’Evaluation of an integrated care pathway for out-of-hospital treatment of older adults with an acute moderate-to-severe lower respiratory tract infection or pneumonia’

PROTOCOL TITLE 'Evaluation of an integrated care pathway for out-of-hospital treatment of older adults with an acute moderate-to-severe lower respiratory tract infection or pneumonia'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

6-CIT	**6-item Cognitive Impairment Test**
ADL	**Activities of Daily Living**
APOP	**Acute Presenting Older Patient**
COPD	**Chronic Obstructive Pulmonary Disease**
COVID-19	**Coronavirus Disease 2019**
ED	**Emergency Department**
EHR	**Electronic Health Record**
EudraCT	**European drug regulatory affairs Clinical Trials**
GA	**Geriatric Assessment**
GP	**General Practitioner**
GPC	**General Practice Centre**
IADL	**Instrumental Activities of Daily Living**
IC	**Informed Consent**
IM	**Intramuscular**
IV	**Intravenous**
LRTI	**Lower Respiratory Tract Infection**
PCR	**Polymerase Chain Reaction**
PIL	**Patient Information Leaflet**
PROMIS	**Patient-Reported Outcomes Measurement Information System**
PSI	**Pneumonia Severity Index**
QoL	**Quality of Life**
RSV	**Respiratory Syncytial Virus**
RTI	**Respiratory Tract Infection**
SARS-CoV-2	**Severe Acute Respiratory Syndrome Coronavirus 2**
SPSS	**Statistical Package for the Social Sciences**

SUMMARY

Rationale: An acute lower respiratory tract infection (LRTI) or pneumonia in older adults is generally characterised by diagnostic uncertainty, a high risk of complications, and negative outcomes, including mortality (e.g. due to overlap with heart failure and chronic obstructive pulmonary disease (COPD)). Care in the home situation often acutely falls short because of increased dependency due to falls, decline in activities in daily living (ADL) or a state of confusion. This often leads to a presentation at the emergency department (ED) with the goal to define the optimal treatment plan which usually consists of a combination of antimicrobials, oxygen suppletion and/or inhalation medication, treatment and/or prevention of delirium, and additional help in ADL; and the optimal treatment location. In principle, this kind of care and treatment could be organised outside the hospital (for example in a patient's home or in a nursing home); however hospitalisation often occurs because of the 24/7 open access of the EDs, and treatment outside the hospital is often considered irresponsible or impossible due to difficulties in ADL and the lack of (available) care.

Such hospitalisations of older adults can be considered unnecessary or avoidable when they are related to poor transmural collaboration and different treatment protocols between regional care partners (e.g. general practitioners (GPs), hospitals, nursing homes and homecare institutions), the lack of diagnostic and treatment possibilities in primary care, the lack of (acute) availability and capacity in nursing homes and homecare, or the presence of financial barriers. Especially in older adults, hospitalisations are associated with iatrogenic harm such as delirium (with the consequence of prescribing sedative medication), falls and functional decline. As a consequence, older patients often show further decline in ADL from these hospitalisations, and as a result are often transferred to a nursing home or revalidation centre for further recovery. We hypothesise that these hospitalisations may be avoided when the care is well coordinated between care partners.

Therefore, recently the multidisciplinary integrated care pathway 'The Hague RTI Care Bridge' has been developed with the aim to support GPs with the diagnostics, treatment and organisation of care for older adults with an acute moderate-to-severe LRTI or pneumonia. In this care pathway, clear collaboration agreements were made between involved regional care partners. Three patients journeys were embedded in the care pathway: a hospital-at-home treatment, an ED-presentation with priority assessment, and admittance to a readily available recovery bed in a nursing home. The care pathway includes a detailed guide upon treatment (e.g. antibiotics, oxygen suppletion) and its monitoring.

Objectives: The primary objective is to determine the feasibility of the care pathway. The secondary objectives are to determine the safety of the care pathway (30 day mortality and occurrence of complications (readmissions, delirium, falls) within 30 days); the satisfaction, usability and acceptance of the care pathway; the total number of days of bedridden status or hospitalisation; sleep quantity and quality; functional outcomes and quality of life (QoL). If possible, cost savings and logistical impact on hospital bed capacities will be evaluated.

Study design: Prospective mixed methods study.

Study population: Older adults (age ≥ 65 years) who visit their GP or present at the ED with a clinical diagnosis of an acute moderate-to-severe LRTI or pneumonia. The informal caregivers and treating physicians of participating patients will also be asked to participate in this study to evaluate their experiences and satisfaction about the received or given care.

Main study parameters/endpoints: The primary outcome of this study is the feasibility of the care pathway, which is defined as the percentage of patients treated outside the hospital, according to the care pathway, whom fully complete their treatment without the need for hospitalisation within 30 days of follow-up. Secondary study outcomes are the safety of the care pathway (30-day mortality and occurrence of complications (readmissions, delirium, falls) within 30 days); the satisfaction, usability and acceptance of the care pathway; the total number of days of bedridden status or hospitalisation; sleep quantity (core Consensus Sleep Diary on day 1, 2 and 7) and sleep quality (Patient-Reported Outcomes Measurement Information System Sleep Disturbance short form 8b on day 7 and 30); functional outcomes (KATZ-15 at 30 days, 6 and 12 months) and QoL (EQ-5D-5L at 30 days, 6 and 12 months). If possible, cost savings and logistical impact on hospital bed capacities will be evaluated.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: As this is a mixed methods study evaluating the feasibility, safety and satisfaction of an integrated regional care pathway in common practice, there are no specific benefits nor risks to be expected from participation in the study. Patients receive standard care according to the care pathway or the hospital guidelines. However, participation in the study will cost the patients (2.0-2.5 hours), informal caregivers (5-35 minutes) and treating physicians (5-35 minutes) extra time compared to not participating in the study.

