RESEARCH PROTOCOL (nWMO)

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PROTOCOL TITLE 'SMEtH – Symptom Management Essentials at Home'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

CCMO	Central Committee on Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek)
Dyspnoea	Shortness of breath
General practitioner (GP)	General Practitioner
Life-limiting illness	an illness that cannot be cured and from which an individual will most likely die
Palliative care (PC)	PC is care that improves the quality of life of patients and their loved ones who are facing a life-threatening condition or frailty, by preventing and relieving suffering through early identification, assessment, and treatment of problems of a physical, psychological, social and spiritual nature.
Quality of life	An individual's perception of their position in life in the context of culture and value system in which they live and in relation to their goals, expectations, standards and concerns
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

1. INTRODUCTION AND RATIONALE

The majority of patients with a life-limiting illness experience symptoms, impairing the quality of life(1). In 2017, a total of 150.000 individuals died in the Netherlands, of whom the vast majority had cancer (41%), cardiac disease (24%) or dementia (16%)(2). The most common experienced symptoms during the last phase of life are fatigue, pain, lack of energy, weakness, lack of appetite and dyspnoea(3,4). The intensity of these symptoms increases as death approaches, in particular the last two months of life(5). To improve the quality of life of patients with a life-limiting illness and family caregivers, adequate palliative care (PC) has proven to be essential(6–8). The World Health Organisation (WHO) defines PC as "*an approach that improves the quality of life of patients (adults and children) and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial, or spiritual*"(9). Multiple studies have shown that PC interventions are associated with a lower symptom burden, greater advance care planning, fewer hospitalizations, lower healthcare expenses, enhanced communication between healthcare professionals and patients, enhanced emotional support, higher patient satisfaction and even improved survival(6,10–14).

PC provided by nursing teams working in primary care, is indispensable for 68% of Dutch population that prefers to stay at home during the last phase of life. However, merely 36% actually dies at home(15,16). The study conducted by Reyniers et al. presents several explanations for inappropriate hospitalization near the end of life. Patients were admitted to the hospital when symptom control (55%) at home was insufficient according to the patient, family was convinced care was better (54%) at the hospital or patients felt safer (35%) at the hospital(17). Nurses play a prominent role in providing PC at home, since they are responsible for the detection of signs and symptoms, the performance of multidimensional assessments, the collaboration of a wide range of disciplines and the communication with patients and their families(18). Additionally, General practitioners (GP) often rely on nurses to optimally assess these needs and report this information back. However, previous studies have shown multiple barriers in the provision of PC by nursing teams working in homecare organizations, which are: the identification of patients with PC needs, the collaboration with GPs and other caregivers, knowledge on quality of PC at home and optimizing autonomy, communication, and competences(19). As a result, patients with a life-limiting illness suffer concurrently from multiple symptoms that are often undetected, impairing the quality of life and making it impossible to stay at home. Family caregivers are also known to be susceptible to emotional, social, physical, and financial distress due to the heavy duty of taking care of a friend or loved one who is no longer able to care for themselves(20). One in ten family caregivers in the Netherlands is overburdened(21). Hence, symptom management in patients and family caregivers dealing with a life-limiting illness, living at home in the Netherlands is suboptimal.

In order to enhance a systematic approach of PC in primary healthcare, the Palliative Reasoning (PR) methodology has been developed(22). This is a stepwise, iterative, multidimensional symptom management approach consisting of a preparatory phase, followed by four phases(23,24). Multidimensional symptom management plays a central role in this approach and is defined as "the treatment of symptoms while taking the physical, psychological, social and spiritual aspect of the

problem into account"(25,26). Due to the number of components, the flexibility of the intervention to fit different contexts and the effect interaction it has with the context, the implementation is considered to be complex. Therefore, the development and implementation strategy of PR is based on the Medical Research Council (MRC)-model, figure 1, which is a framework that is commonly used for developing and evaluating complex interventions(27).

