Res*. 2017;17(1):365.
139. Halvorsen KH, Selbaek G, Ruths S. Trends in potentially inappropriate medication prescribing to nursing home patients: comparison of three cross-sectional studies. *Pharmacoepidemiol Drug Saf*. 2017;26(2):192-200.
140. Nyborg G, Brekke M, Straand J, Gjelstad S, Romoren M. Potentially inappropriate medication use in nursing homes: an observational study using the NORGEH-NH criteria. *BMC Geriatr*. 2017;17(1):220.

141. Kirkevold O, Engedal K. The quality of care in Norwegian nursing homes. *Scand J Caring Sci*. 2006;20(2):177-83.
142. Mjorud M, Engedal K, Rosvik J, Kirkevold M. Living with dementia in a nursing home, as described by persons with dementia: a phenomenological hermeneutic study. *BMC Health Serv Res*. 2017;17(93):1-9.
143. International Psychogeriatric Association. IPA Complete Guides to Behavioral and Psychological Symptoms of Dementia (BPSD) Milwaukee2008 [updated 2017. Available from: <http://www.ipa-online.org/publications/guides-to-bpsd>.
144. Roen I, Kirkevold O, Testad I, Selbaek G, Engedal K, Bergh S. Person-centered care in Norwegian nursing homes and its relation to organizational factors and staff characteristics: a cross-sectional survey. *Int Psychogeriatr*. 2018;30(9):1279-90.
145. Rapaport P, Livingston G, Murray J, Mulla A, Cooper C. Systematic review of the effective components of psychosocial interventions delivered by care home staff to people with dementia. *BMJ open*. 2017;7(2):e014177.
146. Gautun H, Bratt C. Bemanning og kompetanse i hjemmesykepleien og sykehjem (Staffing and Competence in Home Care Services and Nursing Homes). Oslo: Norsk institutt for forskning om oppvekst, velferd og aldring NOVA (Centre for Welfare and Labour Research - Oslo and Akershus University College of Applied Science); 2014.
147. Statistisk Sentralbyrå. Spesialisthelsetjenesten [updated 22.06.2018. Available from: <https://www.ssb.no/helse/statistikker/speshelse/aar>.
148. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on A, Management of Neuropsychiatric Symptoms of D. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc*. 2014;62(4):762-9.
149. Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, Patel N, et al. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. *Br J Psychiatry*. 2014;205(6):436-42.
150. Cohen-Mansfield J. Non-pharmacological interventions for persons with dementia: what are they and how should they be studied? *Int Psychogeriatr*. 2018;30(3):281-3.
151. Rokstad AM, Rosvik J, Kirkevold O, Selbaek G, Saltyte Benth J, Engedal K. The effect of person-centred dementia care to prevent agitation and other neuropsychiatric symptoms and enhance quality of life in nursing home patients: a 10-month randomized controlled trial. *Dement Geriatr Cogn Disord*. 2013;36(5-6):340-53.
152. Freemantle N. Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? *BMJ*. 2001;322(7292):989-91.
153. Andrade C. The primary outcome measure and its importance in clinical trials. *J Clin Psychiatry*. 2015;76(10):e1320-3.
154. Medical Research Council. Developing and Evaluating Complex Interventions - new guidance London2016 [Available from: www.mrc.ac.uk/complexinterventionsguidance.
155. Glasgow RE, Lichtenstein E, Marcus AC. Why Don't We See More Translation of Health Promotion Research to Practice? Rethinking the Efficacy-to-Effectiveness Transition. *Am J Public Health*. 2003;93(8):1261-7.
156. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furburg CD, Altman DG, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*. 2009;62(5):464-75.
157. Egger M, Smith GD, Phillips AN. Meta-analysis: Principles and procedures. *BMJ*. 1997;315(7121):1533-7.
158. Chenoweth L, King MT, Jeon YH, Brodaty H, Stein-Parbury J, Norman R, et al. Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. *Lancet Neurol*. 2009;8(4):317-25.
159. van de Ven G, Draskovic I, Adang EM, Donders R, Zuidema SU, Koopmans RT, et al. Effects of dementia-care mapping on residents and staff of care homes: a pragmatic cluster-randomised controlled trial. *PLoS One*. 2013;8(7):e67325.

160. McGlothlin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. *JAMA*. 2014;312(13):1342-3.
161. Howard R, Phillips P, Johnson T, O'Brien J, Sheehan B, Lindsay J, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *Int J Geriatr Psychiatry*. 2011;26(8):812-7.
162. Cummings J. npITEST 2017 [07.11.2017]. Available from: <http://npitest.net/fags.html>.
163. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. *J Clin Psychiatry*. 2002;63(7):553-8.
164. Sullivan GM, Feinn R. Using Effect Size—or Why the P Value Is Not Enough. *J Grad Med Educ*. 2012;4(3):279-82.
165. Pedersen SKA, Andersen PN, Lugo RG, Andreassen M, Sutterlin S. Effects of Music on Agitation in Dementia: A Meta-Analysis. *Front Psychol*. 2017;8:742.
166. van der Steen JT, Smaling HJ, van der Wouden JC, Bruinsma MS, Scholten RJ, Vink AC. Music-based therapeutic interventions for people with dementia. *Cochrane Database Syst Rev*. 2018;7:CD003477.
167. Cohen-Mansfield J, Thein K, Marx MS, Dakheel-Ali M, Freedman L. Efficacy of nonpharmacologic interventions for agitation in advanced dementia: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2012;73(9):1255-61.
168. Yakimicki ML, Edwards NE, Richards E, Beck AM. Animal-Assisted Intervention and Dementia: A Systematic Review. *Clin Nurs Res*. 2018:1054773818756987.
169. Joranson N, Pedersen I, Rokstad AM, Ihlebaek C. Effects on Symptoms of Agitation and Depression in Persons With Dementia Participating in Robot-Assisted Activity: A Cluster-Randomized Controlled Trial. *J Am Med Dir Assoc*. 2015;16(10):867-73.
170. Kitwood T, Bredin K. A new approach to the evaluation of dementia care. *Journal of Advances in Health and Nursing Care*. 1992;1(5):41-60.
171. Brooker D, Surr C. *Dementia Care Mapping: Principles and Practice*. Bradford: Bradford Dementia Group, University of Bradford; 2005.
172. Brooker D. What is person-centred care in dementia? *Rev Clin Gerontol*. 2004;13(3):215-22.
173. Røsvik J, Brooker D, Mjorud M, Kirkevold Ø. What is person-centred care in dementia? Clinical reviews into practice: the development of the VIPS practice model. *Rev Clin Gerontol*. 2013;23(2):155-63.
174. Fossey J, Ballard C, Juszcak E, James I, Alder N, Jacoby R, et al. Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. *BMJ*. 2006;332(7544):756-61.
175. Sommer OH, Engedal K. Reliability and validity of the Norwegian version of the Brief Agitation Rating Scale (BARS) in dementia. *Aging Ment Health*. 2011;15(2):252-8.
176. Zwijsen SA, Smalbrugge M, Eefsting JA, Twisk JW, Gerritsen DL, Pot AM, et al. Coming to grips with challenging behavior: a cluster randomized controlled trial on the effects of a multidisciplinary care program for challenging behavior in dementia. *J Am Med Dir Assoc*. 2014;15(7):531 e1-10.
177. Rapp MA, Mell T, Majic T, Treusch Y, Nordheim J, Niemann-Mirmehdi M, et al. Agitation in nursing home residents with dementia (VIDEANT trial): effects of a cluster-randomized, controlled, guideline implementation trial. *J Am Med Dir Assoc*. 2013;14(9):690-5.
178. Smeets CHW, Zuidema SU, Hulshof TA, Smalbrugge M, Gerritsen DL, Koopmans R, et al. Efficacy of antipsychotics in dementia depended on the definition of patients and outcomes: a meta-epidemiological study. *J Clin Epidemiol*. 2018;101:17-27.
179. Seitz DP, Gill SS, Herrmann N, Brisbin S, Rapoport MJ, Rines J, et al. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: A systematic review. *Int Psychogeriatr*. 2013;25(2):185-203.
180. Lockhart IA, Orme ME, Mitchell SA. The efficacy of licensed-indication use of donepezil and memantine monotherapies for treating behavioural and psychological symptoms of dementia in