1. INTRODUCTION AND RATIONALE

An acute lower respiratory tract infection (LRTI) or pneumonia in older adults is generally characterised by diagnostic uncertainty, a high risk of complications, and negative outcomes, including mortality (e.g. due to overlap with heart failure and chronic obstructive pulmonary disease (COPD)).[1-2] Care in the home situation often acutely falls short because of increased dependency due to falls, decline in activities in daily living (ADL) function or a state of confusion. This often leads to a presentation at the emergency department (ED) with the goal to define the optimal treatment plan which usually consists of a combination of antimicrobials, oxygen suppletion and/or inhalation medication, treatment and/or prevention of delirium, and additional help in ADL; and the optimal treatment location. In principle, this kind of care and treatment could be organised outside the hospital (for example in a patient's home or in a nursing home); however hospitalisation usually follows because of the 24/7 open access of the EDs, and treatment outside the hospital is often considered irresponsible or impossible due to difficulties in ADL and the lack of (available) care.[3-6]

Such hospitalisations of older adults can be considered unnecessary or avoidable when they are related to poor transmural collaboration and different treatment protocols between regional care partners (e.g. general practitioners (GPs), hospitals, nursing homes and homecare institutions), the lack of diagnostic and treatment possibilities in primary care, the lack of (acute) availability and capacity in nursing homes and homecare, or the presence of financial barriers.[7-11] Especially in older adults, hospitalisations are associated with iatrogenic harm such as delirium (with the consequence of prescribing sedative medication), falls and functional decline.[12-14] As a consequence, older patients show further decline in ADL from these hospitalisations, and as a result are often transferred to a nursing home or revalidation centre for further recovery. We hypothesise that these hospitalisations may be avoided when the care is well coordinated between care partners.

We, therefore, recently developed a multidisciplinary integrated care pathway 'The Hague RTI Care Bridge' with the aim to support GPs with the diagnostics, treatment and organisation of care for older adults with an acute moderate-severe LRTI or pneumonia.[15] In this care pathway, clear collaboration agreements were made between involved regional care partners. Three patient journeys were embedded in the care pathway (**Figure 1** and **Table 1**): a hospital-at-home treatment, an ED-presentation with priority assessment, and an admittance to a readily available recovery bed in a nursing home. The care pathway includes a detailed guide upon treatment (e.g. antibiotics, oxygen suppletion) and its monitoring.[15]

In this prospective mixed-methods study, the implementation of the care pathway will be evaluated. During this 12 months study period, it is hypothesised that in at least 75% of the older adults with an acute moderate-to-severe LRTI or pneumonia who are treated outside the hospital according to the care pathway, hospitalisation can be avoided.

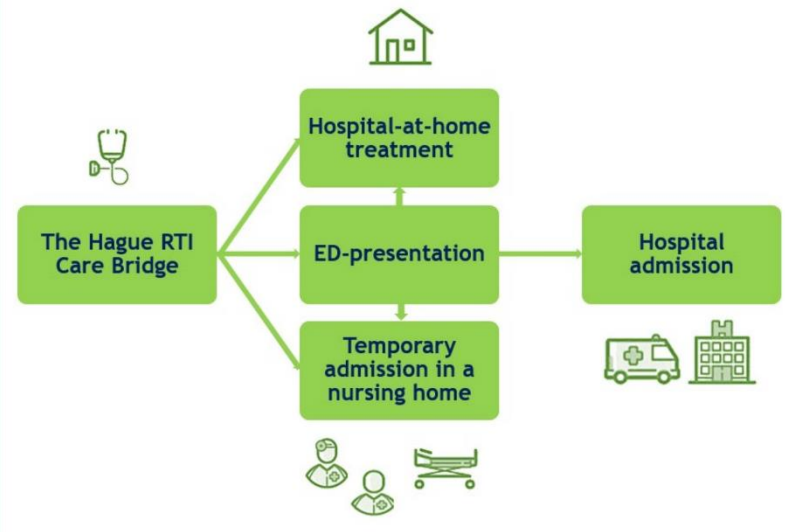

Figure 1: The three patients journeys in the care pathway. ED: Emergency Department; RTI: Respiratory Tract Infection.

Table 1: Overview of the three patient journeys in the care pathway.

	Hospital-at-home treatment	**Presentation at the emergency department**	**Temporary admission in a nursing home**
Treatment location	Home	*Three options:* - Home (pathway) - Nursing home (pathway) - Hospital (regular care)	Nursing home
Treatment	*Possibilities:* - Antimicrobials (oral or intramuscular) - Oxygen suppletion - Inhalation medication - Homecare	*Possibilities:* - Antimicrobials (oral or intravenous) - Oxygen suppletion - Inhalation medication - Hospital care	*Possibilities:* - Antimicrobials (oral or intramuscular) - Oxygen suppletion - Inhalation medication - Multidisciplinary care
Treating physician	General practitioner	Treating physician at ED (and ward when admitted)	Elderly care physician
Monitoring	Home monitoring with monitoring kit and registration form (vitals three times a day)	Depends on chosen treatment location*	Monitoring conform the standard of care in the nursing home

* Hospitalised patients will receive the local standard of care. ED: Emergency Department.