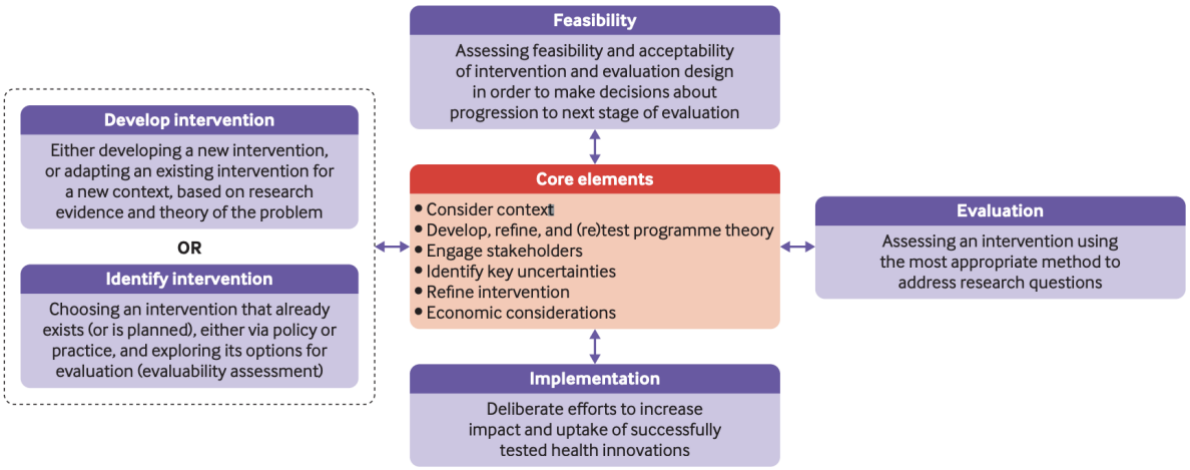

Figure 1. The MRC-model(27).

Prior research revealed the need for a systematic symptom management approach and supportive tools to support clinical decision making and multidisciplinary collaboration, by homecare nursing teams(28). Hence, the feasibility of the PR methodology has recently been tested in primary care. However, the effect of this methodology on symptoms of patients remains unknown. To further develop, optimize and successfully implement the PR methodology in future primary care practice and to improve the quality of life of patients and family caregivers, we aim to determine the effect of the PR methodology on the perceived symptoms of patients and family caregivers dealing with a life-limiting illness, receiving palliative homecare.

2. OBJECTIVES

Primary Objective: The primary objective of this study is to determine the effect of the PR methodology on perceived symptoms of patients and family caregivers dealing with a life-limiting illness and receiving palliative nursing care at home by teaching home care nursing teams the PR methodology and compare it with usual care provided in the Netherlands.

Secondary objectives:

- To adequately and systematically identify patients with a life-limiting illness in need of palliative care by implementing the surprise question in daily practice of nursing teams.
- To adequately and systematically identify, analyse and treat symptoms of patients and caregivers dealing with a life-limiting illness by implementing the PR methodology.

3. STUDY DESIGN

To determine the effect of the PR methodology, a pragmatic open-label multicenter cluster randomized controlled trial (cRCT) will be conducted in nursing teams working in primary care, from January 2024 to March 2026 in Utrecht, the Netherlands. We define a cluster as one nursing team in primary care, which is a group of registered nurses (RNs) and nurse assistants (NAs) collaborating within one home care organization and within the same district with support of specialized nurses (SN) and/or nurse practitioners (NPs). The trial consists of an intervention group and a control group. To enhance heterogeneity of usual care in the control groups and limit the risk of bias, randomization of the intervention will be conducted within one primary healthcare organization.

The intervention starts with the adequate identification of patients in need of palliative care by means of the surprise question “would I be surprised if this patient dies in the next year?”. If the answer to the question is “no”, the patient is suitable for receiving palliative care. After identification the PR methodology is followed by four phases. step 1: map out the individual situation, symptom burden and quality of life of the patient, step 2: summarize the current problems and develop a proactive policy plan, Step 3: evaluate the effect of the proactive policy plan on the symptom burden and quality of life of the patient, step 4: adjust the policy plan if necessary and continue evaluating. The Utrecht Symptom Diary – four dimensional (USD-4D) will be used to monitor the individual situation, symptom burden and quality of life of patients, as described in step 1. This is a Patient Reported Outcome Measure (PROM) and is validated in palliative care populations.

