Statistical Analysis Plan (SAP)

LOw-dose CT Or Lung UltraSonography versus standard of care based-strategies for the diagnosis of pneumonia in the elderly: protocol for a multicentre randomised controlled trial

(OCTOPLUS)

Administrative information

Version	**1.8**
Date	16.12.2025
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Reviewer	Christophe Combescure
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Study information

Title of the study	**LOw-dose CT Or Lung UltraSonography versus standard of care based-strategies for the diagnosis of pneumonia in the elderly: protocol for a multicentre randomised controlled trial**
Principal Investigator (PI)	Virginie Prendki
Trial registration number	NCT04978116 (ClinicalTrials.gov)
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Study type (ClinO)	ClinO-Other (other clinical trials)
Risk category	A

Version history:

Version	**Date**	**Reason for revision**
1.8	Dec 16, 2025	Clarification of block sizes used for randomization
1.7	Nov 17, 2025	Revisions following co-investigators review
1.6	Oct 13, 2025	Minor revisions following co-investigators feedback
1.5	Oct 6, 2025	Completion of the initial SAP draft
1.4	Sept 9, 2025	Revision according to 5th of September meeting
1.3	July 7, 2025	Revision according to 4th of July meeting
1.2	June 30, 2025	Work in progress

Approved by:

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Contents

1. SAP scope and drafting timeline

The current version was written and finalized after patient enrollment and before data analysis is started.

Scope of the current SAP: The current SAP specifies all statistical methods to be used for the analysis of the trial data, including analysis populations, endpoint definitions, handling of missing data, and planned statistical tests for primary and secondary outcomes. It complements the trial protocol, ensures that analyses are predefined before database lock, and applies only to analyses described herein.

The ancillary studies 'Gerobiota' and 'CIRCUS', along with the costs analyses and the association between biological markers and adjudicated pneumonia on the 3-level scale, will be addressed in a dedicated statistical analysis plan. These components fall outside the scope of the present document.

2. Introduction

2.1 Background and rationale

- **Epidemiology and Diagnostic Challenges**
  - By 2050, 1 in 4 people in Europe and North America will be aged 65+.
  - Pneumonia disproportionately affects older adults; in Germany, 2/3 of hospitalized pneumonia patients were over 70.
  - Pneumonia is the leading cause of antibiotic prescriptions in the elderly.
  - Diagnosing pneumonia is challenging due to overlapping symptoms with other conditions (e.g., heart failure, COPD, pulmonary embolism, lung cancer).
  - **Chest X-ray (CXR)** has poor sensitivity and specificity in older patients, often due to comorbidities.

- **Emerging Imaging Strategies**
  - **Low-dose CT (LDCT)** shows improved diagnostic accuracy:
    - In a prior study, CT modified pneumonia diagnosis in 59% of patients.
    - Net Reclassification Improvement (NRI) was 18%.
  - LDCT is promising in elderly patients, given poor quality of CXR and diagnostic uncertainty.
  - A Dutch RCT is evaluating LDCT's impact on antibiotic use and patient safety.
  - **Lung ultrasonography (LUS)** is bedside, non-irradiating, with sensitivity 80–90%, specificity 70–90%.
    - Outperforms CXR in some studies using CT as reference.
    - Evidence in the elderly remains limited.

2.2 Objectives

Primary objective is to evaluate whether a diagnostic strategy using **LDCT** compared with **CXR** leads to a more accurate diagnosis in elderly patients with suspected pneumonia in the emergency room (ER). We hypothesise that an LDCT-based diagnostic strategy will have better accuracy than the standard of care CXR-based strategy for the diagnosis of pneumonia in elderly patients admitted to the ER.

Secondary objectives
To assess the difference in diagnostic performance and clinical outcomes for patients with suspected pneumonia using LUS compared to CXR, and using LUS compared to LDCT.

3. Study methods

3.1 Design

Swiss multicentre superiority randomized clinical study with 3 parallel arms.
Involved centres were Geneva, Bern, Lugano

Each patient was randomly allocated in the ER to one of the three imaging examination (CXR, LDCT or LUS). Imaging examination was immediately performed, interpreted by one independent

radiologist (CXR)
radiologist (LDCT) – different from the radiologist interpreting (CXR)
trained emergency physician (LUS)-different from the physician in charge of the patient

The **physician in charge** of the patient had access to the imaging examination and the corresponding report, in addition to usual clinical and biological data obtained in the diagnostic workup of suspected pneumonia; he/she **was asked to assess the probability of pneumonia before the patient is discharged from the ER**.
For each patient, **the other two imaging examinations were also performed** and interpreted as described above, **but the physician in charge of the patient was blinded to these results**.
The 3 imaging examinations were performed within the first hours of ER admission.

3.2 Randomization

Patients were randomised immediately after inclusion in one of the three arms (CXR, LDCT, LUS). Randomisation was performed using REDCap tool with a 1:1:1 ratio, stratified by centre and using permuted block sizes of 3 or 6.