- patients with Alzheimer's disease: systematic review and meta-analysis. *Dementia and geriatric cognitive disorders extra.* 2011;1(1):212-27.
181. Dyer SM, Harrison SL, Laver K, Whitehead C, Crotty M. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. *Int Psychogeriatr.* 2018;30(3):295-309.
 182. Maglione M, Ruelaz MA, Hu J, Wang Z, Shanman R, Shekelle PG, et al. Off-Label Use of Atypical Antipsychotics: An Update. Rockville: Agency for Healthcare Research and Quality (AHRQ); 2011 [No. 43.]:[Available from: www.effectivehealthcare.ahrq.gov/reports/final.cfm].
 183. Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA.* 2005;293(5):596-608.
 184. Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. *Cochrane Database Syst Rev.* 2002(2):Cd002852.
 185. U.S. Food and Drug Administration (FDA). FDA Expands Mortality Warnings on Antipsychotic Drugs 2008 [Available from: <https://www.fdanews.com/articles/107752-fda-expands-mortality-warnings-on-antipsychotic-drugs>].
 186. Hulshof TA, Zuidema SU, Ostelo RW, Luijendijk HJ. The Mortality Risk of Conventional Antipsychotics in Elderly Patients: A Systematic Review and Meta-analysis of Randomized Placebo-Controlled Trials. *J Am Med Dir Assoc.* 2015;16(10):817-24.
 187. Langballe EM, Engdahl B, Nordeng H, Ballard C, Aarsland D, Selbaek G. Short- and long-term mortality risk associated with the use of antipsychotics among 26,940 dementia outpatients: a population-based study. *Am J Geriatr Psychiatry.* 2014;22(4):321-31.
 188. Selbaek G, Aarsland D, Ballard C, Engedal K, Langballe EM, Benth JS, et al. Antipsychotic Drug Use Is Not Associated With Long-Term Mortality Risk in Norwegian Nursing Home Patients. *J Am Med Dir Assoc.* 2016;17(5):464 e1-7.
 189. Uptodate. Management of neuropsychiatric symptoms of dementia - agitation and aggression 2018 [updated 23.10.2017. Available from: <https://www.uptodate.com/contents/management-of-neuropsychiatric-symptoms-of-dementia?search=agitation%20in%20demen>].
 190. Porsteinsson AP, Drye LT, Pollock BG, Devanand DP, Frangakis C, Ismail Z, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA.* 2014;311(7):682-91.
 191. Schneider LS, Frangakis C, Drye LT, Devanand DP, Marano CM, Mintzer J, et al. Heterogeneity of Treatment Response to Citalopram for Patients With Alzheimer's Disease With Aggression or Agitation: The CitAD Randomized Clinical Trial. *Am J Psychiatry.* 2016;173(5):465-72.
 192. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev.* 2006(1):Cd005593.
 193. Baillon SF, Narayana U, Luxenberg JS, Clifton AV. Valproate preparations for agitation in dementia. *Cochrane Database Syst Rev.* 2018;10:Cd003945.
 194. National Institute for Health and Care Excellence (NICE). Pharmacological interventions for dementia London 2018 [Available from: <https://www.nice.org.uk/guidance/ng97/chapter/Recommendations#pharmacological-interventions-for-dementia>].
 195. Cohen-Mansfield J, Jensen B. Nursing home physicians' knowledge of and attitudes toward nonpharmacological interventions for treatment of behavioral disturbances associated with dementia. *J Am Med Dir Assoc.* 2008;9(7):491-8.
 196. Rittel HWJ, Webber MM. Dilemmas in a general theory of planning. *Policy Sciences.* 1973;4(2):155-69.
 197. Hawe P, Shiell A, Riley T. Complex interventions: how "out of control" can a randomised controlled trial be? *BMJ.* 2004;328(7455):1561-3.
 198. Guastello SJ, Liebovitch LS. Introduction to Nonlinear Dynamics and Complexity. In: Guastello SJ, Koopmans M, Pincus D, editors. *Chaos and Complexity in Psychology - The Theory of Nonlinear Dynamical Systems.* New York: Cambridge University Press; 2009. p. 1-40.

199. Anderson RA, McDaniel RR, Jr. Managing health care organizations: where professionalism meets complexity science. *Health Care Manage Rev.* 2000;25(1):83-92.
200. Bergland A, Johansen H, Sellevold GS. A qualitative study of professional caregivers' perceptions of processes contributing to mealtime agitation in persons with dementia in nursing home wards and strategies to attain calmness. *Nursing open.* 2015;2(3):119-29.
201. Cilliers P. Approaching complexity. *Complexity and Postmodernism.* London: Routledge; 1998. p. 1-24.
202. Cilliers P. Self-organisation in complex systems. *Complexity and Postmodernism.* London: Routledge; 1998. p. 89-111.
203. Stacey RD. The Space for Creativity in an organization. *Complexity and creativity in organizations.* San Fransisco: Berrett-Koehler Publishers; 1996. p. 165-91.
204. Richards DA, Hallberg IR. *Complex interventions in health: an overview of research methods.* New York: Routledge; 2015.
205. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud.* 2013;50(5):587-92.
206. Campbell M, Fitzpatrick R, Haines A, Kinmonth AL, Sandercock P, Spiegelhalter D, et al. Framework for design and evaluation of complex interventions to improve health. *BMJ : British Medical Journal.* 2000;321(7262):694-6.
207. Greenwood-Lee J, Hawe P, Nettel-Aguirre A, Shiell A, Marshall DA. Complex intervention modelling should capture the dynamics of adaptation. *BMC Med Res Methodol.* 2016;16:51.
208. Boersma P, van Weert JC, Lakerveld J, Droes RM. The art of successful implementation of psychosocial interventions in residential dementia care: a systematic review of the literature based on the RE-AIM framework. *Int Psychogeriatr.* 2015;27(1):19-35.
209. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* 1999;89(9):1322-7.
210. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM Framework: A Systematic Review of Use Over Time. *Am J Public Health.* 2013;103(6):e38-e46.
211. Fixsen DL, Naom FL. *Implementation research: a syntesis of the literature.* Louis de la Parte Florida Mental Health Institute, The National Implementation Research Network (FMHI Publication #231). Tampa, FL: University of South Florida; 2005.
212. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions UK Medical Research Council (MRC) guidance: MRC Population Health Science Research Network; 2013 [Available from: <https://www.mrc.ac.uk/documents/pdf/mrc-phsrn-process-evaluation-summary-guidance/>].
213. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ.* 2015;350:h1258.
214. Creswell JW, Clark P. Choosing a Mixed Methods Design. In: Creswell JW, Clark P, editors. *Designing and Conducting Mixed Methods Research.* Los Angeles: SAGE Publications, Inc.; 2011. p. 53-106.
215. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care.* 2012;50(3):217-26.
216. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ.* 2013;347:f6753.
217. Terum TM, Andersen JR, Rongve A, Aarsland D, Svendsboe EJ, Testad I. The relationship of specific items on the Neuropsychiatric Inventory to caregiver burden in dementia: a systematic review. *Int J Geriatr Psychiatry* [Internet]. 2017 Mar 20; 32(7):[703-17 pp.]. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28317166>.
218. Zwijsen SA, Kabboord A, Eefsting JA, Hertogh CM, Pot AM, Gerritsen DL, et al. Nurses in distress? An explorative study into the relation between distress and individual neuropsychiatric symptoms of people with dementia in nursing homes. *Int J Geriatr Psychiatry.* 2014;29(4):384-91.

219. Schon DA. The reflective practitioner: How professionals think in action. London: Hachette UK; 2008.
220. Ellström PE. The meaning and Role of Reflection in Informal Learning at Work. Boud D, Cressey P, Docherty P, editors. London: Routledge; 2006.
221. Lave J, Wenger E. Situated learning: Legitimate peripheral participation. Cambridge: Cambridge university press; 1991.
222. Ellström PE. Integrating learning and work: Problems and prospects. Human Resource Development Quarterly. 2001;12(4):421-35.
223. Lazarus RS. The Person-Environment Relationship, Motivation and Coping. In: Lazarus RS, editor. Emotion and Adaption. Oxford: Oxford University Press on Demand; 1991. p. 112-6.
224. Hawton K, Kirk J. Problem-solving. In: Hawton K, Salkovskis PM, editors. Cognitive Behaviour Therapy for psychiatric problems - a practical guide. Oxford: Oxford Medical Publications; 2002. p. 406-26.
225. Lichtwarck B, Roen I, Selbaek G, Bergh S. TIME - Targeted Intervention Model for Evaluation and treatment of neuropsychiatric symptoms - a qualitative study. In: Psychogeriatrics I, editor. International Psychogeriatric Association. 2015;p. S88.
226. Lichtwarck B, Tverå AM, Nystad HL. TID Tverrfaglig Intervensjonsmodell ved utfordrende atferd ved Demens Opplæringsfilm (Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms - an educational film) Mo i Rana: Rana Kommune; 2013 [Available from: www.tidmodell.no].
227. Joint Action Dementia 2. Quality of Residential Care - Evidence and Recommendation. 2017.
228. Myhre J, Lichtwarck B, Bergh S. Delt forståelse og felles forpliktelse - En kvalitativ studie av personalets erfaringer med TID-refleksjon i en alderspsykiatrisk avdeling. Tidskriftet Aldring og Helse. 2018;22(1):41-5.
229. Beck JS. Cognitive behavior therapy: Basics and beyond. New York: Guilford Press; 2011.
230. Fenell MJV. Depression. In: Hawton K, Salkovskis PM, editors. Cognitive Behaviour Therapy for psychiatric problems- a practical guide. Oxford: Oxford Medical Publications; 2002. p. 194-5
231. Hawton K, Salkovskis PM. Cognitive behaviour therapy for psychiatric problems-a practical guide: Oxford Medical Publications; 2002. 194-5 p.
232. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. Biol Psychiatry. 1988;23(3):271-84.
233. Barca ML, Engedal K, Selbaek G. A reliability and validity study of the cornell scale among elderly inpatients, using various clinical criteria. Dement Geriatr Cogn Disord. 2010;29(5):438-47.
234. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. Eur J Pain. 2014;18(10):1419-30.
235. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982;140:566-72.
236. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. Arch Gen Psychiatry. 1983;40(7):812.
237. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.
238. David L. Consultation skills for the CBM. In: David L, editor. Using CBT in general practice: the 10 minute consultation. Bloxham: Royal College of General Practitioners; 2006. p. 61-81.
239. Røen I, Storlien MS. Strukturert miljøbehandling i demensomsorgen. Tønsberg: Aldring og Helse - Nasjonal kompetansetjeneste for aldring og helse; 2015. Report No.: 978-82-8061-246-5.
240. Rokstad AM, Vatne S, Engedal K, Selbaek G. The role of leadership in the implementation of person-centred care using Dementia Care Mapping: a study in three nursing homes. J Nurs Manag. 2015;23(1):15-26.
241. Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. New York: Guilford press; 1979.
242. Mørch MM, Rosenberg NK. Kognitiv terapi. In: Mørch MM, Rosenberg NK, editors. Kognitiv terapi Modeller og metoder. København: Hans Reitzels forlag; 2005. p. 33-7.