The nursing teams selected as control group will continue to provide usual care to patients with a life-limiting illness. We define usual care as “care that patients with a life-limiting illness, living at home, would be expected to receive as part of normal practice from that specific homecare organization”(29). To gain insight into normal practice of the control group, we will consult the organization’s current safety standards, guidelines, and protocols. Additionally, questions regarding normal practice will be asked during interviews with healthcare professionals.

4. STUDY POPULATION

4.1 Population (base)

The study population consists of patients with a life-limiting illness, receiving palliative care from nursing teams that work at two large homecare organizations in Utrecht, the Netherlands. Patients of different sex and age categories will participate in this study. All patients live at home, in the region of Utrecht and suffer from a wide range of life-limiting illnesses. Family caregivers participating in this study are the primary caregiver of the patient and may live in other regions of the Netherlands than the patient, since they are not bound by the range of a homecare organization.

Nursing teams usually consist of nurse assistants (NAs), registered nurses (RNs), specialized nurses (SNs) and nurse practitioners (NPs). All types of nurses have different educational backgrounds and therefore different job descriptions and responsibilities. NAs have three years of practical educational training after receiving their diploma. RN can be educated at an intermediate or a higher level. An intermediate RN receives at least 6400 hours of practical and theoretical education and RN with a higher level of education receives at least 6720 hours of education, of which a minimum of 1535 hours of theoretical courses and 2300 hours of on-the-job instruction. Both educational programmes take 4 years to complete, however, only the higher level of nursing education results in Bachelor of Nursing degree. Additionally, both RN can specialize in a certain health field, for example to become a district nurse (DN) or oncology nurse, which are SNs. RN with a higher level of nursing education can become NPs by completing a Master's of Advanced Nursing Practice, which comprises of 2 additional years of practical and theoretical education(30,31).

4.2 Inclusion criteria

Patients are eligible if:

1. patient is 18 years or older.
2. The patient is diagnosed with a life limiting illness or frailty syndrome with a life expectancy of less than a year, estimated by the nursing team, based on the Surprise Question.
3. The patient lives at home.
4. The patient suffers from at least 1 symptom identified by means of the problem list of the Distress Thermometer.
5. The primary caregiver/informal caregiver is aged over 18 and able to speak and read Dutch.

A member of the nursing team is eligible if:

1. He/she working as a nurse assistant, registered nurse, specialized nurse, nurse practitioner or palliative care specialist consultant.
2. He/she is 18 years or older.
3. He/she works for at least 16 hours a week.

A nursing team of a participating homecare organizations is eligible if:

1. The nurses that are part of the nursing team are motivated to participate in the study.
2. The Nursing team has a total of ten or more patients under their care suffering from a life-limiting illness.

Chaplains, GPs, paramedics, social workers, and other healthcare professionals are eligible if:

1. He/she is 18 years or older.
2. He/she actively collaborates with one of the included nursing teams.

4.3 Exclusion criteria

Patients diagnosed with cognitive impairment and/or patients unable to read and speak Dutch, will be excluded from the study.

4.4 Sample size calculation

As concluded by Adams et al., there is always a certain degree of uncertainty in estimating the magnitude of the intraclass correlation coefficient (ICC) for cRCTs beforehand(32). Therefore, the following calculation aims to provide the most accurate estimate of the required sample size, in order to demonstrate an effect. Based on our experience required during KWASA, a pilot study, primary nursing teams identify on average twenty patients with a life expectancy of one year or less. Hence, we expect the inclusion of twenty patients per nursing team to be feasible during this study. To estimate the number of clusters as accurate as possible, we considered different ICCs and different effect sizes for the intervention group(I). We calculated the number of clusters necessary assuming a power of 80%, an alpha of 5%, an effect size of 30% in the control group (C) and an effect size of 40% and 60% in the intervention group. Table 1 shows an overview of the results of our calculations.