2. OBJECTIVES

2.1 Primary objective

The primary objective is to determine the feasibility of the care pathway, which is defined as the percentage of patients treated outside the hospital, according to the care pathway, whom fully complete their treatment without the need for hospitalisation within 30 days of follow-up.

2.2 Secondary objectives

The secondary objectives are to determine the safety of the care pathway (30-day mortality and occurrence of complications (readmission, delirium, falls) within 30 days); the satisfaction, usability and acceptance of the care pathway; the total number of days of bedridden status or hospitalisation; sleep quantity and quality; functional outcomes and quality of life (QoL).

3. STUDY DESIGN

The design of the study is a prospective mixed methods study, which will be performed in the urban area of The Hague, the Netherlands. In the Netherlands, over 35.000 adults are hospitalised with an acute LRTI or pneumonia annually, including 1.500-2.000 hospitalisations in the area of The Hague. The study period will be from 1 December 2022 to 30 November 2023, thereby including the 2022-2023 winter season / flu season. In this period, the results will be evaluated frequently for the benefit of interim adjustments.

This is multicenter study including two teaching hospitals (Haga Teaching Hospital and Haaglanden Medical Center), two nursing homes and primary care centers in the urban area of The Hague. The setting will primarily be outside the hospital (in primary care or nursing homes). The care pathway offers three options (**Figure 1** and **Table 1**) for the treatment of older adults with a clinical diagnosis of an acute moderate-to-severe LRTI or pneumonia.

4. STUDY POPULATION

4.1 Population

The study population consists of older adults (age ≥ 65 years) who visit their GP or present at the ED with a clinical diagnosis of an acute moderate-to-severe LRTI or pneumonia. The informal caregivers and treating physicians of participating patients will also be asked to participate in this study to evaluate their experiences and satisfaction about the received or given care. An overview of eligibility criteria is shown in **Table 2**.

4.2 Eligibility criteria for patients

To be eligible to participate, a patient must meet all following inclusion criteria: age ≥ 65 years, clinical diagnosis of an acute moderate-to-severe (Pneumonia Severity Index (PSI) class ≥ 3 or a CURB-65 ≥ 2) LRTI or pneumonia, an oxygen saturation ≥ 92% with maximum five litres O_2 and a respiratory rate ≤ 24/minute (or adjusted oxygen saturation cut-offs for patients as clinically indicated (e.g. for patients with COPD) by the treating physician), and written informed consent (IC) for study participation.[16-17] Exclusion criteria are: chemotherapy for solid organ malignancy (< 2 months before presentation), active hematologic malignancy, immunocompromised status (e.g. solid organ transplants) and/or severe dementia (Clinical Dementia Rating Scale Sum of Boxes score 16-18).[18]

Due to logistical limitations (absence of own GPs, and evening/night/weekend shifts in nursing homes), the care pathway will be active on weekdays (Monday-Friday) between 08.00-18.00 hours for the hospital-at-home treatment and every day (Monday-Sunday) between 08.00-20.00 hours for the admission on a recovery bed in a nursing home. Patients who present at their GP and/or at the ED with an acute LRTI or pneumonia when the care pathway is active will be eligible to be treated according to the care pathway. Patients with an acute LRTI or pneumonia who are hospitalised subsequently to this ED-visit will receive the local standard of hospital care, and will therefore not be included.

4.3 Control group

Patients who fulfil the inclusion criteria and do not meet the exclusion criteria of the care pathway, and are hospitalised on weekdays outside office hours (18.00-08.00) or on weekend days due to the inactivity of the care pathway, will serve as a control group.

4.4 Eligibility criteria for informal caregivers

To be eligible to participate, an informal caregiver must meet all following criteria: age ≥ 18 years, being an informal caregiver of a patient included in the study, and written IC for participation in the study.

4.5 Eligibility criteria for treating physicians

To be eligible to participate in this study, a treating physician must meet all following criteria: physician of a patient included in the study at the main location of treatment, the physician should have treated the patient at least ≥ 2 (consecutive) days, and written IC for participation in the study.

Table 2: Eligibility criteria for patients, informal caregivers and physicians.

	Inclusion criteria	Exclusion criteria
Patients	Age ≥65 years	Chemotherapy for solid organ malignancy (<2 months before presentation)
	Clinical diagnosis of an acute moderate-to-severe LRTI or pneumonia*	Active hematologic malignancy
	Oxygen saturation ≥92% and respiratory rate ≤24/minute with max. 5 litres O_2**	Immunocompromised status (e.g. solid organ transplants)
	Written informed consent	Severe dementia (Clinical Dementia Rating Scale Sum Of Boxes score 16-18)
Informal caregivers	Age ≥18 years	-
	Being an informal caregiver of a patient included in the study	
	Written informed consent	
Physicians	Physician of a patient included in the study at the main location of treatment	-
	The physician should have treated the patient at least ≥2 (consecutive) days	
	Written informed consent	

* Pneumonia Severity Index class ≥3 or CURB-65 ≥2. ** Or adjusted oxygen saturation cut-offs as clinically indicated by the physician. LRTI: Lower Respiratory Tract Infection.