3.3 Outcomes

We present here a summary of the study outcomes. For detailed definitions of the outcomes, see chapter *8.1 Outcome definitions*.

3.3.1 Primary outcome

The primary outcome is the **accuracy** of the clinician's diagnosis using the experts' diagnosis as reference.

3.3.2 Secondary outcomes

The following **additional diagnostic performance measures** were planned to be evaluated

- Sensitivity (Se)
- Specificity (Sp)
- Positive Predictive Value (PPV)
- Negative Predictive Value (NPV)
- Positive Likelihood Ratio (PLR)
- Negative Likelihood Ratio (NLR)

Secondary outcomes consisted in diagnosis, treatment and clinical outcomes.

Diagnosis outcomes

- Unmasked imaging modalities in emergency
- Alternative diagnoses
- Diagnosis of aspiration pneumonia (yes/no)
- Type of pneumonia (viral/bacterial)
- Additional imaging studies ordered

Treatment outcome

- Antibiotic free days

Clinical outcomes

- Time to clinical stability
- Hospital admission
- Length of hospital-stay
- ICU admission
- Transfer to rehabilitation or long-term care facility (LTCF)
- All-cause ICU readmission
- In-hospital mortality
- All-cause mortality at 30 days and at 90 days
- Quality of life at 30 days and at 90 days

3.4 Timing of outcome assessments (timepoints)

Timeline of patient enrolment/allocation, interventions and assessments

Study periods	Screening	Randomisation	Discharge from ER	Discharge from the acute setting	Day 30	Day 90	Reference diagnosis
Visit	1	2	3	4	5	6	7
Time (hour, day)	hr0	hr2*	hr6*	dx	d30	d90	
Demographics	x						
Medical history	x						
Inclusion/exclusion criteria	x						
Physical examination	x						
Vital signs	x						
Laboratory tests	x			x			
CXR, LDCT, LUS		x					
Main diagnosis before ER discharge			x				x
Other diagnosis outcomes			x	x			x
Number of antibiotic free days					x		
Clinical, safety and cost outcomes				x	x		
Readmission and mortality					x	x	
QoL questionnaire				x	x	x	
Panel of experts							x

*Approximately.
CXR, chest x-ray; d, day; ER, emergency room; hr, hour; LDCT, low-dose CT; LUS, lung ultrasonography; QoL, quality of life.

3.5 Sample size, null and alternative hypothesis

The final recruitment objective was 165 patients in each arm, for a total of 495 patients.

The sample size calculation was based on the following hypotheses: based on the PneumO-LD-CT cohort, the expected accuracy of the clinician's diagnosis is 68% when based on CXR and 84% when based on LDCT. With an expected improvement of 16% of the accuracy using LDCT instead of CXR, 150 patients will be required in each arm to demonstrate the superiority of LDCT over CXR with a two-sided alpha error of 0.05 and a power of 90%. Allowing for a 10% drop-out after randomisation, the final recruitment objective is 165 patients in each arm, for a total of 495 patients.

Null hypothesis: the proportion of accurate clinician's diagnosis is the same on CXR and LDCT.
Alternative hypothesis: the proportion of accurate clinician's diagnosis is different between CXR and LDCT.

3.6 Interim analyses and stopping rules

There was no interim analysis for efficacy or futility. An initial safety analysis was planned after 200 patients have reached the 1-month follow-up. The safety monitoring board was free to make the final decision on the continuation of the study or terminating the study. The safety monitoring board did not decide on terminating the study.

3.7 Timing of final analysis

All outcomes collected up to 90 days will be analysed after study completion and expert adjudication. Following the completion of data entry, data validation and cleaning will be performed. Data analysis will start after the database has been locked.

3.8 Blinding

All three imaging examinations were performed for each patient:

- **CXR** was interpreted by **an independent radiologist**
- **LDCT** was interpreted by **a second independent radiologist**, different from the one who interpreted the CXR
- **LUS** was interpreted by **an independent ultrasonographer**

Physician in charge
The treating physician was aware of the allocation group. However, he was blinded to the results of the two non-assigned radiological examinations, which were concealed for 5 days. The examinations to be masked were known to the research staff immediately after randomisation. Emergency unblinding was permitted in the occurence of an immediately life-threatening finding (see Box 2).

Panel of experts

The panel of experts was consulted only after the completion of patient recruitment and had access to all data (clinical information and outcome data), including the results of all radiological examinations (CXR, LDCT, and LUS). However, each expert was blinded to the allocation group and to the final evaluation made by the physician in charge (published in ClinicalTrials.gov).

Box 2 Reasons for emergency unblinding

⇒ Pneumothorax.
⇒ Haemothorax.
⇒ Indirect signs of aortic dissection.
⇒ Indirect signs of aneurysmal rupture (haemomediastinum).
⇒ Massive pericardial effusion.
⇒ Tracheal foreign body.
⇒ Pneumoperitoneum.
⇒ Pneumomediastinum.
⇒ Malignant airway obstruction.
⇒ Suspected acute tuberculosis.

