Trials

STUDY PROTOCOL

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The optimal antibiotic treatment duration for community-acquired pneumonia in adults diagnosed in general practice in Denmark (CAP-D): an open-label, pragmatic, randomised controlled trial

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Abstract

Background Use of antibiotics is the main driver of antimicrobial resistance which is considered one of the biggest threats to human health. In Denmark, most antibiotics are prescribed in general practice. Acute lower respiratory tract infections, including community-acquired pneumonia (CAP), are among the most frequent indications for antibiotic prescribing. Phenoxymethylpenicillin is established as first-line treatment in general practice in Denmark. However, the treatment duration with phenoxymethylpenicillin is mostly based on traditions. Both 5 and 7 days of treatment is recommended in Danish guidelines, and when asking the general practitioners about what treatment duration, they prescribe the variation is even bigger. Several hospital-based studies have proven short course (≤ 6 days) antibiotic treatment non-inferior to long course (≥ 7 days) treatment of CAP. No evidence exists on the optimal treatment duration for CAP in non-hospitalised patients.

This randomised controlled trial aim to investigate the optimal treatment duration with phenoxymethylpenicillin for CAP in adults diagnosed in general practice in Denmark.

Methods This is an open-label, pragmatic, randomised controlled, five-arm DURATIONS trial. Participants will be recruited from at least 24 general practices in Denmark. Eligible participants are adults, with no pre-existing lung disease, presenting with symptoms of CAP, and in whom the general practitioner finds it relevant to treat with antibiotics. The study will compare treatment with phenoxymethylpenicillin 1.2 MIE q.i.d. in 3, 4, 5, 6, and 7 days.

Discussion This study will provide evidence for the optimal antibiotic treatment duration of CAP in general practice and inform future guidelines on CAP in all countries using phenoxymethylpenicillin for the treatment of acute respiratory tract infections in adults. The results of this study might also be used to guide treatment recommendations in other countries using phenoxymethylpenicillin.

Moreover, a (potential) reduction in antibiotic use might lower the development of antimicrobial resistance, increase patient treatment adherence, reduce risks of adverse events, and lower the economical exp

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The Scientific Ethics Committee for the North Denmark Region: N-20230039.

Keywords Community-acquired pneumonia, General practice, Antibiotics, Phenoxymethylpenicillin, Treatment duration

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Name and contact information for the trial sponsor {5b}	The Research Unit of General Practice, Aalborg Contact information: +45 2569 9933 Selma Lagerløfs Vej 249 9220 Gistrup
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Introduction

Background and rationale {6a}

Antimicrobial resistance (AMR) is acknowledged by the World Health Organisation as one of the biggest threats to public health [1]. Higher prevalence of AMR could lead to uncontainable infections in primary care subsequently driving increases in hospital admissions and length-of-stay as well as increased mortality. Antibiotic use in humans and animals is the main driver of AMR, hence optimising the amount of antibiotics prescribed is of great importance [2]. In Denmark, about 90% of antibiotic use in humans are prescribed in the primary care sector [3], with general practice accounting for the majority (75%) of these prescriptions [4]. Acute lower respiratory tract infections (LRTI) are one of the most common indications for antibiotic use in general practice [4, 5]. Importantly, it can be hard to differentiate acute bronchitis, a self-limiting viral infection, from community-acquired pneumonia (CAP), a potentially life-threatening condition [2], in a clinical context of limited access to radiology and laboratory examinations. Due to this diagnostic uncertainty, many prescribers may tend to err on the side of caution and as a result many LRTI patients are treated with antibiotics in general practice [6].

Monotherapy with phenoxymethylpenicillin is established as first-line treatment of CAP in Danish general practice. Recommendations are based on knowledge on *Streptococcus pneumoniae* being a common bacterial pathogen causing CAP [7–9] and the very low prevalence of penicillin resistance in pneumococci in Denmark. However, there is no consensus regarding the duration of antibiotic treatment with phenoxymethylpenicillin as both 5 and 7 days of treatment are recommended in Danish guidelines [10–12]. A recent Danish study have demonstrated significant differences in the treatment duration used for CAP by Danish general practitioners (GPs): 55% treating for 5 days and 34% for 7 days [13]. Importantly, most treatment regimens are based on traditions rather than solid evidence [13].

Several studies have documented that short-course (i.e. ≤ 6 days) antibiotic treatment is equal to long-course (i.e. ≥ 7 days) treatment in hospitalised patients diagnosed with CAP [14–18]. A recent study by Dinh et al. found that 3 days of treatment with oral amoxicillin with clavulanate for stable hospitalised patients was as efficient as treatment for 8 days [19]. However, no evidence exists on the optimal antibiotic treatment duration among non-hospitalised patients [20].

Objectives {7}

Research hypothesis

Most likely, patients diagnosed and treated in general practice have a milder disease course than hospitalised patients. We hypothesised that 3 days of treatment with phenoxymethylpenicillin will be as efficient as current recommended treatment durations.