243. Røsvik J, Kirkevold M, Engedal K, Brooker D, Kirkevold O. A model for using the VIPS framework for person-centred care for persons with dementia in nursing homes: a qualitative evaluative study. *Int J Older People Nurs.* 2011;6(3):227-36.
244. Kitwood T. Cultures of care: tradition and change. In: Kitwood T, Benson S, editors. *The New Culture of Dementia Care.* London: Hawker Publications; 1995. p. 8-11.
245. Malterud K. Qualitative research: standards, challenges, and guidelines. *Lancet.* 2001;358(9280):483-8.
246. Patton M. Designing qualitative studies. In: Patton M, editor. *Qualitative research and evaluation methods.* United States of America: Sage Publications, Inc.; 2015.
247. Krueger RA, Casey MA. Answering questions about the quality of focus groups research. In: Krueger RA, Casey MA, editors. *Focus groups: A practical guide for applied research.* Los Angeles: Sage publications; 2015. p. 237-45.
248. Campbell MK, Mollison J, Steen N, Grimshaw JM, Eccles M. Analysis of cluster randomized trials in primary care: a practical approach. *Fam Pract.* 2000;17(2):192-6.
249. Weiner MF, Martin-Cook K, Svetlik DA, Saine K, Foster B, Fontaine CS. The quality of life in late-stage dementia (QUALID) scale. *J Am Med Dir Assoc.* 2000;1(3):114-6.
250. Roen I, Selbaek G, Kirkevold O, Engedal K, Lerdal A, Bergh S. The Reliability and Validity of the Norwegian Version of the Quality of Life in Late-Stage Dementia Scale. *Dement Geriatr Cogn Disord.* 2015;40(3-4):233-42.
251. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD index 2011 Oslo: Norwegian Institute of Public Health; 2011 [updated 2017.12.20. Available from: https://www.whocc.no/atc_ddd_index/].
252. Lyketsos CG, Galik E, Steele C, Steinberg M, Rosenblatt A, Warren A, et al. The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia. *J Am Geriatr Soc.* 1999;47(4):487-91.
253. Kada S, Nygaard HA, Mukesh BN, Geitung JT. Staff attitudes towards institutionalised dementia residents. *J Clin Nurs.* 2009;18(16):2383-92.
254. Lintern T. *Quality in Dementia Care: Evaluating Staff Attitudes and Behaviour.*: University of Wales Bangor; 2001.
255. Dallner M, Elo A-L, Gamberale F. Validation of the General Nordic Questionnaire (QPSNordic) for psychological and social factors at work. Copenhagen: Nordic Council of Ministers; 2000.
256. Bing-Jonsson PC, Bjork IT, Hofoss D, Kirkevold M, Foss C. Competence in advanced older people nursing: development of 'nursing older people--competence evaluation tool'. *Int J Older People Nurs.* 2015;10(1):59-72.
257. Kvale S, Brinkmann S. *Interviews: Learning the craft of qualitative research.* Los Angeles: Sage Publications; 2009.
258. Bowen GA. Document analysis as a qualitative research method. *Qualitative research journal.* 2009;9(2):27-40.
259. Flick U. Thematic Coding and Content Analysis. In: Flick U, editor. *An introduction to qualitative research.* London: SAGE Publications Inc.; 2014. p. 420-38.
260. Lichtwarck B, Roen I, Selbaek G. Multidisciplinary intervention for challenging behavior in nursing home patients with dementia *International psychogeriatrics / IPA.* 2011;23(S1):S92-S138.
261. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative research in psychology.* 2006;3(2):77-101.
262. Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nurs Health Sci.* 2013;15(3):398-405.
263. Helse og omsorgsdepartementet. Helseforskningsloven. Lov om medisinsk og helsefaglig forskning av 2008-06-20-nr 44. 2008 [Available from: <https://lovdata.no/dokument/NL/lov/2008-06-20-44>].
264. World Medical Association (WMA). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 1964 [updated 09.07.2018. Available from:

<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.

265. Holm S, Hofmann B, Laake P. Ethics and Scientific Conduct. In: Laake P, Benestad HB, Olsen BR, editors. *Research in Medical and Biological Sciences*. Amsterdam: Academic Press; 2015. p. 43-70.
266. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krle AJK, et al. SPIRIT 2013 Statement: defining standard protocol items for clinical trials. *Rev Panam Salud Publica*. 2015;38(6):506-14.
267. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Group C. Consort 2010 statement: extension to cluster randomised trials. *BMJ*. 2012;345:e5661.
268. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349-57.
269. Renger R, Titcomb A. A three-step approach to teaching logic models. *American Journal of Evaluation*. 2002;23(4):493-503.
270. Ballard C, Testad I. TIME in the Context of Emerging Evidence Regarding Training Interventions for Dementia in Nursing Homes. *Am J Geriatr Psychiatry*. 2018;26(1):39-41.
271. Fedorov V, Mannino F, Zhang R. Consequences of dichotomization. *Pharm Stat*. 2009;8(1):50-61.
272. Holle D, Kruger C, Halek M, Sirsch E, Bartholomeyczik S. Experiences of nursing staff using dementia-specific case conferences in nursing homes. *Am J Alzheimers Dis Other Demen*. 2015;30(3):228-37.
273. Stevens I, Hassett P. Applying Complexity Theory to Risk in Child Protection Practice. *Childhood*. 2007;14(1):128-44.
274. Nerland M. Vilkår for reflektert praksis i utdanningsinstitusjoner (Conditions for reflective practice in educational institutions). *Nordic Studies in Education*. 2006;26(01):48-60.
275. Alharbi TS, Ekman I, Olsson LE, Dudas K, Carlstrom E. Organizational culture and the implementation of person centered care: results from a change process in Swedish hospital care. *Health Policy*. 2012;108(2-3):294-301.
276. Boersma P, van Weert JC, van Meijel B, Droes RM. Implementation of the Veder contact method in daily nursing home care for people with dementia: a process analysis according to the RE-AIM framework. *J Clin Nurs*. 2017;26(3-4):436-55.
277. Chenoweth L, Jeon YH, Stein-Parbury J, Forbes I, Fleming R, Cook J, et al. PerCEN trial participant perspectives on the implementation and outcomes of person-centered dementia care and environments. *Int Psychogeriatr*. 2015;27(12):2045-57.
278. Zwijsen SA, Smalbrugge M, Eefsting JA, Gerritsen DL, Hertogh CM, Pot AM. Grip on challenging behavior: process evaluation of the implementation of a care program. *Trials*. 2014;15:302.
279. Spector A, Revolva C, Orrell M. The impact of staff training on staff outcomes in dementia care: a systematic review. *Int J Geriatr Psychiatry*. 2016;31(11):1172-87.
280. Appelhof B, Bakker C, van Duinen-van den IJCL, Zwijsen SA, Smalbrugge M, Verhey FRJ, et al. Process Evaluation of an Intervention for the Management of Neuropsychiatric Symptoms in Young-Onset Dementia. *J Am Med Dir Assoc*. 2018;19(8):663-71.
281. Lichtwarck B, Myhre J, Goyal AR, Rokstad AMM, Selbaek G, Kirkevold O, et al. Experiences of nursing home staff using the targeted interdisciplinary model for evaluation and treatment of neuropsychiatric symptoms (TIME) - a qualitative study. *Aging Ment Health*. 2018;1-10
<https://doi.org/10.1080/13607863.2018.1464116>.
282. Spector A, Hebditch M, Stoner CR, Gibbor L. A biopsychosocial vignette for case conceptualization in dementia (VIG-Dem): development and pilot study. *Int Psychogeriatr*. 2016;28(9):1471-80.
283. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation science : IS*. 2009;4:50.


284. Scalzi CC, Evans LK, Barstow A, Hostvedt K. Barriers and enablers to changing organizational culture in nursing homes. *Nurs Adm Q.* 2006;30(4):368-72.
285. Lichtwarck B, Selbaek G, Kirkevold O, Rokstad AM, Benth JS, Myhre J, et al. TIME - Targeted interdisciplinary model for evaluation and treatment of neuropsychiatric symptoms: protocol for an effectiveness-implementation cluster randomized hybrid trial. *BMC Psychiatry.* 2016;16(233):1-12.
286. Murad MH, Katabi A, Benkhadra R, Montori VM. External validity, generalisability, applicability and directness: a brief primer. *BMJ evidence-based medicine.* 2018;23(1):17-9.
287. Helfrich CD, Li Y-F, Sharp ND, Sales AE. Organizational readiness to change assessment (ORCA): Development of an instrument based on the Promoting Action on Research in Health Services (PARIHS) framework. *Implementation Science.* 2009;4(1):38.
288. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration*; 2011 [updated 01.03.2011. Version 5.1.0:[Available from: handbook-5-1.cochrane.org/].
289. Van Horn PS, Green KE, Martinussen M. Survey response rates and survey administration in counseling and clinical psychology: A meta-analysis. *Educ Psychol Meas.* 2009;69(3):389-403.
290. de Vugt ME, Stevens F, Aalten P, Lousberg R, Jaspers N, Winkens I, et al. Do caregiver management strategies influence patient behaviour in dementia? *Int J Geriatr Psychiatry.* 2004;19(1):85-92.
291. Mahtani K, Spencer EA, Brassey J, Heneghan C. Catalogue of bias: observer bias. *BMJ evidence-based medicine.* 2018;23(1):23-4.
292. Nguyen VN, Miller C, Sunderland J, McGuinness W. Understanding the Hawthorne effect in wound research-A scoping review. *International wound journal.* 2018.
293. Morton V, Torgerson DJ. Effect of regression to the mean on decision making in health care. *BMJ.* 2003;326(7398):1083-4.
294. Krueger RA, Casey MA. *Focus groups: A practical guide for applied research.* Los Angeles: Sage publications; 2015.
295. Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. *BMJ.* 2000;320(7226):50-2.