4.6 Sample size calculation

Ideally, 50 patients will be treated outside the hospital (care pathway group) and 50 patients will be treated in the hospital (control group). A power analysis was performed for the evaluation of the feasibility of the care pathway. In clinical practice, approximately 10% of the hospitalised patients are readmitted to the hospital after discharge. Our hypothesis is that in at least 75% of the older adults with an acute LRTI or pneumonia who are treated outside the hospital (at home or in a nursing home) according to the care pathway (care pathway group), hospitalisation can be avoided (complete treatment outside the hospital during 30 days of follow-up). An 80% power with an alpha of 0.05 for an one-sample study will be achieved if 40 patients are recruited for the care pathway group.

For the qualitative endpoints, data collection (interviews) will be performed until data saturation is reached. When a patient is included and his/her informal caregiver and/or treating physician does not want to participate or cannot participate in the study, the patient will remain in the study and no extra patient will be included to make up for the missing informal caregiver and/or treating physician.

5. TREATMENT OF SUBJECTS

5.1 Treatment in the care pathway group

If the treating physician aims to treat a patient outside the hospital (at home or in a nursing home), the following treatment options are available following the current Dutch national primary care guidelines.[19-21] In case of bacterial pneumonia, the first choice is amoxicillin, which can be switched to doxycycline or another antibiotic in case of insufficient improvement after two days in not severely ill patients.[19] The second choice (in case of hypersensitivity) is doxycycline. In case or suspicion of aspiration, amoxicillin/clavulanic acid is the first choice, and clindamycin is the second choice (in case of hypersensitivity). Patients who are treated at home or in a nursing home after an ED-visit will receive their first dose of antibiotics intravenously (IV) at the ED.

In addition to the treatment options in the Dutch current national primary care guideline for bacterial pneumonia, the treating physician can start moxifloxacin after consultation of an internist or pulmonologist in patients treated outside the hospital according to the care pathway. Besides that, patients with unreliable oral intake or patients where there is little supervision on the intake, can be treated at home or in the nursing home with ceftriaxone intramuscular (IM) once a day for a total of five days, which will be administered by a specialised nurse at home or in the nursing home.

In case of a coronavirus disease 2019 (COVID-19) infection, the patients will be treated at home following the current Dutch national primary care guideline for COVID-19.[20]

In case of an influenza infection, the older adults will be treated according to the current Dutch national primary care guideline for influenza with oseltamivir.[21] In the treatment with oseltamivir, attention will be payed to the kidney function. In addition to the Dutch national primary care guideline for influenza, the treating physician can also treat patients with influenza in the care pathway group with baloxavir.

If patients sound bronchospastic during pulmonary auscultation, the start of inhalation medication can be considered in the form of fenoterol/ipratropium (50 microgram / 20 microgram) per doses aerosol with spacer, consisting of two inhalations at a time with a maximum of eight per day. In patients with underlying obstructive pulmonary disease (asthma/COPD) and/or clinical signs of bronchospasm, it can be considered to start prednisolone 40 milligram once a day for five days.

Patients requiring oxygen suppletion can receive oxygen suppletion (maximum of five litres) at home or in the nursing home. The treating physician can order the oxygen by phone (delivery within a few hours at the patient's home) and individual target values will be noted on the individual care plan of the patient by the treating physician.

5.2 Treatment in the control group

The hospitalised patients in the control group will be treated according to the local hospital standards, which are based on the Dutch national guidelines for the treatment of pneumonia (amoxicillin (IV or oral) or ceftriaxone (IV) for moderate-to-severe pneumonia), COVID-19 and influenza.[22-24]

5.3 Monitoring of patients in the hospital-at-home group

The patient will be registered by the treating physician (GP, or ED-physician after the GP agreed upon the hospital-at-home treatment) at the homecare contact centre for the hospital-at-home treatment. The treating physician will sent the individual care plan digitally to the homecare contact centre, and will also give the patient a printed version to take home. The homecare contact centre makes sure that a nurse will visit the patient at home within four hours after registration. To this visit, the nurse will bring a printed registration form and a monitoring kit (including a pulsoximeter and a thermometer).

During the visit, the nurse will instruct the patient (and his/her informal caregiver) about the use of the monitoring kit and registration form: the patient, informal caregiver and/or nurse will write the vital parameters of the patient down on the registration form at least three times a day. The nurse will discuss the individual care plan and explain how to contact the homecare contact centre, and answer additional questions. In case inhalation medication is prescribed, instructions on the use will be given. In case ceftriaxone IM is prescribed, the first gift will be given during this visit and the nurse will also visit the patient daily to administer the other doses of ceftriaxone. The nurse will also evaluate whether there is need for (additional) homecare, if not already started.

The GP will have contact at least once a day with the patient and/or informal caregiver. This contact will preferably be by video call, but at least by phone. During this contact between patient and GP, the condition of the patient and the vital parameters on the registration form will be discussed together with whether the patient went out of bed that day and whether the patient has fallen. A fall is defined as an event that results in a person coming to rest inadvertently on the ground or floor or other lower level. In case of doubt, the GP will visit the patient. Based on these daily consultations, the GP will monitor

the patient, reduce oxygen suppletion if applicable, and decide when monitoring stops. In case of deterioration, the GP can low-key approach the specialists and refer the patient.