Primary objective

To access the optimal treatment duration with phenoxymethylpenicillin for CAP in adult patients diagnosed in Danish general practice

Trial design {8}

The Community-Acquired Pneumonia DURATION (CAP-D) trial is an open-label, pragmatic, randomised controlled, multicentre, DURATIONS trial with a five-group parallel design [21]. The DURATION design involves investigating multiple treatment durations at once and gaining statistical efficiency (i.e. higher power compared to comparing treatment durations in a discrete manner) by modelling the so-called duration-response curve using fractional polynomial regression methods [21]. The DURATION design is based on a non-inferiority framework.

Methods: Participants, interventions, and outcomes

Study setting {9}

The trial is anchored at the Center for General Practice at Aalborg University, Denmark.

From November 2023 to December 2024, participants will be recruited from at least 24 Danish general practices. The general practices are located in four out of five regions in Denmark: the North Denmark Region, Central Denmark Region, Region of Southern Denmark, and Region Zealand.

Eligibility criteria {10}

All eligible participants must provide a written informed consent before being enrolled in the study.

Inclusion criteria

Eligible participants are adults (≥ 18 years) presenting in general practice with symptoms of an acute LRTI (i.e. acute illness (≤ 21 days) usually with cough and minimum one other symptom such as dyspnoea, sputum production, wheezing, chest discomfort, or fever [22]) in whom the GP finds it relevant to treat with antibiotics.

Exclusion criteria

1. Need for immediate hospitalisation at the time of diagnosis
2. Known allergy to beta-lactam antibiotics
3. Any coinfection necessitating antibiotic treatment
4. Use of systemic antibiotics or antivirals within the last month
5. Pre-existing lung disease (e.g. chronic obstructive pulmonary disease, bronchiectasis, asthma, lung cancer)
6. Known immunosuppression (i.e. long-term treatment with corticosteroid, chemotherapy, or immune disorder)
7. Pregnant or lactating
8. Patients not capable of consenting and/or patients deemed non-suitable for participation by the healthcare professional

Who will take informed consent? {26a}

Relevant participants will be identified during the consultation in general practice.

If the participant meets all the inclusion criteria and none of the exclusion criteria, the GP will provide both oral and written information about the trial. The participants will be informed orally about their right to a lay representative and the right to use some time to think it over—before consenting to participation. Importantly, it will be underlined that consent can be withdrawn at any time without any reason. Two separate consents will be obtained by the GP—one for participation in the study and one for collecting data from Shared Medication Record. However, the time of reflection is limited as CAP is an acute condition and treatment must be initiated immediately. As the study medicine equals standard treatment for CAP—regarding dose and interval—the treatment duration can be prolonged for the short treatment arms if deemed necessary by the consulting GP. This provides all participants a minimum of 3 days to rethink their participation in the trial—without influencing the standard treatment regime for CAP.

The participant will be provided information in accordance with 'guidelines for oral consent' from *The Scientific Ethics Committee for the North Denmark Region*.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Participants will be informed about the storage and use of their data for future research on CAP. The data will be anonymised after complete data collection and deleted 10 years after last publication.

Interventions

Explanation for the choice of comparators {6b}

Previous studies have either included both hospitalised and non-hospitalised patients, compared different types and doses of antibiotics, and/or examined antibiotics no longer available for human use [20]. Also, none of the previous studies have tested the use of phenoxymethylpenicillin. The choice of using different treatment durations with phenoxymethylpenicillin (same dose and administration frequency) as comparator is therefore justified.

Intervention description {11a}

Consenting patients who meet all the eligibility criteria will be randomised (1:1:1:1:1) to either 3, 4, 5, 6, or 7 days of treatment with phenoxymethylpenicillin 1.2 MIE four times daily (Fig. 1). Stratification will be performed to balance the randomisation. The covariates included in the stratification will be age (≥ / < 65 years) and recruitment site. The randomisation will be performed directly in the Research Electronic Data Capture (REDCap®) system by the GP.

The study medication package will contain between 12 and 28 tablets with phenoxymethylpenicillin 1.2 MIE: four tablets for each day. The medication package will be distributed to the patient directly from the GP. The packages will be prepared by the pharmacy at the Aalborg University Hospital. As phenoxymethylpenicillin should be administered four times daily, most participants will take one to three tablets at the day of the consultation (day 0). Participants will be instructed to take remaining tablets for day 0, at the last day of their respective treatment regimens (e.g. if randomised to 3 days of treatment at 1 p.m., the participant should take two pills at day 0, full dose at days 1 and 2, and two pills at day 3).

Criteria for discontinuing or modifying allocated interventions {11b}

Each participant is expected to participate in the trial for 30 days (Fig. 1). The trial will stop on the 38th day of the last enrolled participant to make sure all included participants have a minimum of 30 days, after ended treatment, to report any adverse events (AE). The sponsor (the Research Unit for General Practice in Aalborg) remains the right to end the trial at any time due to *safety concerns*. If the trial is ended prematurely, the sponsor is responsible for informing all participants and plan adequate follow-up.