STUDY PROTOCOL

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TIME – Targeted interdisciplinary model for evaluation and treatment of neuropsychiatric symptoms: protocol for an effectiveness-implementation cluster randomized hybrid trial

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Abstract

Background: Nearly all persons with dementia will experience neuropsychiatric symptoms (NPS) during the course of their disease. Clinicians and researchers emphasize the need for an evidence-informed standardized approach to managing NPS that integrates pharmacological and nonpharmacological treatments for real-world implementation. The Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) represents such an approach and is a multicomponent intervention based on the theoretical framework of cognitive behavioural therapy.

Methods/design: The trial is a 3-month cluster randomized trial conducted in 30 nursing homes including 168 participants with dementia and a high level of agitation. Each nursing home defined as a cluster will be randomized to receive either the TIME intervention (the intervention group) or a brief education-only intervention regarding dementia and NPS (the control group). TIME is a manual-based, multicomponent programme that includes a rigorous assessment, one or more case conferences and the treatment and evaluation of NPS. Patient-level measurements are taken at baseline (prior to randomization) and 8 and 12 weeks later. The primary outcome measure is the change in agitation, as defined by the Neuropsychiatric Inventory-Nursing Home Version, at 8 weeks from baseline. Secondary outcome measures include change in agitation at 12 weeks from baseline, and change from baseline at 8 and 12 weeks in other NPS, quality of life, and the use of psychotropic and analgesic medications. Mixed methods will be used to follow, measure and explore the implementation process and the effect of the intervention at the individual staff level and the organization level. Combining measurements of clinical effectiveness and implementation outcomes define this trial as an effectiveness-implementation hybrid trial.

Discussion: Measuring the implementation and effect of complex interventions aimed at reducing NPS in nursing homes is challenging. In this study protocol, we describe a multicomponent program, TIME, and discuss how an effectiveness-implementation cluster randomized hybrid trial can meet these challenges.

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Background

In Norway, approximately 41,000 persons live in nursing homes, and more than 80 % of these have dementia [1, 2]. Nearly 70 % of persons with dementia in nursing homes exhibit clinically significant neuropsychiatric symptoms (NPS)—also labelled as behavioural and psychological symptoms of dementia (BPSD), such as psychosis, depression, anxiety, agitation and apathy [3]. NPS like agitation, including physical or verbal aggression and excessive motor activity cause patients to experience profound suffering and a reduced quality of life and caregivers to experience increased burden [4]. These symptoms represent great challenges in the care of nursing home patients and are predictors of referral to specialist health care and hospitalization [2, 5]. In a review article published in 2014, a multidisciplinary expert panel emphasized the need to develop comprehensive models for the assessment and treatment of these symptoms. Such models should enable the simple implementation of these recommendations in real-world settings [6].

A literature review by Livingstone et al. concluded that behavioural therapeutic techniques and psychoeducation aimed at altering the caregiver's behaviour seemed to reduce NPS [7]. However, the findings regarding other types of treatment were inconclusive and inadequately documented. In a literature review that Testad et al. performed in 2014 on personalized interventions targeting NPS the authors noted increasing evidence that such interventions reduce NPS [8]. In a controlled trial, Cohen-Mansfield et al. showed that a systematic individual intervention based on a step-by-step algorithm significantly reduced agitation. Unfortunately, this study excluded patients exhibiting physical aggression, and the research team implemented the treatment measures in the wards [9]. Testad et al. conducted a randomized intervention trial in nursing homes in Norway and found that the systematic education and supervision of staff resulted in a reduced use of restraints although the level of agitated behaviour remained unchanged or increased slightly [10]. A systematic review by Reuther et al. including 432 studies of case conferences performed as interventions to address challenging behaviour concluded that four of seven studies in the analysis showed a reduction in the challenging behaviour of people with dementia [11]. The review highlighted

the need for methodologically well-designed intervention studies. A disadvantage of many of these interventions is that they require a substantial amount of additional resources to nursing homes to be implemented successfully. A systematic review performed by Seitz et al. (2012) included 40 studies on various interventions aimed at reducing NPS. Sixteen studies showed positive results, but 75 % of them required a significant increase in the resources available to the nursing homes [12]. To our knowledge no trials have used principles from cognitive behavioural therapy (CBT) to structure care-delivery interventions to manage NPS in nursing homes.

The development of the TIME intervention

The Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) was developed in nursing homes by the first author, BL. This model has been used in clinical practice in many nursing homes since it was first developed in 2007–2008. It requires minimal training, is manual based, and is easy to integrate into everyday clinical practice and care without major additional costs. The model is based on the theoretical frameworks of cognitive behavioural therapy (CBT) and person-centred care (PCC), which state that human behaviour is subject to the continuous influence of biological, social and psychological factors. Thus, the model integrates pharmacological and nonpharmacological treatments for real-world implementation. The primary purpose of the model is to allow an interdisciplinary team of staff and physicians to conduct a thorough assessment and critical systematic reflection in case conferences to achieve a mutual understanding of NPS and, thereby, implement customized actions based on this understanding. In 2010, The Centre for Old Age Psychiatric Research, Innlandet Hospital Trust conducted an open non-controlled trial in nine nursing homes over six months and included 30 persons with dementia and high levels of agitation. The results showed that patients' agitation, mood symptoms and staff's distress were significantly reduced. This study was published as an abstract in *International Psychogeriatrics* [13] and formed the basis for a revision of the TIME manual [14] and a web-accessible short film that can be used for training in the model [15]. In this abstract, the model was referred to as the Multidisciplinary Intervention

Model for Challenging Behaviour in Nursing Home Patients with Dementia (MIND).

Research aim and research questions

The primary purpose of this study is to improve the assessment and treatment of agitation in persons with dementia by examining the effect and implementation of the TIME intervention model. We formulated the following research questions: 1) Can an intervention utilizing TIME reduce agitation in persons with dementia in nursing homes? 2) Does TIME serve as a method of continuous learning and reflection? That is, can the model help develop and strengthen staff members' confidence, mastery and competence at an individual level and at an organizational level? 3) What nursing home factors inhibit or promote the implementation of psychosocial

intervention models such as TIME, and is implementation sustainable?

Methods and design

Study design

The first research question will be answered through a cluster randomized controlled trial with two parallel groups: Intervention Nursing Homes (INH) and Control Nursing Homes (CNH). Fig. 1 shows a flow chart of the clusters and individuals through the phases of the trial based on the power calculation. For the second and third research questions, we will utilise both quantitative and qualitative methods. Data will be gathered from the records of reflection meetings (case conferences) held during the trial, implementation checklists completed during the trial, four focus group interviews performed

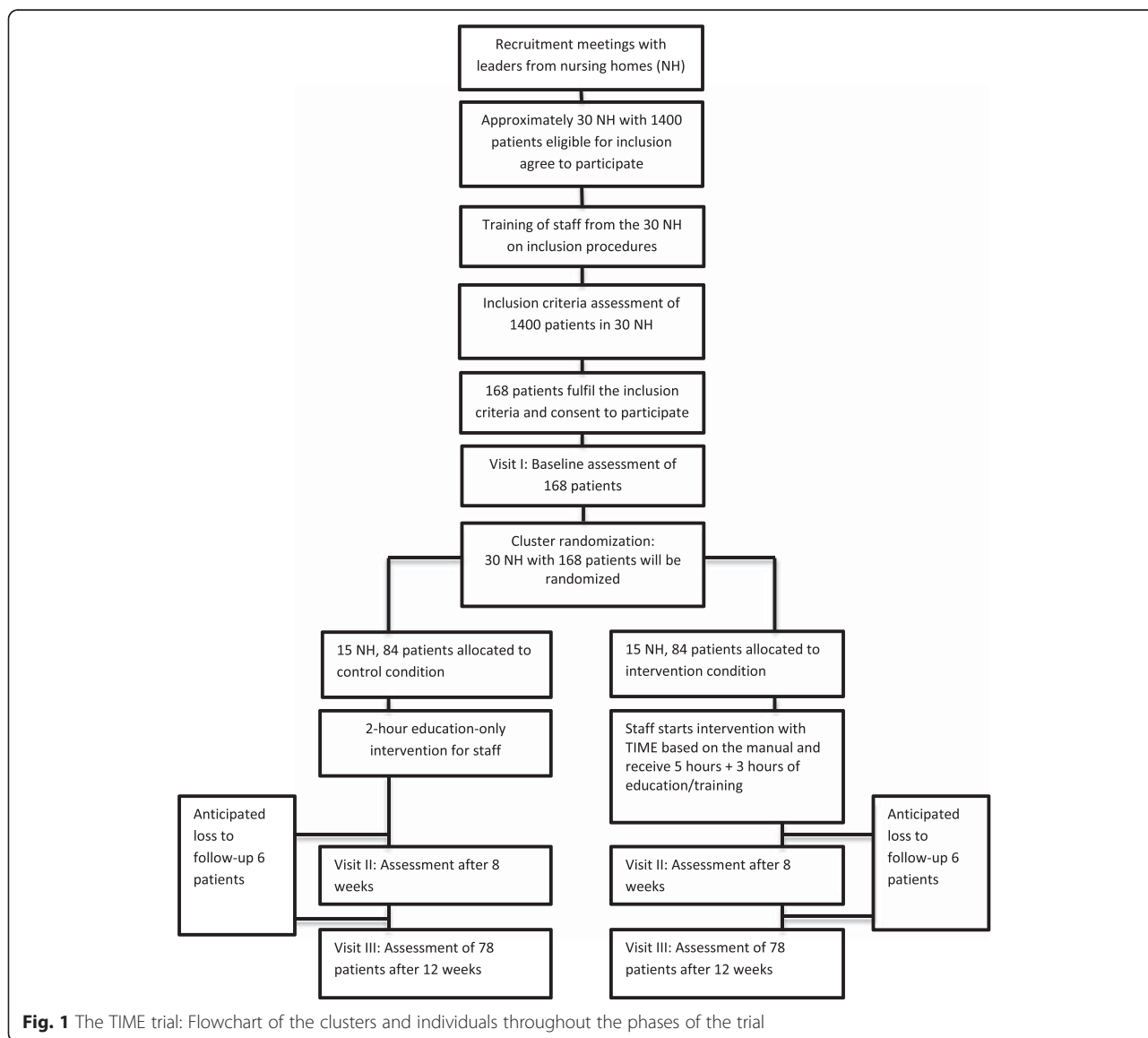


Fig. 1 The TIME trial: Flowchart of the clusters and individuals throughout the phases of the trial

after the trial, and questionnaires administered before and after the trial. The trial is defined as an effectiveness-implementation cluster randomized hybrid trial because of the use of various types of data and the study design.