To guarantee a safety net 24/7, the GP will inform the general practice centre (GPC) about the patient being treated at home according to the care pathway. Besides that, the GP will ask the patient to give permission to open their national exchange point to guarantee that the GPC will also have all patient information after office hours if needed. The GP will also make explicit arrangements about the continuation of care after office hours (e.g. a contact moment during weekend days).

5.4 Monitoring of patients in the nursing home group

If the GP or the treating physician on the ED decides treatment in a nursing home is favourable, they will contact the elderly care physician in case temporary admission on a recovery bed in a nursing home (estimated length of admission ≤ 14 days) is indicated. The patient will then be registered by the treating physician at the homecare contact centre. The treating physician will sent the individual care plan digitally to the homecare contact centre and will also give a printed version with the patient to the nursing home. At the nursing home, the monitoring will be conform the standard of care in nursing homes. Nurses will monitor the vital parameters of the patient three times a day and discuss them with the treating elderly care physician, who will reduce the oxygen suppletion if applicable, and decide when the monitoring stops and the patient is fit enough to go back to his own living environment.

5.5 Monitoring of patients in the control group

The monitoring of the hospitalised patients in the control group will be according to the local hospital standards.

5.6 Use of co-intervention

Not applicable.

5.7 Escape medication

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable. The treatment as described in the regional care pathway is considered the golden standard.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable. The pulsoximeter and thermometer as described in the regional care pathway are considered the golden standard.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study endpoint is to determine the feasibility of the care pathway, which is defined as the percentage of patients treated outside the hospital, according to the care pathway, whom fully complete their treatment without the need for hospitalisation within 30 days of follow-up.

8.1.2 Secondary study parameters/endpoints

The secondary study endpoints are to determine:

- Safety of the care pathway (30-day mortality and occurrence of complications (readmissions, delirium, falls) within 30 days).
- Satisfaction, usability and acceptance of the care pathway (30-day satisfaction questionnaires with a five or ten point Likert scale in patients, informal caregivers and treating physicians; and semi-structured interviews with the first ten patients and their informal caregivers in the hospital-at-home group (and the treating GPs), nursing home group and control group).
- Total days of bedridden status or hospitalisation.
- Sleep quantity as assessed by the core Consensus Sleep Diary on the first two days and on the seventh day after inclusion.[25]
- Sleep quality as assessed by the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance short form 8b on day 7 and day 30 after inclusion.[26-27]
- Functional outcomes as assessed by KATZ-15 (including the KATZ-ADL and Lawton instrumental ADL (IADL)) and living situation at 30 days, 6 and 12 months.[28-30]
- QoL as assessed by EQ-5D-5L at 30 days, 6 and 12 months.[31-32]

If possible, cost savings and logistical impact on the hospital bed capacities will be evaluated. Cost savings will be roughly estimated using the length of the hospital or nursing home admission or homecare use, and the average care costs per day for care in a hospital, care in a nursing home or homecare. We aim to evaluate the logistical impact on the hospital bed capacities by simulating a scenario in which the patients treated outside the hospital would have been admitted to the hospital at the time of care pathway inclusion. If this analysis is possible, it will be possible to make a rough estimation of the logistical impact on the hospital bed capacities.

8.1.3 Other study parameters

Not applicable.

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

When a GP decides to treat a patient at home or in a nursing home according to the care pathway, the GP will perform a physical examination, measure the vital parameters (heart rate, blood pressure, respiratory rate, oxygen saturation and temperature), and will perform the standard diagnostics package (**Table 3**): nasopharyngeal swab (Polymerase Chain Reaction (PCR) on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), influenza A/B and Respiratory Syncytial Virus (RSV)) and the adjusted Acute Presenting Older Patient (APOP) screening.[33] The GP will inform the patient (or representative (e.g. in case of incapacity due to dementia/delirium)) about the study upon care pathway inclusion, and asks for oral informed consent (IC). When a patient or representative (on behalf of the patient) agrees to participate in the study, the GP will hand over the patient information leaflet (PIL) and inform the research personnel about the patient. Within one workday, a research team member will visit the patient (and representative if applicable) at home or in the nursing home to provide written IC and collect data.

When a patient does not want to participate in this study, no research data will be collected and the patient will still be managed according to the care pathway.

When the GP decides to refer the patient to the ED for additional assessment, a predefined diagnostics package (**Table 3**) will be performed on the ED: laboratory tests (blood cell count including differentiation, sodium/potassium, glucose, kidney function (creatinine/urea), C-reactive protein, and optional are d-dimer and N-Terminal pro Brain Natriuretic Peptide), nasopharyngeal swab (PCR on SARS-CoV-

2, influenza A/B, RSV), chest imaging (X-ray or CT-scan), and electrocardiogram. All of the data above will be collected on the ED for patients included in the control group. The treating ED-physician will inform the patient (and representative if applicable) about the study (including handing over the PIL) upon inclusion in the care pathway (hospital-at-home treatment or admission in a nursing home) or upon hospitalisation for patients eligible for the control group, and will ask the patient (or representative if applicable) for oral IC to participate. Within one workday, a research team member will visit the patient (and representative if applicable) at home, in the nursing home, or in the hospital to provide written IC and collect data.

Table 3: Diagnostics packages at the primary care center and at the emergency department.