Discontinuation from the trial could occur due to the following reasons:

- Withdrawn consent
- Other violations of the protocol

The participants will be informed that they are not obliged to provide a reason for discontinuation. If an AE is a contributory factor to the discontinuation, it must be followed up appropriately. Regardless of any discontinuation, the participants should, if possible, be retained in the study for follow-up. Data until discontinuation will be included in the analyses. No leaving participants will be replaced by new participants. If an exclusion criterion is met during the 30 days follow-up period, it will not automatically lead to discontinuation. In most cases, ongoing treatment will be paused, and an individual assessment will be performed by a medical doctor.

Strategies to improve adherence to interventions {11c}

To improve adherence to the intervention, the antibiotics is provided to the participant for free and is handed out from the general practice site. The participant receives the exact number of tablets needed based on the allocated treatment duration. It is a pragmatic trial, which is why no further adherence-enhancing strategies are planned.

Relevant concomitant care permitted or prohibited during the trial {11d}

The GPs are instructed to provide the usual care to the participants including relevant safety netting.

Provisions for post-trial care {30}

The participating patients are covered by the Danish Patient Compensation Association, as the consultations are performed by authorised health care professionals.

Outcomes {12}

The primary outcome measure is the proportion of participants experiencing *treatment failure* at day 30.

Treatment failure is defined as any hospitalisation *OR* change in the antibiotic strategy (i.e. prolongation of the duration, change in antibiotic type, new antibiotic prescription) due to symptoms of acute respiratory tract infection—between randomisation and day 30.