Settings and target population

Municipalities located in the north, middle and south-eastern part of Norway will be contacted to participate in the trial. To ensure collaboration and implementation throughout the trial, we will arrange meetings with the health care leaders in the municipalities and the managers and physicians working in each nursing home. We will strive to recruit nursing homes located in both rural and urban areas of Norway and to obtain an equal distribution of large and small nursing homes to ensure a representative nursing home population. Nursing homes already using TIME as part of their clinical routines will not be invited to take part in the trial.

All patients in wards in participating nursing homes will be considered eligible for inclusion in the trial, and will be assessed to determine if they meet the inclusion criteria. Trained nursing home staff will perform the assessments. The research team will train these staff members on the inclusion procedure and the assessment of patients' capacity to provide consent. The data obtained from screening individual eligible patients will not be recorded. Patients who fulfil the inclusion criteria and agree to participate will be included in the trial. For patients who lack the capacity to provide consent, written consent will be obtained from their next of kin.

The inclusion criteria for patients are as follows:

- NH patients with probable dementia, defined as a Clinical Dementia Rating scale (CDR) [16] score of one or higher.
- A moderate to high degree of agitation, defined by an NPI-NH agitation item score equal to or above six points.
- Long-term patients who have resided in the nursing home for a minimum of two weeks before inclusion.

The exclusion criterion for patients is a life expectancy of less than 4–6 weeks.

Sample size calculation based on the primary outcome

The primary outcome of the trial is the change in the level of agitation from baseline at eight weeks, as measured by the agitation item of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) [17, 18]. Power calculation was based on the following assumptions. A previous non-controlled pilot study of TIME showed that the intervention decreased the NPI-NH agitation item score by on average 2.8, with a standard deviation (SD) for change of 3.1 [13]. One can reasonably

assume that the simple education-only intervention and baseline and follow-up assessments may have some effect on the control group. Therefore, we expect that the difference in the effect between the control and intervention groups will be lower. We have assumed a mean difference between the groups to be 1.5 as measured by NPI-NH agitation item, and that this difference will have a SD of 3.1. Based on this assumption, we calculate that 65 persons must be included in each group to observe a statistically significant difference with a power of 80 % and a significance level of 5 %. We assume an intra-cluster (nursing home) correlation coefficient (ICC) of 0.05. The ICC is assumed to be low because the persons included will be located in different departments and units in the nursing home (the cluster). Adjusting power calculations for cluster effect, we find that at least 78 persons have to be included in the intervention group and 78 in the control group for the effect to be statistically significant. That is, we need a total of 156 persons. Based on previous studies, we assume that the average size of the nursing homes is 46 patients and that each nursing home will recruit five patients, on average. In the pilot study, we found that approximately 12 % of patients had dementia and an NPI-NH agitation item score of six or higher, which is our main criterion for inclusion. Previous studies have shown that we can anticipate a 30 % loss to follow-up per year (due to, e.g., mortality, relocation, or withdrawal from the study)—that is, 7.5 % in three months. Thus, we will need a total of 168 people (84 persons in each group), indicating that we will need to screen approximately 1400 nursing home patients. Given approximately 46 patients on average per nursing home, we will need to recruit approximately 30 nursing homes. The nursing homes will be randomized after the baseline assessment to avoid bias. The recruitment of new patients to the study will therefore occur only through the recruitment and randomization of new nursing homes, as described above.

This study must perform cluster randomization, with the nursing home as the cluster, for two main reasons. The TIME intervention is a biopsychosocial intervention that involves the entire interdisciplinary team and staff in the wards of the participating nursing homes to optimize the treatment provided to a group of patients in the wards. In addition, the study runs the risk of transmitting all or parts of the intervention model to the control units or individual control patients at the same nursing home [19].

Randomization

Nursing homes will be stratified by size into three blocks to assure approximately equal number of patients in the two trial arms. Block size will be fixed—block 1: 1–5

patients, block 2: 6–9 patients, and block 3: 10 or more patients. Then, nursing homes within each block will be randomly assigned to either the intervention group or the control group. A researcher will perform the randomization procedure independently of the project management team and the nursing homes. The project management team will provide the nursing homes with the randomization and allocation results immediately following this procedure. Specially trained project nurses who are not affiliated with the nursing homes will assess patients' baseline characteristics before randomization. These assessors will also assess the effect of the intervention via telephone at weeks eight and 12 and will be blinded to the randomization result.

Control and intervention phases of the study

Similar education and training for the staff in CNH and INH—CNH continue practice as usual

Three nurses in each unit in both the INH and CNH will be given a special responsibility in the trial. Before randomization, these nurses will complete a three-hour training on the procedure. Their main task will be to facilitate the interviews for the assessments at baseline, and after 8 and 12 weeks. These nurses will be selected by the leading ward registered nurse based on the following criteria: nurses who work on a nearly full-time basis, have shown interest in professional development and have gained legitimacy with the rest of the staff. Thus, these nurses can be selected among registered nurses, auxiliary nurses, nursing aides or members of other professional groups in the nursing homes.

After randomization, the staff in the INH and the CNH will be offered a two-hour lecture about dementia and NPS. This lecture represents the education-only intervention administered to the staff in the CNH. These staff members will then continue practice as usual for the patients throughout the remainder of the trial.

Exclusive education and training of staff in the INH—intervention utilizing TIME in the INH

In addition to the two-hour lecture about dementia and NPS, the staff in the INH will complete three hours of lectures, training and roleplay related to TIME. The education and training team responsible for conducting the education and training sessions consists of the project management team (a physician with special competence in nursing home medicine and two specialist registered nurses in geriatrics) and four specialist registered nurses in old age psychiatry, all of whom are familiar with TIME. The lectures will be standardized according to the steps listed in the TIME manual.

The leading ward registered nurse of each ward in the INH will attend these lectures to ensure that this leading nurse provide support to the staff during the trial. We

will also encourage the nursing home physician to participate. Each staff member in the INH will be provided with the TIME manual, which describes the intervention step by step. They will also be given access to an educational film about TIME and a website to support the intervention. The three nurses who participated in the coeducation for the inclusion criteria in each unit in the INH will now hold the special responsibility for putting the model into practice based on the manual. These nurses will therefore receive three additional hours of education, training and role play related to the different components of TIME and the implementation of the intervention. In the trial, they are referred to as TIME administrators. Immediately after randomization and allocation, the project management team will contact the TIME administrators via telephone and instruct them to begin to implement the intervention according to the TIME manual for the patients included in the trial. This telephone call is made from a few days up to 1 week before the education and training sessions are given. The TIME manual is available online.

One specialist registered nurse from the education and training team will attend and supervise the TIME administrators' first case conference on their first patient in their nursing home. For the remainder of the TIME intervention, and for the other patients included in the trial, the TIME administrators and the staff will carry out the intervention independently.

Description of the TIME intervention

The actual assessment and treatment programme for individual patients is described in detail in the TIME manual, which provides a step-by-step guide to implementing the model. TIME consists of three overlapping phases: a registration and assessment phase; a guided reflection phase, including one or more case conferences; and an action and evaluation phase. These phases were adapted from and based on problem-solving methods in CBT [20] and are in line with reviews describing the "state of the art" for the management of NPS [4, 6]. The different components of TIME acting together thus provide an evidence-informed standardized approach to managing NPS.

In the registration and assessment phase, the nursing home physician performs an examination of the patient and the patient's previous medical records and medications are critically reviewed. The staff gather personal background information, pain is assessed, behaviour and symptoms are registered in detailed 24-h daily records, and behaviour and symptoms are monitored with established clinical instruments, including the NPI-NH. This phase is described in detail in Table 1. The duration of this phase varies from one day up to 4 weeks, depending on the nature and burden of the symptoms. Following

Table 1 The registration and assessment phase

Checklist for the registration and assessment phase of TIME

Activity	Target symptoms:		
	Agree on the primary challenges for the patient using the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH) to define precise target symptoms for the assessment		
	Observation of the target symptoms using a 24-h observation form	Staff	Responsible
	NPI-NH to assess other neuropsychiatric symptoms	Staff	
	^a Cornell Scale of Depression in Dementia (CSDD) or another scale to assess possible symptoms of depression	Staff	
	Physical assessment	Nursing home physician	
	Review of medication	Nursing home physician	
	^b Mobilisation-Observation-Behaviour-Intensity-Dementia Scale (MOBID-2) to assess possible pain	Staff Nursing home physician	
	The Clinical Dementia Rating Scale (CDR) and/or the ^c Mini-Mental State Examination (MMSE) to assess the dementia stage	Staff Nursing home physician	
	^d The Physical Self-Maintenance Scale (PSMS) to assess activities in daily life	Staff	
	Collection of resident life history, including preferences and resources, using an optional questionnaire	Staff interview the resident (if possible) and/or the next of kin	
	Make an appointment, i.e., set the date, time and place for the case conference	Staff/TIME administrator	

^aCornell Scale of Depression in Dementia (CSDD) [26, 27]^bMobilisation-Observation-Behaviour-Intensity-Dementia Scale (MOBID-2) [45]^cMini-Mental State Examination (MMSE) [46]^dPhysical Self-Maintenance Scale (PSMS) [21]

the registration and assessment stage, a guided reflection phase begins. In this stage, a case conference for the entire group of staff, including the physician, is conducted. Systematic reflection based on cognitive therapeutic principles is carried out. The goal of this guided reflection is to create a mutual understanding of the actual NPS of the patient and to tailor a detailed treatment plan that will be tested in the coming weeks. The case conference participants reflect on the situation using the cognitive problem-solving method, in which one problem is analysed at a time [20]. This reflection is performed systematically using a five-column sheet technique on a whiteboard, and the following five aspects are reviewed: assessed facts, interpretation, emotions, actions to take, and evaluation. The time frame and the agenda for the case conferences are outlined in Table 2. The last stage is the action and evaluation phase. In this phase, each treatment measure in the plan is put into action and is then systematically evaluated with the same assessment tools employed in the registration phase.