	Primary care center	**Emergency department**
Laboratory tests	Optional	- Blood cell count incl. differentiation - C-reactive protein - Sodium/Potassium/Glucose - Kidney function (Creatinine/Urea) - Optional: D-dimer / NT-proBNP
Microbiology	*Nasopharyngeal swab (PCR):* - SARS-CoV-2 - Influenza A/B - Respiratory Syncytial Virus	*Nasopharyngeal swab (PCR):* - SARS-CoV-2 - Influenza A/B - Respiratory Syncytial Virus
Radiology	Optional	X-Thorax and/or CT-Thorax
Clinical prediction rules	- Adjusted APOP screening	- APOP screening - PSI or CURB-65 measurement
Electrocardiogram	Optional	Yes

APOP: Acute Presenting Older Patient; NT-proBNP: N-Terminal pro Brain Natriuretic Peptide; PCR: Polymerase Chain Reaction; PSI: Pneumonia Severity Index; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

Besides data from the registration forms of the patients in the hospital-at-home group, GPs will collect information regarding illness duration during their treatment and monitoring of the patient, thereby providing insight into the occurrence of complications (readmissions, delirium, falls), and the percentage of complete treatments at home. The elderly care physicians will collect similar information in the electronic health records (EHR) of patients in the nursing home group. For patients in the control group, this information will be extracted from the hospital EHRs.

A research team member will visit the patient on location (at home, in the nursing home or in the hospital) on the first workday after the start of treatment. During this visit, patients (and their representatives if applicable) will be able to ask additional questions about the PIL and the study. If a patient (or representative on behalf of the patient) agrees to participate in the study, written IC will be asked for participation in the study. In case a representative has provided written IC for an incapacitated patient (e.g. in case of delirium), and the patient's medical condition improves over time, the patient will be asked for written IC when the patient is considered competent again. When a patient has given written IC, their informal caregiver and treating physician will also be approached to participate in the study.

During this first visit (+/- 1 hour), baseline information will be collected from the patients. This baseline information will include demographic information (including ethnicity/religion) and a geriatric assessment (GA). Ethnicity and religion are included in the demographic information as the area of The Hague has a multicultural society and these factors may influence a patient's care system and thereby the choice of the treatment location. Dementia research has shown that a considerable amount of the people with a migration background makes limited use of professional homecare, and needed care is often taken over by family members.[34-35] A GA is an evidence-based, systematic procedure used to objectively describe the health status of older adults, focusing on somatic, functional, and psychosocial domains, and aimed at constructing a multidisciplinary treatment plan. As our study population consists of patients who are in a vulnerable phase of life, we want to keep the study load as low as possible. The GA will include the following validated tests: the Charlson Comorbidity Index, G-8 screening tool, 6-item cognitive impairment test (6-CIT), functional status (KATZ-15 and living situation) and QoL (EQ-5D-5L) one week prior to the onset of disease.[36-38]

During this first visit, patients will also be given a core Consensus Sleep Diary to fill in on the two upcoming days and on the seventh day after inclusion. Patients will also be given a PROMIS Sleep Disturbance short form 8b to fill in on the seventh day after inclusion. The sleep quality/quantity forms will be collected one week after inclusion. In the hospital-at-home group, the registration forms will be collected together with the monitoring kits when the patient is released from the care pathway. **Figure 2** and **Table 4** show an overview of the different moments of data collection.

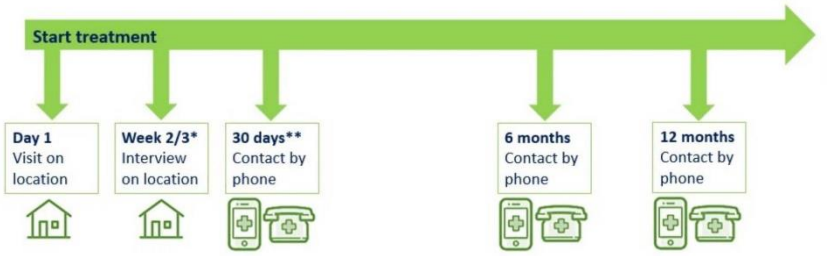

Figure 2: Overview of preferable contact moments with patients. * The interview will be held with the first ten patients and informal caregivers in the hospital-at-home group (and general practitioners), the nursing home group and the control group. ** Informal caregivers and treating physicians will also receive a phone call at 30 days.

Table 4: Overview of the data collection at the different time points.

	Day 1	Day 2	Day 7	Week 2-3	30 days	6 months	12 months
Mortality	X	X	X		X	X	X
KATZ-15	X				X	X	X
Living situation	X				X	X	X
EQ-5D-5L	X				X	X	X
Demographics	X						
Charlson Comorbidity Index	X						
G-8 screening tool	X						
6-item cognitive impairment test	X						
Core Consensus Sleep Diary	X	X	X				
PROMIS Sleep Disturbance short form 8b			X		X		
Satisfaction				X*	X**		
Complications					X		

* An interview will be held with the first ten patients and informal caregivers in the hospital-at-home group (and general practitioners), the nursing home group and the control group. ** Questionnaires will be conducted with the patients, their informal caregivers and their treating physicians. PROMIS: Patient-Reported Outcomes Measurement Information System.