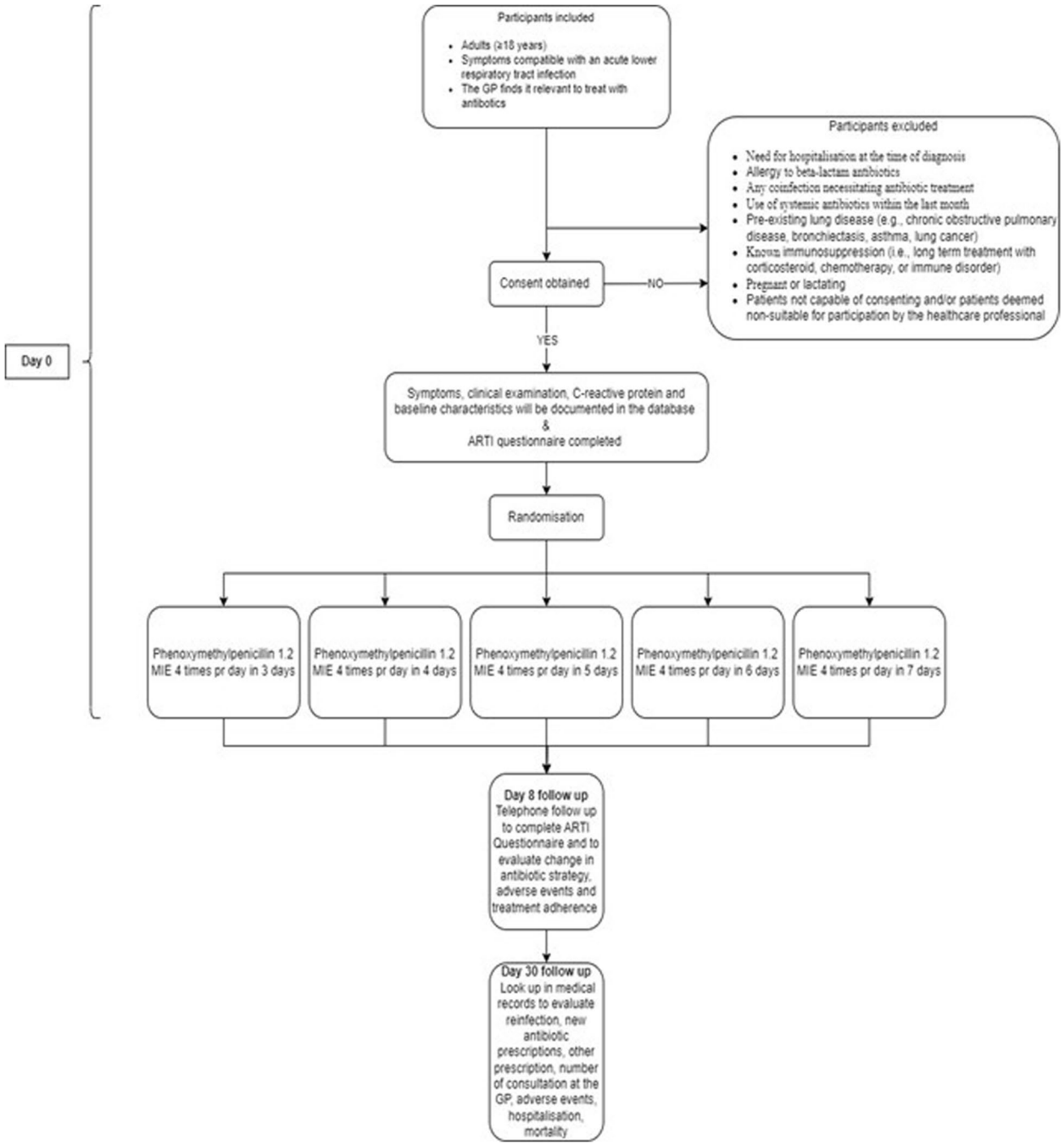

Fig. 1 The participant timeline. The eligible, consenting participants are enrolled in general practice at day 0. Baseline data will be obtained before randomisation to one of five treatment durations. Furthermore, the participants will receive the Acute Respiratory Tract Infection Questionnaire by e-mail at day 0. Follow-up consists of a telephone interview at day 8 and a look up in the medical records at day 30. The participants are part of the trial for 30 days

Secondary outcomes measures include:

Symptoms and daily activities

Clinical recovery at day 8. Clinical recovery is defined as:

The participant scores below a pre-defined cut-off point for being recovered at the Acute Respiratory Tract Infection Questionnaire (ARTIQ) OR reports feeling recovered by themselves

AND

The participant is no longer treated with any antibiotics.
The ARTIQ score at index consultation and day eight.

A total sum for each dimension will be calculated. Each symptom will be scored on a three-point scale: "No", "Yes – some" or "Yes – a lot". Ten items are dichotomized (Yes or No) [23].
The total ARTIQ score is calculated as the sum of each dimension [23].

- *Illness deterioration and complications*

Proportion of participants in need of prolonged antibiotic treatment (i.e., continuing antibiotic treatment longer than seven days of duration).
Proportion of participants who had prescribed another type of antibiotic within 30 days.
Proportion of participants with relapse of acute LRTI within 30 days.
Number of reconsultations in general practice or out-of-hour (OOH) services within 30 days.
Prescriptions of new medication within 30 days (e.g., bronchodilator, prednisolone, mucolytics etc.).
Hospitalisation within 30 days (yes/no).
All-cause mortality at day 30.

- *Adverse events and adherence*

Any reported adverse events or serious adverse events.
Adherence to medication [24]

Initiation: Days until intake of initial dose of the prescribed medicine.
Implementation: Number of missed doses per day.
Discontinuation: Days from initiation until the intake of the last dose of the prescribed medicine.

Participant timeline {13}

The participant timeline is shown in Fig. 1. A schematic diagram with the time schedules for enrolment, interventions, and assessments is shown in Fig. 2. Eligible participants are identified and included in general practice. Consenting participants will be randomised to the various treatment durations with phenoxymethylpenicillin. Baseline data will be documented in an electronic case report form in REDCap® (see the " Plans for assessment and collection of outcomes {18a}" section). Furthermore, all participants are asked to complete the Acute Respiratory Tract Infection Questionnaire (ARTIQ) [23] at the day of randomisation.

At day 8, a follow-up telephone consultation will be performed with each of the participants by a member of the research team (EJ). Symptoms presented at the index consultation will be re-evaluated—and the ARTIQ completed again. Any change in antibiotic strategy will be registered. The participant will be asked to report time of initiating and ending intake of tablets and the number of missed doses per day (i.e. number of remaining tablets for each day). Furthermore, potential adverse events will be evaluated. The research team member will rate the likelihood of the reported event for coherence (i.e. unlikely, potential, likely) and the severity of the infection (mild, moderate, severe).

At day 30, a member of the research team (EJ) will evaluate the medical record for each participant. The evaluation will be performed in general practice and will not necessitate participation from the participant.

Sample size {14}

We aim to randomise 600 participants in total across five treatment arms (120 participants per duration). This number is based on an assumed treatment success rate of 90% (i.e. 10% treatment failure rate) for those allocated to the 7-day duration, an absolute non-inferiority margin of 10%, and a one-sided alpha of 0.025 (i.e. we will conclude non-inferiority of a given duration if the limit of the one-sided 97.5% CI for the absolute % increase in treatment failure rate compared to 7 days does not include 10%) and is inflated to account for 10% drop-out.