The time frame for the complete intervention with TIME will vary from 1 or 2 weeks up to 8 weeks depending on the severity and complexity of the NPS to be approached and the resources available in the nursing homes.

Procedures for data collection

The patients' demographic data, baseline data and primary and secondary outcomes will be collected by

project nurses not affiliated with the nursing homes. All 10 assessors are nurses with substantial experience and formal training on the use of the assessment scales. They attended a one-day course on the use of the assessments scales before start of the trial. The assessments of all outcomes and covariates will be repeated at 8 and 12 weeks after baseline. The assessors will collect the data via telephone by interviewing staff members who know the patient best. The assessors will be blinded to the randomization of the nursing homes. The following data from patients' medical records will be collected: age, gender, marital status, type of ward the patient lives in (regular somatic, special care units for dementia patients or other types), known diagnoses (chronic diseases), and dementia diagnosis.

The following data describing the nursing homes will be assessed by a questionnaire sent to the leading ward registered nurse at the start of the trial: the size of the nursing home (number of patients); the size of the unit and ward (the number of patients per unit and ward); the care factor (the number of nurses working per patient per work shift); the number of hours the nursing home physician works per patient per week in the nursing home/unit; and the number of employees per leading ward registered nurse.

Covariates that will be measured are: level of dementia, as assessed by the CDR; level of functioning in daily activities, as measured by the Physical Self-Maintenance Scale (PSMS; [21]; and physical health, as measured by

Table 2 Agenda and time frame for the guided reflection meeting (case conference)

Agenda for guided reflection meeting (case conference) 1.5 h			Responsible
Activity	Preparation: Convene a meeting and prepare a meeting room with a blackboard or similar facilities (projector, if available). Check that a flip pad and markers are available	TIME administrators:	
		One is chairman for the meeting.	
		One takes notes on the whiteboard.	
		One writes the minutes on the 5-column sheet.	
1. Status Report: Personal history and main points from the patient's medical record are presented.	10–15 min	Decide in advance who should prepare and present the patient's personal history and the main points from the medical record.	
2. Create a problem list	10 min	Staff (as many as possible should attend the conference)	
3. Prioritize problems from the list			
4. Draw a 5-column sheet on the whiteboard: facts – interpretations (thoughts) – emotions – actions – evaluation	60 min	The leading registered nurse and the nursing home physician should attend the conference, if possible.	
5. Describe facts from the registration and assessment phase: one problem at a time			
6. Suggest interpretations – guided discovery – discuss and reflect on them			
7. Describe any emotions experienced by the staff – with interpretations by the staff			
8. Suggest ^a SMART actions – based on the interpretations – decide how and when to perform an evaluation of the actions			
9. Summarize interpretations and actions – close the meeting	5–10 min	TIME – administrator (chairman)	

^aSMART (Specific-Measurable-Actual-Realistic-Time framed)

the General Medical Health Rating Scale (GMHR; [22]. PSMS is a six-item scale that produces a sum score ranging from 6 to 30. A higher score denotes more severe functional impairment. GMHR is a one-item global rating scale with the categories good, fairly good, poor and very poor.

Baseline data and primary and secondary outcome measures

A full description of the screening instruments used to assess the inclusion criteria and the primary and secondary outcomes is provided in Table 3. The primary outcome of the TIME trial is the difference in the change between intervention and control group in agitation/aggression at 8 weeks from baseline, as measured by the NPI-NH [17]. The Norwegian version of the NPI-NH has shown high inter-rater reliability and validity [23].

The secondary outcomes include the difference in the change between the two groups in agitation/aggression at 12 weeks from baseline, as measured by the NPI-NH, in the change from baseline to 8 and 12 weeks in each of the other items of the NPI-NH, the NPI-NH 10 sum score, NPI-subsyndromal agitation score (aggression/agitation + disinhibition + irritability), NPI-subsyndromal psychosis score (delusion + hallucination) and affective symptoms (depression + anxiety). These subsyndromes are based on data from a previous principal component

analysis [24]. The other secondary outcomes include the difference between the two groups in the change from baseline to 8 and 12 weeks in the following measures: agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI; [25]; symptoms of depression, as measured by the Cornell Scale for Depression in Dementia (CSDD); [26, 27]; drug use and dosage of psychotropic and analgesic medications given both regularly and on demand, coded as defined daily dosage (DDD) and grouped according to the Anatomical Therapeutic Chemical index [28]; and quality of life, as measured by the Quality of Life in Late-stage Dementia Scale (QUALID); [23, 29].

Qualitative and quantitative methods employed in the trial to answer research questions 2 and 3

Focus group interviews

Focus group interviews will be conducted after the intervention is completed. Four groups of five to eight caregivers and leaders of the INH will participate. One group of nursing home leaders, one group of TIME administrators and two groups of caregivers from the staff in different nursing homes will be arranged. Because of group dynamics, the questions posed can be discussed from several points of view. These dynamics can create new perspectives and views during the discussion. We will use an interview structure based on a semi-

Table 3 Primary and secondary outcome measures

What is measured (scales/tools)	Characteristics and psychometric properties of scales/tools
Primary outcome measure: The difference between the intervention group and the control group in change from baseline at 8 weeks	
Agitation/aggression (single item from the NPI-NH)	Change from baseline of agitation and aggression, as defined by the Neuropsychiatric Inventory-Nursing Home version (NPI-NH) item agitation/aggression. The NPI-NH assesses the frequency (0–4) and the severity (0–3) of 12 psychiatric and behavioural symptoms. An item score is generated by multiplying frequency and severity (0–12). A higher score indicates more frequent and severe presence of NPS.
Secondary outcome measures: The difference between the intervention group and control group in change from baseline at 8 and 12 weeks	
Neuropsychiatric symptoms (NPI-NH)	12 items described in the Neuropsychiatric Inventory Nursing Home Version (NPI-NH). Range 0–12, as described above.
Subsyndrome of agitation (NPI-NH)	The NPI-NH subsyndrome agitation is defined as the sum of the scores of the agitation/aggression, irritability, and disinhibition items. Range 0–36.
Subsyndrome affective symptoms (NPI-NH)	The NPI-NH subsyndrome affective symptoms is defined as the sum of the scores of depression and anxiety items of the NPI-NH. Range 0–24.
Subsyndrome psychotic symptoms (NPI-NH)	The NPI-NH subsyndrome psychosis is defined as the sum of the hallucinations and delusions items. Range 0–24.
Neuropsychiatric symptoms (NPI-10 NH sum score)	The NPI-10 NH sum score is the sum of the first ten items in the NPI-NH, omitting the sleep disturbances and eating disorders (primarily vegetative symptoms) items. Range 0–120.
Caregiver occupational disruptiveness (NPI-NH)	In NPI-NH, the caregiver must rate how disruptive they consider each behaviour or symptom on a five-point scale. Range 0–5. A higher score indicates a more disruptive behaviour.
Agitation (CMAI)	The Cohen-Mansfield Agitation Inventory (CMAI), which measures 29 different types of agitation and the frequency at which they occur. Range for each item 1–7. Range total score 29–203. A higher score indicates more frequent agitation. Good validity and inter-rater reliability.
Depressive symptoms (Cornell)	The Cornell Scale for Depression in Dementia, which measures the frequency of symptoms of depression.
Quality of life (QUALID)	Quality of Life in Late-stage Dementia Scale, which measures 11 behaviours rated on a 5-point Likert scale. Range 11–55. A lower score indicates higher quality of life. Good validity and inter-rater reliability
Use and dosage of psychotropic and analgesic medication (defined as daily dosage (DDD))	Psychotropic and analgesic medication given both regularly and on demand. This will be assessed using a questionnaire and extracted from patients' records. The assessment of the medication given on demand will be obtained from patients' records at each visit and presented as the sum in mg used for the last 21 days. These drugs will be grouped according to the Anatomical Therapeutic Chemical Index.

structured interview guide that asks informants to reflect on two main themes and follows up with open and exploratory questions posed by the interviewer [30]. These two themes are 1) the feasibility of the intervention, with an emphasis on the factors that promote or inhibit the implementation of TIME, and 2) the effects that the model has on learning and staff members' experience of coping and mastery of strain in the face of the challenging behaviour of persons with dementia. If other key themes emerge spontaneously during the interviews, time will be allotted to develop these themes. Interviews will be transcribed. A qualitative content analysis will be used to explore the findings. Systematic text condensation [31] will be performed to provide a systematic description and to develop new concepts and understandings of the phenomena. Researchers will identify units in the text and then code and reorganize these units repeatedly to emphasize the meaning content of the data.