4. Statistical principles

4.1 Significance level, confidence interval, multiple testing

All statistical tests will be two-sided at the significance level of 0.05.

4.2 Analysis populations

In this document the term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects.

4.2.1 Full analysis set (FAS)

The full analysis set will include all randomized patients, except those who met one of the following criteria:

- *the failure to satisfy major entry criteria (eligibility violations)*
- *the failure to undergo any of the trial exams*
- *the lack of any data post randomization*

4.2.2 Per-protocol (PP)

The per-protocol analysis set will be limited to patients who actually received the exam to which they were randomly assigned and who have no major protocol violations.

4.2.3 Safety population

The safety analysis set includes all participants who underwent at least one of the imaging diagnostic procedures under investigation, regardless of protocol adherence. This set will be used for all safety-related analyses, including the assessment of adverse events potentially related to the imaging procedures, any procedural complications, and other safety parameters collected during the study. Participants will be analysed according to the imaging method actually received. No exclusions will be made based on deviations from the protocol or missing data for the safety analysis.
This approach ensures that all safety information associated with the diagnostic procedures is comprehensively captured, independent of the primary efficacy analysis, which focuses on diagnostic accuracy.

5. Protocol compliance and deviations

Protocol deviations will be identified prospectively and retrospectively.
Major protocol deviations are deviations that may affect the integrity of the trial, compromise the evaluation of the primary outcome, or threaten the validity of the randomization. The following cases are predefined as major protocol deviations:

- The blinding of the radiological examinations to be masked from the treating physicians was broken before or during the clinician assessment of the probability of pneumonia

No **minor protocol deviations** have been predefined in the protocol. However, any deviations not meeting the definition of a major deviation will be reviewed and, if applicable, **summarized descriptively** (number and frequency) for reporting purposes.

All protocol deviations will be documented and summarized by study arm in the clinical study report and/or manuscript (e.g., in the CONSORT flow diagram or descriptive tables).

6. Study population

6.1 Screening data, eligibility

Patient eligibility criteria
To be eligible for study participation, all patients will be required to meet the following inclusion criteria, and none of the exclusion criteria:

Inclusion criteria

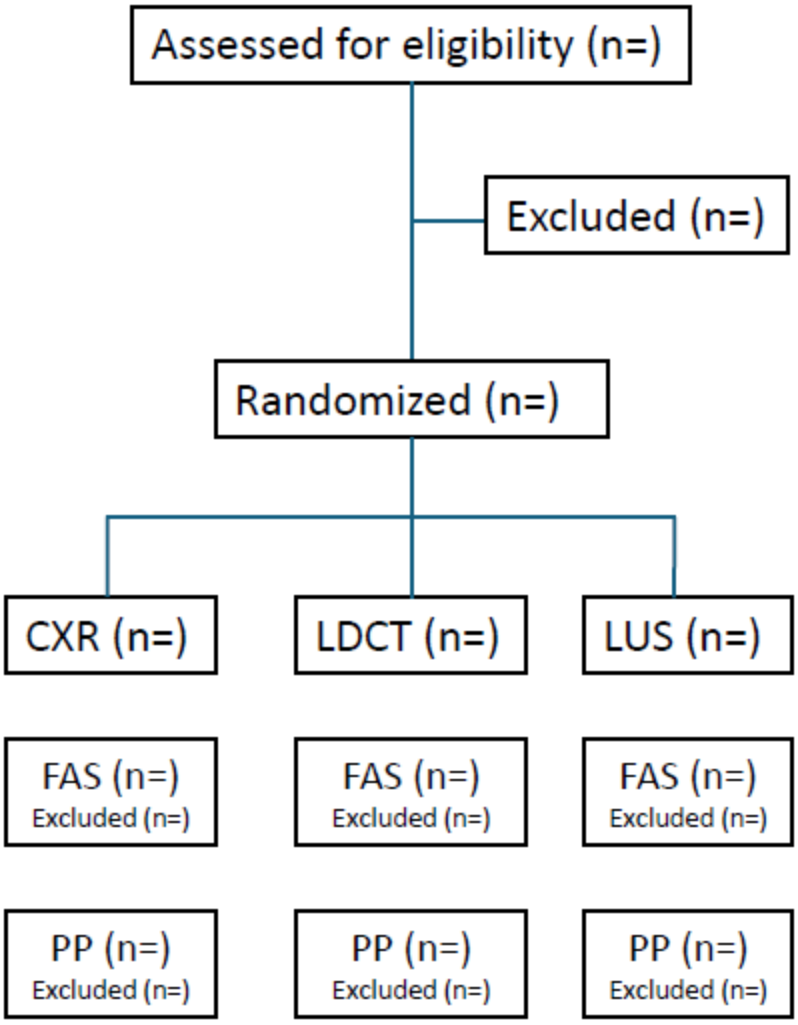
1. Suspicion of community acquired pneumonia (CAP) or nursing-home acquired pneumonia consulting to the ED
2. Age>65 years
3. Signed informed consent
4. Presence of at least one respiratory symptom (new or increasing cough or dyspnoea, purulent sputum, pleuritic chest pain, respiratory rate >20/min, focal auscultatory findings or oxygen saturation <90% on room air)
5. At least one sign or laboratory finding compatible with an infection will be required
   temperature >37.8°C or <36.0°C
   CRP >10 mg/L
   PCT >0.25µg/L
   leukocyte count >10G/L with >85% neutrophils or with band forms