Table 1. Overview results sample size calculation with different ICC and effect size.

ICC	N patients	I	C	N clusters
0.02	20	0.4	0.3	26
0.01	20	0.4	0.3	23
0.005	20	0.4	0.3	21
0.001	20	0.4	0.3	20
0.02	20	0.6	0.3	5
0.01	20	0.6	0.3	4
0.005	20	0.6	0.3	4
0.001	20	0.6	0.3	4

* ICC = Intraclass correlation coefficient. N patients = Number of patients in the cluster.
I = Intervention group. C = Control group. N cluster = Number of clusters.

According to our calculation a total of 20 clusters in each arm is the best fit for this study, assuming an effect size of 40% and an ICC of 0.001. A higher ICC results in a limited number of extra clusters, therefore, a total of 800 patients divided into 40 clusters is in our opinion the most appropriate. All calculations have been conducted with help of a methodologist from the Julius Centre and by means of the ClusterPower package of RStudio (Vienna, Austria), version 2022.12.0+353.

5. METHODS

5.1 Study parameters/endpoints

5.1.1. Main study parameter/endpoint

The main study parameter is “perceived symptom control of patients and family caregivers dealing with a life-limiting illness, after one month of implementing the SMEtH-intervention”. Perceived symptom control is defined as the perception of symptom control by a patient, assessed at enrolment and after one month by a one item question: “Do you feel your symptoms are under control? Yes/ No?”. The endpoint of one month has been chosen to limit the number of missing data due to death of participating patients.

5.1.2. Secondary study parameters/endpoints

The Quality of life of patients is assessed at enrolment, at one, three and six months by means of the EORTC QLQ C15 pal(33). This is a 15-item questionnaire developed by the European Organisation for research and treatment of cancer Quality of Life Group. The questions are answered on a scale from 1 to 4, in which the number 1 refers to “not at all”, 2 refers to “a little”, 3 refers to “quite a bit” and 4 refers to “very much”. The EORTC QLQ C15 pal is a shorted version of the original EORTC QLQ C30 pal, which is specifically developed for palliative care. To optimize the feasibility of measures, this shortened version will be used to reduce the risk of missing items and decrease the burden on participating patients.

Symptom burden of patients is assessed at enrolment, at one, three and six months by means of the Utrecht Symptom Diary Four Dimensional (USD4D), which is a patient reported outcome measure (PROM)(34). The USD4D comprises of questions regarding the physical, psychological, social, and spiritual dimension, which are rated on a scale from 0-10 (0 = symptom is absent to 10 = severity symptom is the worst imaginable).

Primary caregiver burden is defined as the perceived burden of the individual that is faced with the primary responsibility of taking care of a disabled friend or loved one. The primary caregiver burden Is assessed at enrolment, one, three and six months by means of the Self Rated Burden Scale, which is a one item numerical scale answering the question “How do I perceive the care for my loved one at the moment?”(35–38). The question is answered on a scale of 0 to 10, in which 0 refers to “not at all straining” and 1 refers to “much to straining”. In

addition, the perceived burden of informal care (Dutch: Ervaren Druk Informele Zorg (EDIZ)) will be used, assessing aspects of informal care contributing to the perceived burden(39). The EDIZ is developed for the use in caregivers of patients suffering from dementia at home, however, this measurement instrument is widely used to assess the level of burden of caregivers of patients with a life-limiting illness. This instrument contains 9 statements to which patients must answer “no!”, “no”, “more or less”, “yes” or “yes!”.

Current symptom management practices, roles and responsibilities, collaboration, communication, and competences are assessed by means of a questionnaire for all participating nurses and GPs at enrolment and after six months.