Questionnaire surveys administered to the staff. Methods evaluating the extent and duration of the implementation of the model by use of the RE-AIM framework

A full description of the questionnaires, including respondents and the time point(s) at which they are administered, is provided in Table 4. The implementation of TIME will be followed and assessed from the start of the study to 1 year following the study based on the RE-AIM framework [32]. RE-AIM is a widely used system for following and evaluating interventions in organizations that aim to implement new methods of practice. RE-AIM is an acronym for Reach, Efficacy, Adoption, Implementation and Maintenance. In our trial, "Reach" refers to the proportion of the staff participating in the training, routine patient assessment, and subsequent conference meetings. This information will be recorded using a registration form to assess staff participation in education and training sessions and a self-developed questionnaire administered to the staff. "Efficacy" refers

Table 4 Questionnaires distributed to the staff and the leading ward registered nurse based on the RE-AIM-framework^a for the evaluation of complex interventions

What is assessed	Questionnaire	Corresponding dimension of the RE-AIM framework	Time frame	Respondents in the nursing homes (NH)
Proportion of staff members participating in education and training sessions	A registration form to assess participation of staff in education and training sessions	Reach: proportion of staff in INH that actually participated in the intervention during the trial	At the start of the intervention during education sessions	All staff members in intervention nursing homes (INH)
Individual participation of staff members in effectuating the components of the model	Self-developed questionnaire	Reach: as above Maintenance: extent to which the model is sustained over time	6 and 12 months after the start of the intervention	All staff members in INH
Attitudes towards persons with dementia, mastery, social interaction, job satisfaction and self-assessment of competence with neuropsychiatric symptoms (NPS)	Approaches to the Dementia Questionnaire ^b , QPS-Nordic ^c and a self-developed questionnaire for assessment of competence with NPS	Efficacy: outcomes regarding knowledge, skills and/or attitudes of the staff in NH	1 month before, and 6 and 12 months after the start of the intervention	All staff members in control nursing homes (CNH) and in INH
Clinical routines in place in NH, i.e., questions assessing daily routines of practice for assessment and treatment of NPS	Self-developed questionnaire based on evidence-informed best practice for assessment and treatment of NPS	Adoption: proportion of wards that will adopt the intervention Maintenance: extent to which the model is sustained over time	1 month before and 6 and 12 months after the start of the intervention	Leading ward registered nurse in INH and CNH
Fidelity to the main components in the model	Interview of TIME administrators by telephone using a checklist based on the components in the TIME manual	Implementation: extent to which the intervention is actually implemented	3 brief interviews, the first one 3 weeks after the start of the intervention and then at 1-month intervals	TIME administrators in INH
Organizational structure in the nursing homes: size of wards, type of unit, number of staff, etc.	Self-developed questionnaire	Implementation: possibility to assess and analyse implementation barriers and facilitators	At the start of the intervention	Leading ward registered nurse in INH and CNH

^aRE-AIM framework: Reach-Efficacy-Adoption-Implementation-Maintenance [32]

^bGeneral Nordic Questionnaire for Psychological and Social Factors at Work (QPS-Nordic) [33]

^cApproaches to Dementia Questionnaire (ADQ) [34]

to each staff member's intervention outcomes in terms of attitudes, mastery, knowledge and skills, which we will assess and analyse using data from the focus group interviews and questionnaires. The following questionnaires will be administered for this purpose: the General Nordic Questionnaire for Psychological and Social Factors at Work regarding mastery and social interaction (QPS-Nordic) [33], the Approaches to Dementia Questionnaire (ADQ) [34], and a brief self-developed questionnaire assessing perceived competence regarding NPS. Both QPS-Nordic and ADQ are validated questionnaires used to assess these domains.

In this type of intervention, "Adoption" refers to the proportion of wards and the percentage of the staff who actually adopt this method to manage NPS. We will use data from the focus group interviews and a self-developed questionnaire about participation in the routines of practice in the unit. "Implementation" refers to whether the intervention is carried out at the organization level as planned and with integrity. It will be assessed with a checklist once per month for 3 months after the start of the intervention. The checklist includes only the main components of the intervention

derived from the checklist in the TIME manual. "Maintenance" refers to the degree to which the organization succeeds in maintaining the intervention after the project period. Maintenance will be measured with a self-developed questionnaire administered to units at 6 and 12 months after the intervention is implemented. This questionnaire will assess the extent to which the model and its components continue to be systematically applied. To answer the question of which factors inhibit or promote implementation, we will analyse the data from the focus group interviews and from the questionnaires.

Data processing and statistical analysis of quantitative data

All data regarding the cluster randomized trial will be collected via telephone. The data will be registered online in the dataset prepared for the study using the data tool Checkbox via a web survey to the SQL database. The questionnaires used to collect all other data will be distributed to staff (regardless of job position) by mail and the results will be stored in the same manner as the trial data. At the 6- and 12-month assessments,

questionnaires will be sent only to the staff who responded to the previous questionnaires.

The data will be presented as frequencies and percentages for categorical and means (standard deviations) for the continuous variables. The normality of continuous variables will be assessed graphically. If necessary, skewed data will be transformed. Differences in the changes in outcomes between the intervention group and the control group will be assessed by a linear mixed model with fixed effects for time component and group and the interaction between the two. A significant interaction will imply the differences in change between the groups. Random effects for patients nested within nursing homes and slopes (if significant) will be included into the model. Individual time point contrasts will be derived within each group at each time point with the corresponding 95 % confidence intervals and *p*-values. Linear mixed model correctly adjusts estimates for intra-cluster correlations as well as for intra-individual correlations due to repeated measurements in time. The model also handles unbalanced data by allowing inclusion of all available information, also from drop-outs.

Trial status

The cluster randomized trial will be carried out from January to the end of June 2016.

Focus groups will be held in September and October 2016. The part of the trial evaluating the implementation process started in December 2015 and continue until the end of April 2017.

Discussion

The main purpose of this trial is to improve the assessment and treatment of agitation in persons with dementia by examining the effect and implementation of the TIME intervention model. The strength of the model is that it was developed in nursing homes over a period of several years; thus, it takes into account the nursing home context. A pilot study showed its feasibility and further developed the model [13]. The model integrates pharmacological and nonpharmacological treatments for use in real-world implementation. The components of the model have a solid theoretical foundation [6, 20, 35]. Given that NPS often represent complex problems with multifactorial causes that interact with each other, often in unpredictable ways, multifaceted and complex interventions must be applied.

One of the challenges of psychosocial interventions is effectively and sustainably implementing them. Fixsen defined implementation as a specific set of activities combined in practice to introduce an activity or a programme with known components. Similar to an actual intervention (programme or model), implementation includes a set of

activities and a set of outcomes [36]. Richards and Hallberg defined complex interventions as “Activities that include multiple components with the potential for interactions between them. When such an intervention is applied to the target population a number of possible and varied results are created” [37]. Based on this description, we claim that TIME satisfies the definition of a complex intervention [14]. An intervention’s complexity must also be considered based on the context—that is, the type of organization and the organization’s various participants [38]. A lack of an effect may reflect the failure of implementation rather than shortcomings of the implemented programme or model [38]. Therefore, the implementation of complex interventions is particularly demanding.

The Medical Research Council (MRC) defines an overarching framework for the development and evaluation of complex interventions. This recommendation was revised in 2008 to place greater emphasis on the importance of the process evaluation and adaptation to local contextual conditions compared with the previous recommendations [39]. In our trial, we will follow these recommendations and simultaneously apply an experimental design for measurements of effectiveness at the patient level and conduct an experimental evaluation of the implementation. Our reports on the TIME trial will follow the recommendations presented in the CONSORT 2010 statement: extension to cluster randomized trials [40].

A design that combines clinical effectiveness and implementation outcomes in one trial is called an effectiveness-implementation hybrid design [41, 42]. The main advantage of this hybrid design is that it can accelerate the translation of research findings into routine practice. It also allows the research team to evaluate the results regarding effectiveness in light of the degree of fidelity and adoption of the model. For this advantage to be realized, the implementation strategies in the trial cannot be overly complex. Thus the implementation strategies should not demand basic structural changes within the organization receiving the intervention. Although TIME is a complex intervention, we experienced during the pilot study that the intervention does not require significant changes within the organizations’ structures or routines, and the implementation costs were estimated to be low.

Our study design has some limitations. We do not require a precise diagnosis of dementia as an inclusion criterion; instead, we include patients with probable dementia, defined as a CDR score of one or higher. A previous study on a Norwegian NH showed that only approximately one-third to one-half of residents with dementia were assessed and given a diagnosis of

dementia [1, 43]. In addition, several studies have shown that CDR staging based solely on an informant interview is a valid substitute for patient examinations [43, 44]. Therefore, even if a few patients included in our study do not fulfil all the criteria for a dementia diagnosis, the use of the CDR as a criterion for inclusion instead of a precise diagnosis of dementia will strengthen the external validity of our findings. Another limitation is the rather short follow-up time. The last visit in which the patient outcomes will be assessed is the 12-week visit, primarily due to resource limitations and to ensure staff compliance. To be considered clinically important, an intervention aimed at reducing NPS should show some measurable effects after 8 to 12 weeks. The data collection concerning the implementation process will nevertheless span a year to measure the sustainability of the intervention.

Conclusion

The increasing percentage of the population with dementia will be a major challenge for health and care facilities in the coming years. Nearly all people who suffer from dementia experience NPS in the course of their disease. NPS like agitation, including physical or verbal aggression and excessive motor activity cause patients to experience profound suffering and a reduced quality of life and caregivers to suffer increased burden [4]. TIME is a multicomponent intervention based on the theoretical framework of CBT. The TIME trial is an effectiveness-implementation cluster randomized trial designed to assess both effects on NPS in persons with dementia residing in nursing homes and the implementation process at the staff and organization levels. An open pilot study conducted in 2010 showed that the intervention is feasible and found a reduction in patients' agitation and mood symptoms and caregiver strain. The trial will take place in 30 nursing homes and will include 168 patients with dementia and a high degree of agitation. The aim of this project is to make an important contribution to improve the treatment of NPS. Furthermore, the project may result in an evidence-based model for assessment and treatment in both primary care and specialist care. The project will provide additional insight into how to sustainably implement complex interventions.