   Presence of acute delirium or unexplained acute fall can substitute for the presence of either the respiratory or the infectious symptom in patients older than 80 years

Exclusion criteria:

1. Need for an immediate admission to the intensive care unit (ICU)
2. Diagnosis of pneumonia in the past 3 months
3. SARS CoV-2 infection diagnosed by PCR or antigenic test within the past 3 weeks
4. Transfer from another hospital with a diagnosis of pneumonia
5. Thoracic CXR or CT scan or US already performed during the present episode
6. Need for an immediate contrast-enhanced CT
7. Advanced care planning limiting therapy to comfort care only
8. Prisoners
9. Known uncontrolled psychiatric disorders
10. Previous enrolment into the current study

6.2 CONSORT flow diagram



FAS: full analysis set ; PP: per protocol

6.3 Baseline patient characteristics

Patient characteristics measured at baseline consist of:

- Demographic data (Age, gender, place of living etc.)
- Comorbidities
- Vaccination status
- Current medication
- Vital signs
- Clinical status (symptoms, etc.)

Severity score (CURB65, PSI, etc.)
Biological data
Microbiological data
Radiological data
Treatment
Quality of life

Which characteristics will be described and how they will be presented are detailed in chapter 8.2.1 Patients' characteristics (table1).

7. Data Management

7.1 Data export

Data were collected using REDCap. Data will be exported from REDCap using the “R statistical software” export format. Technically, raw data will be exported as CSV files and REDCap will provide R scripts to preprocess the data for analysis in R. All data will be stored on the secure servers of the Geneva University Hospitals (HUG).

7.2 Data validation

The data validation was performed in accordance with the central data monitoring plan developed by the UIC.

7.3 Data sharing

UAM will not share the data.

8. Statistical analysis

8.1 Outcome definitions

8.1.1 Definition of primary outcome

The primary outcome is the **accuracy** of the treating physician's diagnosis using the panel of study experts' diagnosis as reference.

I. The physician in charge assessed the probability of pneumonia using a three-point Likert scale
   1. 'low'
   2. 'intermediate'
   3. 'high'

II. The panel of study experts assessed the probability of pneumonia using a five-point Likert scale
   1. 'excluded' (<10% probability); considered as '**low'** on a three-point Likert scale
   2. 'improbable' (10-33%); considered as '**low'** on a three-point Likert scale
   3. 'possible' (34-66%); considered as '**intermediate**' on a three-point Likert scale
   4. 'likely' (67-90%); considered as '**high**' on a three-point Likert scale
   5. 'confirmed' (>90% probability); considered as '**high**' on a three-point Likert scale

Finally, the diagnosis of pneumonia will be classified as follow

I. When assessed by the physician in charge:
   - positive (pneumonia) if the probability is rated as 'intermediate' or 'high'
   - negative (pneumonia-free) if the probability is rated 'low'

II. When assessed by the panel of study experts (**reference standard**):
   - positive (**pneumonia**) if the probability is rated 'possible', 'likely' or 'confirmed'
   - negative (**pneumonia-free**) if the probability is rated as 'excluded', or 'improbable'

By defining the following elements:

Actual positives are those diagnosed with pneumonia by the **panel of study experts**
Actual negatives are cases that experts have diagnosed as pneumonia-free
True Positives are actual positives diagnosed with pneumonia by the physician in charge
False Positives are actual positives that clinician has diagnosed as pneumonia-free
False negatives are actual negatives diagnosed with pneumonia by the physician in charge
True negatives are actual negatives that clinician has diagnosed as pneumonia-free

The clinician's diagnosis will be considered **accurate** if it is a true positive or a true negative.

The primary endpoint is **diagnostic accuracy**, the proportion of correct diagnoses made by the treating physicians. **Diagnostic accuracy** will be calculated as:

$$\boldsymbol{Accuracy} = \frac{True\ Positives + True\ Negatives}{Total\ Number\ of\ Cases}$$

Additional diagnostic performance measures of the treating physician (sensitivity, specificity, PPV, NPV, PLR, NLR) will be evaluated according to the aforementioned definitions.

8.1.2 Definition of secondary outcomes

8.1.2.1 Medical imaging specialists' diagnosis

The CXR radiologist, the LDCT radiologist and the LUS ultrasonographer assessed the probability of pneumonia using a three-point Likert scale

1. 'low'
2. 'intermediate'
3. 'high'

The diagnosis of pneumonia will be classified as follow

- positive (pneumonia) if the probability is rated as 'intermediate' or 'high'
- negative (pneumonia-free) if the probability is rated 'low'

cf. previous paragraph for actual positives and actual negatives definitions.