We estimated the optimal power (i.e. the probability that the trial ends up identifying the actual optimal duration) and acceptable power (i.e. the probability that the trial ends up identifying an effective duration that is shorter that the maximum) via simulation, fixing the design (in terms of number of arms and spacing between

	STUDY PERIOD										
	Enrolment	Allocation	Post-allocation								Close-out
TIMEPOINT (day)	**0**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**30**
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Randomisation		X									
INTERVENTIONS:											
3 days Phenoxymethylpenicillin			♦	—	—	♦					
4 days Phenoxymethylpenicillin			♦	—	—	—	♦				
5 days Phenoxymethylpenicillin			♦	—	—	—	—	♦			
6 days Phenoxymethylpenicillin			♦	—	—	—	—	—	♦		
7 days Phenoxymethylpenicillin			♦	—	—	—	—	—	—	♦	
ASSESSMENTS:											
[Baseline variables as outlined in the protocol]	X										
[Acute Respiratory Tract Infection Questionnaire]	X									X	
[Telephone follow-up: Reevaluation of symptoms Change in antibiotic strategy Treatment adherence Hospitalisation Mortality Adverse events]										X	
[Medical record follow-up: Change in antibiotic strategy Number of contacts to primary care Hospitalisation Mortality Adverse events]											X

The schedule of enrolment, interventions, and assessments.

Fig. 2 The schedule of enrolment, interventions, and assessments

arms, alpha, estimated treatment success rate, and non-inferiority margin). Our analytical model in our simulations assumed a binomial distribution for our event rate and a fixed-2 fractional polynomial for our 'durations' trial arm. We estimated standard errors initially using the delta method (1000 simulations) and subsequently with bootstrapping (100 simulations owing to the computational intensity of bootstrapping a high number of samples).

Using the delta method to estimate confidence intervals, our simulations demonstrated that optimal power would be 0.79 and acceptable power would be 0.99 under these assumptions. Using bootstrapping, our simulations demonstrated optimal power at 0.80 and acceptable power at 0.98.

To identify subgroups of patients, with a potential need for a different treatment duration, various covariates will be considered. Covariates included will be multimorbidity, age, and C-reactive protein (CRP) value. These variables will be treated as both categorical and continuous. A full description of the explicit exploratory analysis of subgroups will be stated in the statistical analysis plan (SAP).

Recruitment {15}

The initial recruitment of participating general practices took place between 1 June 2023 and 31 December 2023. However, due to slower patient recruitment rate than anticipated, additional general practices were recruited between 1 August 2024 and 31 September 2024.

The following recruitment strategi was used:

- Phone call to general practices asking for e-mail address for GP(s)
- Introductory e-mail—informing briefly about the project
- Follow-up phone call
- Introduction meeting
- Social media (e.g. Facebook, LinkedIn etc.) was used to make the project visible

CAP is an acute infection needing immediate treatment. Consequently, it is not possible to plan for additional time for inclusion of patients within the general practice setting. To promote optimal pace of recruitment of patients, the following strategies will be applied:

1. General practices are encouraged to perform data entry, randomisation, and handing out medicine after the initial consultation/outside the consultation room—perhaps done by practice staff
2. Handout of a direct phone number to project lead to answer any questions and to support data entry in the data capture program (REDCap)
3. Monthly e-mails to the GPs with information about, e.g. recruitment status, and feedback on how to improve recruitment and data quality

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be randomly allocated to one of the five treatment arms with a 1:1:1:1:1 allocation as per a computer-generated allocation sequence. The randomisation will be stratified by recruitment site and age (< / ≥ 65 years). The allocation sequence is generated using Microsoft Excel.

Concealment mechanism {16b}

The generated allocation sequence is prepared and entered in the eCRF by a member of the research team (EJ) not directly involved in recruitment. The allocation sequence remains concealed until last participant is enrolled.

Implementation {16c}

The allocation sequence will be prepared by a member of the research team, whereas enrolment of participants and assignment to interventions will be conducted by GPs and practice staff at the various recruitment sites.

Assignment of interventions: blinding

Who will be blinded {17a}

As the study is open-labelled, participants and GPs will not be blinded to the intervention. Data analysts will be blinded to the intervention until final data analyses have been conducted.

Procedure for unblinding if needed {17b}

As both participants and GPs are not blinded to the intervention, a procedure for unblinding is not applicable for this trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Baseline characteristics

The GP will obtain baseline information about the participant and register symptoms reported by the patient at the day of randomisation (day 0).

> Baseline information: age, gender, comorbidities, smoking status (yes/no), pneumococcal and/or influenza vaccination (yes/no)
> Symptoms of LRTI: cough, dyspnoea, sputum production, chest discomfort, fever, other symptoms

Furthermore, a clinical examination (i.e. vital signs and lung auscultation) and a point-of-care CRP test will be performed at the index consultation. GPs will be asked to assess the severity of the lung infection using the CRB65 score [12]. Data are entered in REDCap®.

Patient reported data

Participants will be asked to complete the Acute Respiratory Tract Infection Questionnaire [23] (ARTIQ) twice: at day 0 and during a telephone interview at day 8. The ARTIQ is a validated, self-administered, multidimensional, sum-scaling symptom score monitoring the severity and functional impact of acute respiratory tract infections in general practice. The questionnaire is validated in Danish [23]. The questionnaire consists of five single items and 38 items covering five independent dimensions: upper respiratory tract symptoms, lower respiratory tract symptoms, physiological, sleep, and medicine [23]. The item 'taken antibiotics' will be excluded from the questionnaire as all participants receive antibiotics due to the intervention.