Abbreviations

ADQ, approaches to dementia questionnaire; BPSD, behavioural and psychological symptoms in dementia; CBT, cognitive behavioural therapy; CDR, clinical dementia rating scale; CMAI, cohen-mansfield agitation inventory; CNH, control nursing homes; CSDD, cornell scale of depression in dementia; DDD, daily drug dosage; GMHR, general medical health rating scale; ICC, intracluster correlation coefficient; INH, intervention nursing homes; MOBID-2, mobilisation-observation-behaviour-intensity-dementia scale; NPI-NH, neuropsychiatric inventory-nursing home version; NPS, neuropsychiatric symptoms; SD, standard deviation; PSMS, physical self-maintenance scale; MMSE, mini-mental state examination; QUALID, quality of life in late-stage dementia; RE-AIM, reach-effectiveness-adoption-implementation-

maintenance; QPS, general nordic questionnaire for psychological and social factors at work; SMART, specific-measurable-actual-realistic-time; SQL, structured query language; SPSS, statistical product and service solution; TIME, targeted interdisciplinary model for evaluation and treatment of neuropsychiatric symptoms

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Availability of data and materials

The datasets supporting the conclusions of this article are available on the website www.tidmodell.no.

Authors' contributions

BL is the chief investigator of the TIME trial. BL and SB designed and wrote the manuscript. BL, AMMR, SB, ØK, and GS developed the study design. ØK, AMMR and GS assisted with the preparation of the manuscript. JSB is responsible for data management. JM and SN coordinated the project and SB supervised the project. All authors read and approved the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Patients with the capacity to provide consent will be asked to give their written consent. For patients who lack the capacity to provide consent, their next of kin will be informed of the study and asked to give consent on behalf of the patients. The Regional Ethics Committee for Medical Research in eastern Norway (REC-east) has approved the project on 19 October 2015 (project number: 2015/1549).

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References

- Selbaek G, Kirkevoeld O, Engedal K. The prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. *Int J Geriatr Psychiatry*. 2007;22(9):843–9.
- Vossius C, Selbaek G, Ydstebø AE, Benth JS, Godager G, Lurås H, et al. Resource use and Disease Course in Dementia (REDIC). Ottestad: Alderspsykiatrisk forskningscenter, Sykehuset Innlandet og Regionalt kompetansesenter for eldremedisin og samhandling i Helse Vest (SESAM); 2015.
- Selbaek G, Engedal K, Benth JS, Bergh S. The course of neuropsychiatric symptoms in nursing-home patients with dementia over a 53-month follow-up period. *Int Psychogeriatr*. 2014;26(1):81–91.
- Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.
- Brodsky H, Connors MH, Xu J, Woodward M, Ames D. Predictors of institutionalization in dementia: a three year longitudinal study. *J Alzheimers Dis*. 2014;40(1):221–6.

6. Kales HC, Gitlin LN, Lyketsos CG. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc.* 2014;62(4):762–9.
7. Livingston G, Johnston K, Katona C, Paton J, Lyketsos CG. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. *Am J Psychiatry.* 2005;162(11):1996–2021.
8. Testad I, Corbett A, Aarsland D, Lexow KO, Fossey J, Woods B, et al. The value of personalized psychosocial interventions to address behavioral and psychological symptoms in people with dementia living in care home settings: a systematic review. *Int Psychogeriatr.* 2014;26(7):1083–98.
9. Cohen-Mansfield J, Libin A, Marx MS. Nonpharmacological treatment of agitation: a controlled trial of systematic individualized intervention. *J Gerontol A Biol Sci Med Sci.* 2007;62(8):908–16.
10. Testad I, Ballard C, Bronnick K, Aarsland D. The effect of staff training on agitation and use of restraint in nursing home residents with dementia: A single-blind, randomized controlled trial. *J Clin Psychiatry.* 2010;71(1):80–6.
11. Reuther S, Dichter MN, Buscher I, Vollmar HC, Holle D, Bartholomeyczik S, et al. Case conferences as interventions dealing with the challenging behavior of people with dementia in nursing homes: a systematic review. *Int Psychogeriatrics/PA.* 2012;24(12):1891–903.
12. Seitz DP, Gill SS, Herrmann N, Brisbin S, Rapoport MJ, Rines J, et al. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review. *Int Psychogeriatrics/PA.* 2013;25(2):185–203.
13. Lichtwarck B, Roen I, Selbaek G. Multidisciplinary intervention for challenging behavior in nursing home patients with dementia. *Int Psychogeriatrics/PA.* 2011;23(S1):S92–S138.
14. Lichtwarck B, Tverå AM, Røen I. TID Tverrfaglig Intervensjonsmetode ved utfordrende atferd ved Demens Manual. 2nd ed. Ottestad: Sykehuset Innlandet, Alderspsykiatrisk forskningsenter; 2015.
15. Lichtwarck B, Tverå AM, Nystad HL. TID Tverrfaglig Intervensjonsmodell ved utfordrende atferd ved Demens Opplæringsfilm. <http://tidmodell.no>. Accessed 18 Dec 2015. Mo i Rana: Rana Kommune; 2013.
16. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566–72.
17. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology.* 1997;48(5 Suppl 6):S10–6.
18. Selbaek G, Kirkevold O, Sommer OH, Engedal K. The reliability and validity of the Norwegian version of the Neuropsychiatric Inventory, nursing home version (NPI-NH). *Int Psychogeriatr.* 2008;20(2):375–82.
19. Campbell MK, Mollison J, Steen N, Grimshaw JM, Eccles M. Analysis of cluster randomized trials in primary care: a practical approach. *Fam Pract.* 2000;17(2):192–6.
20. Hawton K, Salkovskis PM. Cognitive behaviour therapy for psychiatric problems—a practical guide. Oxford: Medical Publications; 2002.
21. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9(3):179–86.
22. Lyketsos CG, Galik E, Steele C, Steinberg M, Rosenblatt A, Warren A, et al. The General Medical Health Rating: a bedside global rating of medical comorbidity in patients with dementia. *J Am Geriatr Soc.* 1999;47(4):487–91.
23. Roen I, Selbaek G, Kirkevold O, Engedal K, Lerdal A, Bergh S. The Reliability and Validity of the Norwegian Version of the Quality of Life in Late-Stage Dementia Scale. *Dement Geriatr Cogn Disord.* 2015;40(3–4):233–42.
24. Selbaek G, Engedal K. Stability of the factor structure of the Neuropsychiatric Inventory in a 31-month follow-up study of a large sample of nursing-home patients with dementia. *Int Psychogeriatr.* 2012;24(1):62–73.
25. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol.* 1989;44(3):M77–84.
26. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell Scale for Depression in Dementia. *Biol Psychiatry.* 1988;23(3):271–84.
27. Barca ML, Engedal K, Selbaek G. A reliability and validity study of the Cornell scale among elderly inpatients, using various clinical criteria. *Dement Geriatr Cogn Disord.* 2010;29(5):438–47.
28. World Health Organization: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2011. Oslo, Norway: Norwegian Institute of Public Health; 2011.
29. Weiner MF, Martin-Cook K, Svetlik DA, Saine K, Foster B, Fontaine CS. The quality of life in late-stage dementia (QUALID) scale. *J Am Med Dir Assoc.* 2000;1(3):114–6.
30. Riessmann CK: Narrative Analysis (Qualitative Research Methods). Boston: Sage Publications Ltd; 1993
31. Malterud K: Kvalitative metoder i medisinsk forskning, 3 edn. Oslo: Universitetsforlaget; 2011
32. Boersma P, van Weert JC, Lakerveld J, Droes RM. The art of successful implementation of psychosocial interventions in residential dementia care: a systematic review of the literature based on the RE-AIM framework. *Int Psychogeriatr.* 2015;27(1):19–35.
33. Dallner M, Elo A-L, Gamberale F. Validation of the General Nordic Questionnaire (QPSNordic) for psychological and social factors at work, vol. 12. Copenhagen: Nordic Council of Ministers; 2000.
34. Kada S, Nygaard HA, Mukesh BN, Geitung JT. Staff attitudes towards institutionalised dementia residents. *J Clin Nurs.* 2009;18(16):2383–92.
35. Beck JS: Cognitive behavior therapy: Basics and beyond. New York: Guilford Press; 2011
36. Fixsen DL, Naoom SF, Blase KA, Friedman RM, Wallace F. Implementation research: A Synthesis of the Literature. Tampa: University of South Florida, Louis de la Parte Florida Mental Health Institute, The National Implementation Research Network (FMHI Publication #231);2005.
37. Richards DA, Hallberg IR. Complex interventions in health: an overview of research methods. New York: Routledge; 2015.
38. Anderson LM, Petticrew M, Chandler J, Grimshaw J, Tugwell P, O'Neill J, et al. Introducing a series of methodological articles on considering complexity in systematic reviews of interventions. *J Clin Epidemiol.* 2013; 66(11):1205–8.
39. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud.* 2013;50(5):587–92.
40. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. *BMJ.* 2012;345:e5661.
41. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care.* 2012;50(3):217–26.
42. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ.* 2013;347:f6753.
43. Nygaard HA, Ruths S. Missing the diagnosis: senile dementia in patients admitted to nursing homes. *Scand J Prim Health Care.* 2003;21(3):148–52.
44. Waite L, Grayson D, Jorm AF, Creasey H, Cullen J, Bennett H, et al. Informant-based staging of dementia using the clinical dementia rating. *Alzheimer Dis Assoc Disord.* 1999;13(1):34–7.
45. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. *Eur J Pain.* 2014;18(10):1419–30.
46. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. *Arch Gen Psychiatry.* 1983;40(7):812.

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