By defining the following elements:

True Positives are actual positives diagnosed with pneumonia by the imaging specialist
False Positives are actual positives diagnosed as pneumonia-free by the imaging specialist
False negatives are actual negatives diagnosed with pneumonia by the imaging specialist
True negatives are actual negatives diagnosed as pneumonia-free by the imaging specialist

Diagnostic performance measures (accuracy, sensitivity, specificity, PPV, NPV, PLR, NLR) will be evaluated for each **medical imaging specialist**:

the CXR radiologist
the LDCT radiologist
the LUS ultrasonographer

8.1.2.2 Diagnostic outcomes

The outcomes to be analysed may consist of either

(1) the response provided by the physician in charge, or

(2) the response from the study expert investigator following the first round of the Delphi survey. At that stage, the expert only has access to REDCap data — i.e., the examination results — but not the imaging series or the full patient record.

- **Unmasked imaging modalities in emergency.** Urgent need to unblind the examination in case of immediately life-threatening findings (yes/no) was collected for each exam (CXR / LDCT / LUS). See Box2.
- **Alternative/concomitant diagnoses** provided by (2) **the study expert** following the 1st round of the Delphi survey. Experts were asked about:
  - ***alternative*** diagnosis in case of a *low* probability of pneumonia
  - ***concomitant*** diagnosis in case of an *intermediate* or *higher* probability of pneumonia.

  the experts could choose among
    - Cardiac Failure
    - Exacerbation COPD/emphysema/asthma
    - Acute bronchitis
    - Pulmonary malignancy
    - Interstitial lung disease
    - Pneumothorax
    - Other
- **Probability of aspiration pneumonia** provided by (2) **the study expert**. Experts were asked to rate the probability as low/intermediate/high in case of a *low* probability of pneumonia
- **Type of pneumonia** according to (2) **the study expert** (viral or bacterial). Experts were asked to provide the type of pneumonia in case of a *low* probability of pneumonia.
- **Additional imaging studies ordered during the acute setting** by (1) **the physician in charge**
  The following additional imaging performed by the physician in charge were collected. For each type of imaging, its number was also collected
    - Chest X Ray
    - Pulmonary CT scanner
    - Lung ultrasound by radiologist
    - Echocardiography by a cardiologist
- **Other procedures prescribed during the acute setting** by (1) **the physician in charge**
    - Non-invasive ventilation
    - Pleural puncture (“*thoracentesis”,* indicated in the one month visit *instrument*)

8.1.2.3 Treatment outcome

- **Antibiotic free days** at day 30. The number of days of antibiotics during the first month was collected in REDCap (*antibiotic_days_firstmonth*). The number of antibiotic free days will be calculated as follow:

$$\boldsymbol{Antibiotic\ free\ days} = 30 - antibiotic\_days\_firstmonth$$

  For deceased patients, the number of antibiotic free days will be calculated as:

$$\boldsymbol{Antibiotic\ free\ days} = \text{number of days alive} - antibiotic\_days\_firstmonth$$

8.1.2.4 Clinical outcomes

- **Number of days requiring oxygen therapy** will be analysed for descriptive purposes only.

- **Length of stay (in the acute care setting** will be calculated as the number of days between the emergency entry date (*emergencydate*) and the hospital discharge date (*hospital_discharge_date*)
  - A stay of 1 day corresponds to admission and discharge on the same calendar day.
  - A stay of 2 days corresponds to discharge on the day after admission, and so on.

- **Discharge after emergency** will be defined as a hospital stay of 1 day – that is, when the emergency entry date (*emergencydate*) and the hospital discharge date (*hospital_discharge_date*) fall on the same calendar day.

- **Transfer to the ICU/IMCU within 30 days** after the initial emergency admission/evaluation will be considered as having occurred if **either** of the following conditions is met:
  - The time between emergency entry date (*emergencydate*) and the hospital discharge date is ≤ 30 days **and** the discharge destination (*discharge_place*) is ICU or IMCU; or
  - The 1-month follow-up visit reports a transfer to ICU (*transfer_to_icu*) or IMCU (*transfer_imcu*), **and** the delay between the emergency entry date (*emergencydate*) and the ICU/IMCU admission date (*icu_transfer_date* or *imcu_transfer_date*) is ≤ 30 days

- **Transfer to rehabilitation unit within 90 days** after the initial emergency admission/evaluation will be considered as having occurred if **either** of the following conditions is met:
  - The discharge destination (*discharge_place*) is rehabilitation and the delay between *emergencydate* and *hospital_discharge_date* is ≤ 90 days; or
  - A transfer to rehabilitation (*rehabilitation*) with a corresponding admission date (*rehabilitation_date*) ≤ 90 days after *emergencydate* is reported at the 1- or 3-month follow-up.