Two-three weeks after inclusion, a semi-structured in-depth interview (+/- 30 minutes) will be held on voluntary basis with the first ten patients in the hospital-at-home group, the nursing home group and the control group. If these ten patients in each group agree to participate in the interview, their informal caregivers will also be asked if they want to participate in a similar interview to collect information about their experiences with the received/given care. The interview of the patient and their informal caregiver can take place simultaneously. If the patients in the hospital-at-home group agree to participate in the interview, their GPs will also be asked for an interview to collect information about their experiences with the care pathway. The interview with the GP will take place separately. By selecting participants in this way, the interviews will be taken without purposive sampling.

The framework that is used to develop the interview guide is the Consolidated Framework for Implementation Research (https://cfirguide.org/), which provides a framework of constructs that have been associated with effective implementation.[39-41] There are five different domains with corresponding example questions. These questions have been adapted and tailored to the intervention program, and will form the basis for a process evaluation of the implementation of the care pathway focusing on the implementation, the mechanisms of impact and context (facilitators and barriers to implementation).[42] The information collected during these interviews will be used to adjust the care pathway.

At 30 days, all patients will receive a phone call (or a visit at request of the patient) from a research team member (+/- 30 minutes) in which they will be asked about the occurrence of complications (readmissions, delirium, falls), sleep quality (PROMIS Sleep Disturbance short form 8b), functional status (KATZ-15 and living situation), QoL (EQ-5D-5L) and their satisfaction. The questions to evaluate satisfaction are based on the Consumer Quality Index, Patient Reported Outcome Measures and other research evaluating the out-of-hospital treatment of patients, and adjusted if applicable.[43-44]

At 30 days, all participating informal caregivers and treating physicians (GPs, elderly care physicians and hospital ward doctors) will receive a short phone call from a research team member (+/- 5 minutes) in which they will be asked about their satisfaction, usability and acceptance of the care pathway. In this call, the treating physicians will also be asked about the occurrence of complications.

At six and twelve months, all patients will receive a phone call (or a visit at request of the patient) from a research team member (+/- 15 minutes) in which they will be asked about their functional status (KATZ-15 and living situation) and QoL (EQ-5D-5L).

The research group has longstanding experience in performing questionnaires by telephone in the older population, which has proven to be feasible and was validated in previous studies.[45]

8.4 Withdrawal of individual subjects

All patients/representatives, informal caregivers and treating physicians can withdraw their consent at any time if they wish to do so without any consequences.

8.5 Replacement of individual subjects after withdrawal

The individual subjects will not be replaced after withdrawal.

8.6 Follow-up of subjects withdrawn from treatment

The follow-up of the individual subjects withdrawn from treatment will be stopped.

8.7 Premature termination of the study

Not applicable

9. SAFETY REPORTING

Not applicable.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter

The primary study parameter is the feasibility of the care pathway, which is quantitative data. Categorical variables will be presented as counts and frequencies. The quantitative data will be analysed by the use of Statistical Package for the Social Sciences (SPSS).

10.2 Secondary study parameters

The secondary study parameters will be established by the comparison of the patients in the care pathway group and the control group during follow-up. The secondary study parameters are the safety of the care pathway (30-day mortality and the occurrence of complications (readmissions, delirium, falls) within 30 days); the satisfaction, usability and acceptance of the care pathway; the total days of bedridden status or hospitalisation; sleep quantity and quality; functional outcomes, and QoL. If possible, cost savings and the logistical impact on the hospital bed capacities will be evaluated.

Categorical variables will be presented as counts and frequencies. Differences between groups will be tested with Chi-square tests and multivariate logistic regression models. Continuous data (scale questions) will be presented as means (standard deviations) for normally distributed data or medians (interquartile ranges) for not-normally distributed data. Differences between groups will be tested with independent t-tests or one way ANOVA's (normal distribution) or Mann-Whitney U or Kruskal Wallis tests (no normal distribution) depending on the amount of groups to be compared per analysis and by multivariate linear regression models. All tests of significance will be at two-tailed 0.05 level. The 95% confidence intervals will be used to assess the presence/absence of associations. The quantitative data will be analysed with SPSS version 28.

All recorded interviews will be transcribed by two research team members and hereafter then coded with the program Atlas.ti version 22. The interview recordings will be saved in a secured folder on the network of the coordinating hospital and will be deleted after verbatim transcription. The transcriptions will be saved on the network of the coordinating hospital. We will apply thematic content analysis to identify and categorise recurrent themes/elements. Thereby, we aim to classify the qualitative data in the right sections (implementation, methods, context) of the process evaluation of the implementation.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (2013) and the General Data Protection Regulation. The Medical Research Ethics Committee Leiden Den Haag Delft (reference number: N22.078) has evaluated the research protocol and has confirmed that the Medical Research Involving Human Subjects Act does not apply to this study. The Haga Teaching Hospital Scientific Review Board approved this study (reference number: T22-066).

11.2 Recruitment and consent

The treating physician will inform the patient (or representative (e.g. in case of incapacity due to dementia/delirium)) about the study upon inclusion in the care pathway (care pathway group) or upon hospitalisation (control group). The treating physician will orally explain the purpose and the methodology of the study. Sufficient time will be given for consideration before the patient (or representative) will be asked for oral IC to participate in the study. When the patient or representative (on behalf of the patient) agrees to participate, the treating physician will hand over the PIL and inform the research team about the potential study candidate.