5.1.3. Other study parameters

The following demographic characteristics will be collected of all participating parties:

- Patient demographics: age, gender, marital status, education level, employment status (retired, unemployed, employed), (past) illness, type of employment (in the past), duration of illness, treatment, phase of illness, comorbidity, performance status (KPS), time under nursing care, number of visits per day/week. These demographics will be collected by means of a questionnaire at baseline.
- Primary caregiver demographics: age, gender, education level, role, employment status assessed at enrolment. These demographics will be collected by means of a questionnaire, at baseline, three, six and twelve months after enrolment.
- Nurse demographics participating in individual assessments: age, gender, education level, employment status (fulltime/parttime), duration of current employment at enrolment. These demographics will be collected by means of a questionnaire, at baseline, six and twelve months after enrolment.
- GP demographics: age, gender, employment status (fulltime/parttime), duration of current employment at enrolment. These demographics will be collected by means of a questionnaire, at baseline.
- Nursing team demographics: education level, local collaborations with GP and paramedics, symptom management practices at enrolment. These demographics will be collected by means of a questionnaire, at baseline, six and twelve months after enrolment.

The demographics mentioned above will also be used during the process evaluation that is part of phase four of this study.

5.2. Study procedures

Firstly, this study will start with the assessment of team characteristics, to develop a suited implementation strategy that fits the team and local context but does not influence the fidelity of function. Depending on the composition of the team, education levels and competences in the team, education and training content will be established by a team of coaching experts,

consisting of independent NPs and GPs with extensive experience in PC and PR. The intervention group will be educated in identifying patients with PC needs and will be taught how to apply PR in a four-day training with practical assignments. After two weeks of providing this four-day training to the nursing team, team coaches will be coached by means of a coaching on the job trajectory once a fortnight by the team of expert coaches. Team coaches that will be trained work as NP or SN within one of the organizations and are teamed up with RNs of the general nursing team. The team coaches will perform day to day coaching on the job. The implementation of the intervention will take approximately one month and will be planned in collaboration with the teams and the coaches.
Additionally, nurses who are enrolled in the study will be invited to complete questionnaires individually at enrolment and at six months about their own current symptom management practices, roles and responsibilities, collaboration, communication, and competences.

Secondly, the research team will perform an assessment of baseline measurements in participating patients and request to complete a questionnaire regarding demographic characteristics. The assessment of baseline measurements will be performed by post, mail, telephone, or teleconsulting depending on what is the most suitable and least burdensome for the patient. Subsequently, patients will complete at one-, three- and six-months a questionnaire containing questions regarding symptom control, quality of life and symptom burden. If these questionnaire reveals that a patient does not suffer from any symptoms, it will be excluded from the study. However, the excluded patients will be asked to complete the Lastmeter questionnaire to detect symptoms that may develop at a later stage, to be able to reconsider their inclusion in the study. After each questionnaire and/or assessment patients will be offered support of a NP, specialised in PC to talk about possible thoughts or concerns raised by completing the questionnaires.

Lastly, an assessment of demographic characteristics and perceived care burden on the primary caregiver is performed by the research team. Thereafter, at one-, three- and six-months perceived care burden is evaluated by telephone using the EDIZ rating scale. After each assessment the primary caregiver will be offered support of a NP, specialised in PC to talk about possible thoughts or concerns raised by completing the questionnaires.

Blinding:
In causal studies, blinding is performed ideally at participant, data collection and data analysis level. In this case, however, blinding at the analysis level is the only feasible.

- The participants are not blinded. Patients, primary caregivers, and the nursing teams will all be aware of their allocation to the intervention group, since the method Palliative Reasoning will be implemented in daily care.
- The data collection will not be performed blindly. Firstly, the data are collected by local nurses who are aware of their allocation. Secondly, the research team who is involved in training the participants are also aware of the allocation, which is necessary to ensure an in-depth exploration of the experiences of the nursing team

during the up-following qualitative part of this study. This part will be described in a different research protocol, which is part of phase 4 of this study.

- Data analysis will be performed blinded. The researcher performing the data analysis will be blinded for the group allocation using labels. The labels will be opened after the analysis.

Randomization and allocation:
The clusters will be randomized through a simple randomization method with the Clinical Trial Randomization Tool from the National Cancer Institute(40,41). To minimize the risk of allocation bias, we will stratify between both homecare organization. The teams are informed about their allocation by the research team.