- **Transfer to a long-term care facility (LTCF) within 90 days** after the initial emergency admission/evaluation will be considered as having occurred if **either** of the following conditions is met:

- The discharge destination (*discharge_place*) is LTCF and the delay between *emergencydate* and *hospital_discharge_date* is ≤ 90 days; or
- A transfer to LTCF (*transfer_ltcf*) with a corresponding admission date (*ltcf_transfert_date*) ≤ 90 days after *emergencydate* is reported at the 1- or 3-month follow-up.

- **All-cause mortality within 30 days** will be defined as a death date (*death_date* or *deathdate*) occurring within **30 days** of the emergency entry date (*emergencydate*)

- **All-cause mortality within 90 days** will be defined as a death date (*death_date* or *deathdate*) occurring within **90 days** of the emergency entry date (*emergencydate*)

- **In-hospital mortality** will be defined as a death occurring on or before the hospital discharge date (*hospital_discharge_date*), based on the recorded death date (*death_date* or *deathdate*)

- **All-cause readmission within 90 days** after initial emergency admission/evaluation will be defined as a readmission date (*readmission_date*) occurring within **90 days** of the emergency entry date (*emergencydate*)

- **Quality-of-life at 30 days and 90 days** (*eq5d_score*)

  Note: If an event is reported at multiple follow-up visits, the earliest available date will be used for analysis.

8.2 Analysis methods

If not otherwise stated, the analyses will be performed on the full analysis set.

8.2.1 Patients' characteristics (table 1)

The following summary statistics will be reported for quantitative variables:

- mean (sd)
- median (IQR)
- range (min – max)

The descriptive analysis will allow completion of the following table

Table 1 – Baseline Demographic and Clinical Characteristics (Full Analysis Set)

Patients' characteristics	**CXR (n=XXX)**	**LDCT (n=YYY)**	**LUS (n=ZZZ)**
Age* (years)			
>80 yr			
Gender, n (%)			
Male			
Female			
BMI* (kg/m²)			
Underweight (< 18.5)			
Normal (>= 18.5 & < 25)			
Overweight (>= 25 & < 30)			
Obese (>= 30)			
Smoking status			
Never smoked			
(Past or current) smoker			
Place of living			
Living at home			
Living in nursing home / supportive residence			
Activities of daily living before admission (Katz)			
Independent (ADL<5)			
Partially dependent (ADL=5)			
Dependent (ADL=6)			
Instrumental activities of daily living before admission (Lawton)			
Independent (IADL<5)			
Partially dependent (IADL>=5 et <7)			
Dependent (IADL>=7)			
Frailty (Rockwood scale)			
Robust (=0)			

Pre-frail (=1 ou 2)
Frail (>=3)
NRS score (malnutrition)
No risk (< 3)
At risk (>= 3)
Cognition (MMSE)
Normal (>= 24)
Mild impairment score (>= 18 & < 24)
Severe impairment (< 18)
Hospitalisation during the past 6 months, n/N (%)
Influenza vaccination within the past year, n/N (%)
Pneumococcal vaccination in the past 5 years, n/N (%)
Vaccination against SARS CoV-2, n/N (%)

Comorbidities
Chronic cardiac disease, n (%)
COPD, n (%)
Kidney disease, n (%)
Liver disease, n (%)
Diabetes, n (%)
Stroke, n (%)
Active neoplasia, n (%)
Cognitive disorders, n (%)
Swallowing disorders, n (%)
Immunosuppression, n (%)
Number of comorbidities, n (%)
0
1
2 or more
Polymedication (≥5 medications taken daily)
No
Yes
Charlson comorbidity index*

Clinical characteristics of pneumonia
Type of pneumonia
Community-aquired pneumonia
Nursing-home pneumonia
Temperature ⩾38.0 °C
Cough
Dyspnea
Sputum production
Chest pain
Crackles
Pleural effusion
Decrease in respiratory sounds
Peripheral oxygen saturation <90% on room air
Respiratory rate

Anorexia
Asthenia
Delirium
Fall
Rhinorrhea
Maylgia

Severity scores
CURB-65*
  Low (<=1)
  Moderate (=2)
  High (>=3)
Fine score
  Classe I (<50)
  Class II (>= 50 & <= 70)
  Class III (>= 71 & <= 90)
  Class IV (>= 91 & <= 130)
  Class V (>130)

Biological data
White blood cell count G/l (on admission)
Neutrophils (G/l)
Banded forms (G/l)
proBNP ng·L−1
CRP mg·L−1
PCT µg·L−1
Urea mmol·L−1
Creatinine µmol·L−1

Microbiological data
Positive culture
  Blood culture, n/N (%)
  Urinary culture, n/N (%)
  Sputum culture, n/N (%)
Positive urinary antigen
  Legionella, n/N (%)
  Pneumococcal, n/N (%)
PCR positive for Mycoplasma pneumoniae, n/N (%)
PCR positive for Chlamydia pneumoniae, n/N (%)
PCR positive for viruses, n/N (%)
PCR positive for SARS-CoV-2, n/N (%)
Endotracheal aspirate, n/N (%)
Bronchoalveolar lavage, n/N (%)
Pleural culture, n/N (%)