The questionnaire will be sent automatically to the participant (via e-mail) at the day of randomisation and at day 8 after randomisation.

Follow-up

At day 8 after randomisation, a follow-up telephone consultation will be performed by a member of the research team (EJ). The symptoms presented at day 0 will be re-evaluated and the ARTIQ completed again. The participants will be asked if they feel fully recovered and, if they do, for how many days. Any change in antibiotic strategy will be registered. The participant will be asked to report time of initiating and ending intake of tablets and the number of missed doses per day (i.e. number of remaining tablets for each day). Furthermore, potential adverse

event will be evaluated. The research team member will rate the likelihood of the reported event for coherence (i.e. unlikely, potential, likely) and the severity (mild, moderate, severe). The data collection form is attached in the appendix.

Data from medical records

The medical records including the Shared Medication Record (i.e. in Danish 'Fælles Medicin Kort') of all enrolled participants will be evaluated at each study site. The Shared Medication Record is a database at the Danish Health Authority, storing data on all Danish citizens' medication plans, electronic prescriptions, and medicine purchases. The evaluation will be performed at day 30 of the last enrolled participants at each study site. The participants will be informed about this before consenting to the project.

The following data will be obtained from the medical records for each participant (from day 0 to 30 after randomisation):

New prescriptions of antibiotic(s)
Prolongation of antibiotic prescriptions
Number of consultation(s) at a general practice and/or out-of-hour service due to infections related to the respiratory tract system
Hospitalisation(s)
Mortality

Data will be obtained by an independent investigator of this research project. Data will be entered directly into the e-CRF at the study sites (general practice). A staff member (e.g. a secretary, nurse, or GP) from the specific study site (general practice) will conduct the data extraction from the Shared Medication Record.

Plans to promote participant retention and complete follow-up {18b}

The participants must contribute actively by answering the ARTIQ at days 0 and 8 as well as answering a few questions at the telephone interview at day 8. All other data collections are performed without active involvement of the participant. To promote the response rate of the questionnaire, the participants are asked to complete it immediately after the index consultation at the GP. Participants who do not have access to an e-mail will be handed a paper-based questionnaire by the GP. These questionnaires will be collected and stored at the recruitment sites. At the follow-up at day 8, the interviewer will remind the participants to complete the ARTIQ again. If needed, the ARTIQ can be completed during the telephone interview guided by the researcher.

Data management {19}

Data will be entered into standardised patient-specific e-CRF provided by REDCap®, which is a secure electronic platform for building and managing online surveys and databases used by Aalborg University [25]. To enhance data quality, field validation is used. Furthermore, all new data is checked once a week by a member of the research team, and any irregular data will be discussed with the specific investigator responsible for the data entry.

Confidentiality {27}

All study-related data will be handled in accordance with the Danish General Data Protection Regulation (GDPR). Data will be stored at secure servers at Aalborg University, Denmark. In REDCap®, data which potentially can identify individual participants will be marked as 'identifier' allowing no export of this information after finalising enrolment.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This is not applicable as no biological specimens will be collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary research question is as follows: in adult patients (≥ 18 years) diagnosed with CAP in general practice, what is the absolute difference in the proportion who experience treatment failure within 30 days after randomisation in those prescribed 3, 4, 5, 6, and 7 days of phenoxymethylpenicillin treatment?

Therefore, our primary estimand is defined by the following attributes:

- Population: adults (age ≥ 18 years) presenting to their GP with symptoms of pneumonia whom the GP finds relevant for treatment with phenoxymethylpenicillin
- Outcome/variable of interest: treatment failure within 30 days defined as hospitalisation or any change in antibiotic strategy due to symptoms of respiratory tract infection. As change in antibiotic strategy is incorporated in the outcome, a potential intercurrent event (ICE) is handled (composite strategy)
- Treatment condition: phenoxymethylpenicillin, tablet 1.2 MIE four times daily for either 3, 4, 5, 6, or 7 days

Table 1 Overview of analyses for secondary outcomes

Outcome	Variable type	Analysis—regression model
Clinical recovery at day 8	Binary	Logistic
Total ARTIQ score day 0	Continuous	Linear
Total ARTIQ score at day 8	Continuous	Linear
Proportion of participants in need of prolonged antibiotic treatment	Binary	Logistic
Proportion of participants in need of another type of antibiotic	Binary	Logistic
Proportion of participants with reconsultations to general practice or out-of-hour services	Binary	Logistic
Hospitalisation within 30 days	Binary	Logistic
All-cause mortality within 30 days	Binary	Logistic
Adverse events	Binary	Logistic
Treatment initiation, days until initiation	Continuous	Linear
Treatment implementation, number of missed doses	Count	Poisson
Treatment persistence, days until treatment termination	Continuous	Linear

- Remaining ICEs:
    - Discontinuation of randomised treatment for any reason (e.g. hospitalisation, death, non-response, adverse events, withdrawn consent, etc.)
    - Lost to follow-up due to withdrawn consent
    - Change in medicine administration strategy: missed intake of dose(s), delayed initiation of intake, prescription of additional types of medicine (excl. antibiotics)

The remaining ICEs is handled by using a treatment policy strategy. Further details on this are given in the SAP.