5.3. Withdrawal of individual subjects

Patients and caregivers will be informed that consent may be withdrawn at any stage of the study, without stating a reason or any consequences.

5.4. Replacement of individual subjects after withdrawal

After the withdrawal of a patient, the patient will specifically be asked if the collected data up to that point may be used for the purposes of this study. If not, data regarding this patient will be removed from the database.

6. STATISTICAL ANALYSIS

6.1. Primary study parameter(s)

To determine the effect of the SMEtH-intervention on the perceived symptom control after 1 month of patients of each nursing team, a mixed effects logistic regression analysis will be conducted. We will control for the following baseline measurements: age, gender, primary diagnosis, and performance status. Missing data are imputed using multiple imputation (MICE package in R) or if necessary, Bayesian imputation and analysis (Joint AI package in R). The quantitative data will be presented as odds ratio and 95% confidence interval (CI) in tables and graphs for the visualization of the results. Additionally, all analyses of primary and secondary study parameters are conducted by means of the statistical program RStudio, version 2022.12.0+353. (Vienna, Austria), and are considered statistically significant if $\alpha \leq 0.05$.

6.2. Secondary study parameter(s)

Primary caregiver burden, symptom burden and quality of life of patients will be analyzed longitudinally using joint models for longitudinal analyses per symptom. Due to the fragility of the population, censoring of data will increase over time. Therefore, we will control for death, as well as age, gender, primary diagnosis, and performance status. Additionally, subgroup analyses for gender, age and primary diagnosis will be conducted for each secondary study parameter.

6.3. Other study parameters

To provide characteristics of patients, primary caregivers, individual nurses, nursing teams and GPs at baseline, descriptive statistics will be used and displayed in tables.

7. ETHICAL CONSIDERATIONS

7.1. Regulation statement

This study will be performed according to GDPR (AVG), WGBO and code of conduct.

The risk of adverse health effects if patients participate is low since the intervention focuses on the methodological application of nursing essential care symptom management. In other words, it does not impose specific interventions to each participant, it rather is a systematic approach and deployment of current guidelines in palliative care.
As sign of gratitude for participating in the study and to ensure uniformity of practice within both healthcare organizations, all control groups will be offered the intervention after completing the study.

7.2. Recruitment and consent

Recruitment and consent of participants takes place on multiple levels:
Home care organizations will be recruited from a convenience sample of existing cooperation partners of the University Medical Centre Utrecht and from interested home care organizations. Contact with the organizations will take place through mail and telephone. If directors of the organizations consent to participation, regional and team managers will be contacted for further information. Information regarding this study will be provided digitally and verbally, however, the local routing of consent can alter per organization depending on the structures of the organization.

After consent of the home care organizations, team managers will receive written information about the study and if a team is interested, an information session will be organized to provide detailed information. During and after the information session, nursing teams will have the opportunity to ask questions that arise from the provided information. Verbal and oral consent for participation of a nursing team will be given by each team manager of the corresponding team.

The attending nurse and a contact person of each nursing team will screen patients on eligibility, to ensure a structured patient selection. During the study period the cohort will be accessible for the enrolment of new patients that meet the inclusion criteria. Eligible patients will be approached and asked by the attending nurse to participate. In case of a positive response, the nurse will ask the patient for permission to share their contact details with the research team to receive further information regarding the study. Patients will receive oral and written information and detailed participant information forms. The need for additional information or questions arising from the provided information will be answered by the

researchers in person or by telephone. After obtaining the written informed consent of the patient and the primary caregiver, both will be enrolled in the study. In case of unwillingness to participate in the study by a family caregiver, a patient still can be enrolled if desired.

8. ADMINISTRATIVE ASPECTS

8.1. Handling and storage of data and documents

Castor will be used to collect and store the data. Data are pseudonymized by coding. A local key will be stored on location and an overall key will be stored separately from the data on a privacy server, according to the data management guidelines of the Julius Centre. All documents will be stored in the study server of the Julius Centre. Further information can be found in the Data Management Plan (DMP).

8.2. End of study

This investigation is scheduled to end in March 2026.

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