Radiological data
Chest x ray
  Patient position

Upright
Seated
Supine
Lateral image, n/N (%)
Quality
Inadequate
Adequate
Good
Years of experience of the radiologist
LDCT
Quality
Inadequate
Adequate
Good
Years of experience of the radiologist
LUS
Position
Sitting
Supine (and lateral)
Quality
Inadequate
Adequate
Good
Years of experience of the echographist

At ER discharge
Antibiotic prescription, n/N (%)
Indication
Pneumonia
Acute bronchitis
Exacerbation of COPD
Urinary tract infection
Other
At hospital discharge
Place of discharge
Rehabilitation
Home
LTCF
ICU
IMCU

Quality-of-life at admission*

8.2.2 Analysis of the primary outcome

Data analysis should enable the completion of the following table:

Clinician diagnosis	**CXR (n=XXX)**	**LDCT (n=YYY)**	**LUS (n=ZZZ)**
Accuracy, n (%) [95%CI]			
Sensitivity, n/N (%) [95%CI]			
Specificity, n/N (%) [95%CI]			
PPV, n/N (%) [95%CI]			
NPV, n/N (%) [95%CI]			
PLR [95%CI]			
NLR [95%CI]			

With [95%CI] estimated using the Clopper-Pearson method.

8.2.2.1 Primary analysis

- The **accuracy of the clinician's diagnosis** will be described by arm using counts and percentages.
- Ninety-five percent confidence interval (95%CI) around **diagnostic accuracy** percentage will be estimated using the Clopper-Pearson method.
- The diagnostic accuracy percentage will be compared between CXR and LDCT using the Cochran-Mantel-Haenszel method stratified on centre. This method allows to estimate:
    - the absolute difference (LDCT - CXR)
    - the standard error of the absolute difference

Under the null hypothesis (imaging examination modality has no effect on diagnostic accuracy), the test statistics (i.e. DR/SE(DR)) follows a standard normal distribution.
We will use the "rr_rd_mantel_haenszel" function of the "risks" package in r:

- *rr_rd_mantel_haenszel(data, arm, OUTCOME, center, estimand="rd")*

8.2.2.2 Secondary analysis

Similar analysis will be performed to compare the diagnosis accuracy percentage between

- LUS and CXR
- LUS and LDCT

8.2.2.3 Analysis of the additional diagnostic performance measures of the clinician

Sensitivity and specificity

- Will be described by arm using counts and percentages.
- Ninety-five percent confidence interval (95%CI) will be estimated using the Clopper-Pearson method.
- The Cochran-Mantel-Haenszel method stratified on centre will be used to assess the absolute difference in sensitivity (resp. specificity) between
    - CXR and LDCT
    - CXR and LUS

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

- will be described by arm using counts and percentages.
- Ninety-five percent confidence interval (95%CI) will be estimated using the Clopper-Pearson method.
- Will not be compared between arms

Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR)

- Confidence interval will be estimated by arm using the same asymptotic formula than for risk ratio, since it is a ratio of proportions.
- Will not be compared between arms

8.2.2.4 Interrater agreement analysis

For each method (CXR, LDCT, LUS), interrater agreement on the probability of pneumonia – rated on the original three-level Likert scale (low/intermediate/high) – will be assessed between trial physicians and the third (and final) round of reviews by a consensus panel of experts.

Interrater agreement will be evaluated using a weighted kappa score and by calculating the observed percentage of agreement.

The weighted kappa will be estimated using the following "prerecorded" weights:

		Probability of pneumonia at round 3 (**panel of experts**)		
		Low (excluded or improbable on the 5-point Likert scale)	Intermediate (intermediate on the 5-point Likert scale)	High (likely or confirmed on the 5-point Likert scale)
Probability of pneumonia (**Clinician**)	Low	**1**	**0.5**	**0**
	Intermediate	**0.5**	**1**	**0.5**
	High	**0**	**0.5**	**1**

A weight of 1 indicates that an observation should count as perfect agreement. A weight of 0.5 means the clinician and the consensus panel of experts are in half agreement (or half disagreement). Finally, they are in complete disagreement when the weight is zero.

8.2.2.5 Sensitivity analysis

In a sensitivity analysis, the **diagnosis of pneumonia will be modified** as follows:

III. Diagnosis of pneumonia will be considered
- positive if the probability is rated 'high'
- negative if the probability is rated 'low' or 'intermediate'

The same analyses as the primary analysis will be performed with this modification of the definition of the diagnosis of pneumonia.