During the visit on location (at home, in the nursing home or in the hospital) by a research team member on the first workday after inclusion, the patient (or representative) will be able to ask additional questions about the PIL and study. If the patient or representative (on behalf of the patient) agrees to participate, written IC will be asked for participation. In case a representative has provided written IC for an incapacitated patient (e.g. in case of delirium), and the patient's medical condition improves over time, the patient will be asked for written IC when the patient is considered competent again. When a patient has given written IC to participate in the study, their informal caregiver and treating physician will also be approached to participate in the study.

All patients/representatives, informal caregivers and treating physicians will be informed that they can withdraw their consent at any time if they wish to do so without any consequences.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment

As this is an mixed methods study evaluating the feasibility, safety and satisfaction of a care pathway in common practice, there are no specific benefits nor risks to be expected.

The patients included in the study will have a PSI-score of three or higher, which means they have a mortality risk of 0.9%-27.0% (average 30-day mortality 10%) within 30 days depending on the height of the score.[16] Therefore, the baseline mortality risk of all patients in the study is relatively high, regardless of the treatment location (either at home, in a nursing home or in the hospital). The hospital-at-home treatment may have a higher risk when a patient deteriorates since the monitoring might be less strict than during an admission in a nursing home or in a hospital. However, earlier studies have shown that patients with higher PSI-scores can safely be treated at home.[3-6]

In the care pathway group, all patients in the hospital-at-home group will be provided with a monitoring kit (including a thermometer and pulsoximeter), and will be instructed by a specialised nurse from the homecare organisation how to monitor their vital parameters at home, thereby stimulating the autonomy of patients (and their informal caregivers). The homecare contact centre is 24/7 reachable by phone. This way, the risk of the hospital-at-home treatment is reduced and a safety net is implemented in case of clinical deterioration.

The benefit of a treatment outside the hospital for patients is prevention of unnecessary and unnecessary long hospitalisations with unnecessary risks of iatrogenic harm, such as delirium, falls and functional decline. Therefore, it is expected that patients will be better off outside the hospital (at home or in a nursing home) than in the hospital. It is good to realise that a patient's prognosis depends on the underlying medical condition of the patient and the specific treatment (which is the same outside of the hospital as in the hospital) and not on the degree of monitoring.

11.5 Compensation for injury
Not applicable.

11.6 Incentives
Not applicable as patients will not receive compensation for participating in the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The written IC forms will be safely stored at the internal medicine research department in the coordinating hospital (Haga Teaching Hospital). Data will be stored using Castor EDC through direct data entry by the investigators or research nurses. Age will be represented in years. Therefore, the data will not be traceable to the individual patient. The data will be coded in the coordinating hospital.

Every participant will get a unique study code, which will not contain any personal details. The code will be based on the number of the study participant (patient). For example, the first patient in the study will receive code 000001, while the third patient in the study will receive code 000003. In Castor EDC, the interviews and questionnaires with the informal caregivers and treating physicians will be stored in the file of the patient where they are related to. Therefore, the informal caregiver and treating physician will receive the same code as the patient upon inclusion in the study. For example, the informal caregiver and treating physician of patient 000001 will also receive code 000001, while the informal caregiver and treating physician of patient 000003 will also receive code 000003.

A SPSS file will be extracted from Castor EDC and will therefore not contain any names, birth dates and patient numbers. The key of the code will be stored on a secured drive in the coordinating hospital. After the collection of all data, a combined (coded) database will be stored at a secured drive at the coordinating hospital. The data will be stored for a period of 15 years.

The datasets, including the coded participant level data, will be made available to other researchers upon reasonable request after the publication of the study results. Requests should be directed to the coordinating investigator. Data requestors will need to sign a data access agreement. These datasets will only contain the coded individual-level data that underlie the results of the publication the researcher is referring to in his/her request. Study participants will be asked for their consent to share their coded data upon reasonable request with researchers in other countries.

12.2 Monitoring and Quality Assurance

Monitoring will be performed by the Haga Science Bureau. In addition to the monitoring, periodic evaluations by a group of stakeholders (including patient/public representatives) will take place after every time five patients have been treated at home according to the care pathway. During these periodic evaluations, the group of stakeholders will evaluate

the experiences and outcomes of care, and whether to continue, adjust or stop the use of the care pathway.

12.3 Amendments

Amendments are changes made to the research/protocol after a favourable opinion has been given. All amendments will be notified to the Haga Science Bureau that gave a favourable opinion.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the Haga Science Bureau once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the Haga Science Bureau of the end of the study within a period of 8 weeks. The end of the study is defined as the last contact moment with the last patient.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the Haga Science Bureau.

12.6 Public disclosure and publication policy

The study is registered at the ISRCTN registry (www.isrctn.com) with reference number: ISRCTN68786381. All relevant results will be disseminated through publications in international peer-reviewed journals and presentations at scientific conferences. The study protocol will be published in BMJ Open. The coordinating and principal investigator will be responsible for the publication of the study results, which will be disclosed unreservedly. The principles of generally accepted specifications of authorship shall be followed in the appointing of authors and co-authors. All contributors of articles will have the opportunity to evaluate the final text before submission to a peer-reviewed journal.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Not applicable.

13.2 Synthesis

In paragraph 11.4 of this study protocol, a benefits and risks assessment of this study is performed. All antimicrobial therapy in the care pathway are registered products and already part of the Dutch national guidelines for the treatment of LRTI or pneumonia. Therefore, there are no expected risks due to the therapy for subjects participating in study compared to the risks in normal clinical practice. For this study, paragraph 13.1 is therefore not applicable and additional safety measurements are not indicated.

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