- Population-level summary: adjusted risk difference between 7 days of phenoxymethylpenicillin to each of the other shorter durations
- Rationale for estimand: to define the optimal treatment duration with phenoxymethylpenicillin for CAP diagnosed in general practice

Prior to enrolment of the last trial participant, a SAP specifying the statistical evaluation of the data will be published.

For the primary analysis, duration-response curves will be estimated using a logistic regression, treatment duration (i.e. 3, 4, 5, 6, and 7 days) parameterised as a fixed-2 fractional polynomial [21, 26, 27]. Our model will adjust for recruitment site and age $\geq$ / $<$ 65 years in the duration-response curves. Bootstrapping will be used to estimate 95% confidence intervals around the absolute difference in response between each duration and the longest duration. Bootstrapped confidence intervals will be used to identify the shortest duration non-inferior to the longest duration, with respect to the non-inferiority margin.

The non-inferiority margin is an absolute margin of 10% with a one-sided alpha of 0.025.

The secondary outcome will be analysed depending on the variable type (Table 1). Binary outcomes will be analysed using logistic regression, continuous outcomes using linear regression, and count outcomes using Poisson regression or negative binomial regression in the event of overdispersion (Table 1). We will adjust for recruitment site and age $\geq$ / $<$ 65 years. Treatment duration will be similarly parameterised as a fixed-2 fractional polynomial. Results will be presented as per the primary analysis.

Interim analyses {21b}

No interim analysis will be performed.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Sub-group analysis will be performed to determine if the optimal treatment duration differs depending on the following sub-groups:

- Participants aged $<$ / $\geq$ 65 years
- Participants with a CRP $<$ 50 mg/L; CRP 50–99 mg/L; CRP $\geq$ 100 mg/L
- Multimorbidity (yes/no)

These variables will be treated as both categorical and continuous—if possible. A full description of the explicit exploratory analysis of subgroups will be stated in the SAP.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

We expect missing data for the primary outcome to be low. The primary outcome will be evaluated by an evaluation of the medical records at day 30; hence, only withdrawing of the consent for participation will lead to missing data for this outcome. Baseline characteristics will be summarised for all treatment arms, depending on if the primary outcome is available or missing. A logistic regression model will explore any association between each baseline characteristic and the availability of the primary outcome. Our approach to handling missing data will depend on the exact pattern of missing data but may include data imputation approaches (e.g. multiple imputation).

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The sponsor and research team will have access to the full dataset. Participating GPs will only be able to view data originating from their own study sites while recruiting. The datasets, statistical code, and full protocol are available from the corresponding author on reasonable request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The primary investigator (EJ) will be scientifically responsible and responsible for the communication internally in the trial steering committee. The day-to-day running of the trial will rely on the primary investigator with support from the main supervisor (MH). Weekly meeting will be held with the main supervisor. The trial steering committee will consist of all the Ph.D. supervisors. The trial steering committee will meet monthly.

Composition of the data monitoring committee, its role and reporting structure {21a}

The study is deemed to be a low-risk study due to the intervention being within the boundaries of what phenoxymethylpenicillin is already approved for in Denmark. Therefore, the risk and harms of the intervention is low, waiving the need of a data monitoring committee. However, to enhance the data quality, a monitoring committee consisting of one member of the research team—not directly involved in data management—and two external researchers will conduct a data quality assessment at two timepoints (i.e. when 200 and 400 participants have been recruited, respectively) during the recruitment period.

Adverse event reporting and harms {22}

All participants will be informed in both oral (by the GP) and written (the patient information leaflet) form about safety issues. Participants are informed that if symptoms worsen or fail to improve, they need to contact the GP/OOH service immediately. This approach is in line with usual management of patients with acute LRTI symptoms in general practice.

All participants will be informed by the GP to take contact to a physician if experiencing any potential adverse events. Furthermore, participants are informed to declare that they are participating in a clinical trial if contacting any other healthcare professionals.

Adverse events

The use of phenoxymethylpenicillin is authorised in Denmark and is, in the present clinical trial, planned to be used in accordance with the terms of the marketing authorisation. As AE for phenoxymethylpenicillin are well known, not serious adverse events (SAE) must be handled in accordance with standard practice. Furthermore, the risk of SAE is low.

When assessing AEs and SAEs, the GPs will refer to the summary of product characteristics. All potential AE will be evaluated regarding expectedness, severity, and causality by all members of the research team.

Potential AEs or SAEs will be treated according to standard practice, and relevant follow-ups will be scheduled with relevant healthcare professionals.

Reporting

SAEs will be reported by the GPs and reviewed by the research team and the sponsor. Both the sponsor and the primary investigator must be notified of SAE via e-mail or phone within 24 h. All SAE must be reported to the regional ethical committee within 7 days. The sponsor is obligated to perform an annual subject safety report and submit it to the regional scientific ethical committee.

Frequency and plans for auditing trial conduct {23}

Regular monitoring will be conducted—both of data entered in REDCap® and by site visits. This is done in accordance with the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) to ensure that the trial is conducted in compliance with the protocol and that relevant consent procedures are fulfilled.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any potential important protocol modifications will be discussed within the research team. If amendments are made, it must be (1) approved by *the Scientific Ethics Committee for the North Denmark Region*, (2) communicated to the funding agencies, and (3) listed in the final publications with the main results of the CAP-D study.

Dissemination plans {31a}

The results of this study will be published in international, peer-reviewed, medical journals.

Also, we plan to inform the public about the results of this study via Danish press and media. Furthermore, the study will be presented at both national and international conferences. Authorships are agreed on within the research team—and specified in the PhD protocol for the project lead (EJ).

Discussion

Trials testing pharmaceutical treatments in general practice are relatively rare in general practice in Denmark. Consequently, the set-up regarding for example enrolment, randomisation, and data entry in general practice is relative naive, hence resulting in some challenging processes. This situation combined with a lower recruitment rate than first anticipated has led to an extended recruitment period (i.e. from 5 months to about a year). However, this extended recruitment period will provide participants from all four seasons in the year, likely strengthening the generalisability of the results.

Trial status

Protocol version 3; 16 April 2024. In November 2023, the first participant was included. However, all recruitment sites were not active until January 2024. As of May 2024, 168 participants have been enrolled. Recruitment is ongoing and is expected to be completed by end of March 2025.

Abbreviations

AMR	Antimicrobial resistance
LRTI	Lower respiratory tract infection
GP	General practitioner
REDCap	Research Electronic Data Capture
AE	Adverse event
SAE	Serious adverse event
OOH	Out-of-hour
CRP	C-reactive protein
CRB65	Confusion, respiratory rate, blood pressure, age ≥ 65 years
SAP	Statistical analyses plan
ARTIQ	Acute Respiratory Tract Infection Questionnaire
ICE	Intercurrent event
GDPR	General Data Protection Regulation

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No acknowledgements to declare.

Authors' contributions {31b}

EJ is the primary investigator and has led the development of the protocol as part of his Ph.D. study at the Research Unit of General Practice in Aalborg. All other authors are supervisors of the Ph.D. study—MH is main supervisor—and have all contributed to protocol development and revising. DG is a statistician and has experience in working with the DURATION design. All authors approved the final manuscript.

Funding {4}

The four Research Units for General Practice in Denmark are funded by the Danish Research Foundation of General Practice, established by the Danish Organisation of General Practitioners (PLO) and the Danish Regions. However, most projects conducted at the research units are funded by external sources. The primary investigator (lead of the project) Eskild Johansen is employed as a PhD student at the Research Unit for General Practice in Aalborg.
Two grants for this specific trial have been[DH1] granted from the Danish Research Foundation for General Practice - 212,500 DKK and 114,000 DKK—covering some of the salary of the primary investigator as well as some operating costs. In addition, the project has been granted 50,000 DKK from the A.P. Moller Foundation—for covering operating costs. Furthermore, three grants have been received covering the honorary of the GPs at the recruitment sites (i.e. approximately 600 DKK per included participant)—100,000 DKK from the Quality Unit for General Practice in the Northern Denmark Region (Nord-KAP), 100,000 DKK from the Quality Unit for General Practice in the Southern Denmark Region (Syd-KAP), and 70,000 DKK from the Committee of Multipractice Studies in General Practice (MPU). Copies of the grant notification letters and English translations have been attached. [DH1]LE: All decimal commas in the "Funding" section were changed to decimal points. Please check if the action taken is correct/appropriate. Otherwise, amend if deemed necessary.

Availability of data and materials {29}

The sponsor (the Research Unit of General Practice in Aalborg) and members of the research team with a data processing agreement will have full access to the final dataset. The final dataset will be stored at a secure server at the Aalborg University for 10 years before deletion. Any data required to support the protocol can be supplied on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate {24}

The study protocol is approved by *The Scientific Ethics Committee for the North Denmark Region* (N-20230039). The original approval was until April 2024, and extension of the recruitment period until March 2025 has been approved. The final approval and an English translation for both the original approval and the extension have been attached. All participants will receive oral and written information before consenting to participation. Written, informed consent will be obtained for both participation and for obtaining information from Shared Medical Record.

Consent for publication {32}

Not applicable—no personal identifiable data of participants will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on reasonable request.

Competing interests {28}

The authors declare no competing interests.

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