8.2.2.6 Subgroup analysis

The same analyses as the primary analysis will be restrained to the following subgroups:
- Per protocol analysis set
- ≥80 vs. <80 years old
- SARS-CoV-2 infection vs non SARS-CoV-2 infection
- Aspiration pneumonia vs non aspiration pneumonia
- Chronic pulmonary disease vs. no chronic pulmonary disease (Charlson score subscale)
- Patients with obesity (BMI>=30)

8.2.3 Analysis of the secondary outcomes

For the secondary outcomes that will be compared between arms using a regression model, a single model including all three arms will be used. Effect sizes will be reported for each pairwise comparison:

CXR vs. LDCT
LUS vs. CXR
LUS vs. LDCT

8.2.3.1 Diagnosis by imaging specialists

Diagnostic performance metrics – including overall accuracy, sensitivity, specificity, PPV, and NPV, will be calculated for each imaging specialist across all patients in the full analysis set, regardless of treatment arm. Results will be presented as counts and percentages, with confidence interval estimated using the same method as for the primary analysis.

8.2.3.2 Diagnostic outcomes

Unless otherwise stated, diagnostic outcomes will be analysed solely for descriptive purposes, as count and percentages for qualitative variables, and mean and standard deviation for quantitative variables.

- **Non-invasive ventilation**, **pleural puncture**, and **additional imaging studies ordered** during the acute setting will be described as follow

Diagnostic outcomes	**CXR (n=XXX)**	**LDCT (n=YYY)**	**LUS (n=ZZZ)**
Patients with additional studies ordered, n (%)			
Yes (*nb_imaging_ordered*>0)			
No			
Number of additional studies ordered, mean (sd)			
Overall number (*nb_imaging_ordered*)			
Number of chest X Ray			
Number of Pulmonary CT scanner			
Number of Lung US			
Number of Echocardiography			
Patients with non-invasive ventilation, n (%)			
Patients with pleural puncture, n (%)			

The proportion of patients with additional studies ordered will be compared between arms using a linear probability model (binomial model with link Identity)

- The **following outcomes** will be described in **patients with a 'low' probability of pneumonia** according to the study expert:
  - Alternative diagnosis according to the study expert

- The **following outcomes** will be described in **patients with a 'intermediate' or 'high' probability of pneumonia** according to the study expert:
  - Probability of aspiration pneumonia according to the study expert
  - Type of pneumonia (viral & aspiration) according to the study expert

Diagnostic outcomes in patients with 'low' probability of pneumonia according to the study expert	CXR (n=XXX)	LDCT (n=YYY)	LUS (n=ZZZ)
Alternative diagnosis according to the study expert, n (%)			
Cardiac Failure			
Exacerbation COPD/emphysema/asthma			
Acute bronchitis			
Pulmonary malignancy			
Interstitial lung disease			
Pneumothorax			
Other			
Probability of aspiration pneumonia according to the study expert, n (%)			
Low			
Intermediate			
High			
Type of pneumonia according to the study expert, n (%)			
Viral			
Bacterial			

- **Concomitant diagnosis according to the study expert** will be described in **patients with an 'intermediate' or 'high' probability of pneumonia** according to the study expert:

Diagnostic outcomes in patients with 'intermediate' or 'high' probability of pneumonia according to study expert	CXR (n=XXX)	LDCT (n=YYY)	LUS (n=ZZZ)
Concomitant diagnosis according to the study expert, n (%)			
Cardiac Failure			
Exacerbation COPD/emphysema/asthma			
Acute bronchitis			
Pulmonary malignancy			
Interstitial lung disease			
Pneumothorax			
Other			

- **Unmasked imaging modalities in emergency (CXR, LDCT, LUS)** will be described overall as count and frequency (one overall description).

8.2.3.3 Treatment outcome

Number of antibiotic free days at day 30 will be compared between the three arms using a linear regression model adjusted on centre with a bootstrap method for 95%CI. P values will be computed by inverting the corresponding confidence interval (Thulin 2024: modern statistics with R).

- a subgroup analysis excluding exacerbation of COPD, where the need for antibiotic therapy is still debated, will be performed.

8.2.3.4 Clinical outcomes

- **All-cause mortality at 30 days** will be
    - estimated by arm using the Kaplan-Meier method
    - compared between arms through pairwise comparisons using a log-rank test stratified by centre (three pairwise tests will be performed)
    - and the complementary log-log transformation will be applied to calculate the 95% confidence intervals for the 30-day survival estimates
- **All-cause mortality at 30 days** will be described only
- **In-hospital mortality**
    - will be described by arm as count and percentages
    - will be compared between arms using a logistic regression model adjusted on centre. Odds ratio will be reported with 95% confidence intervals
- Number of patients hospitalised after emergency and number of patients discharged after emergency will be described by arm as count and percentages
- **Length of hospital stay**
    - Will be analysed **among all randomized patients**, and **repeated among hospitalized patients only** (excluding those discharged after emergency department presentation)
    - Will be compared between arms using a linear regression model adjusted on centre with a bootstrap method for 95%CI.
    - Pvalues will be computed by inverting the corresponding confidence interval (Thulin 2024: modern statistics with R).
- **Unplanned transfer to the ICU/IMCU within 30 days after initial admission/evaluation**
    - Will be analysed **among all randomized patients**, and **repeated among hospitalized patients only** (excluding those discharged after emergency department presentation)
    - Will be described by arm as count and percentages
    - Will be compared between arms using a logistic regression model adjusted on centre. Odds ratio will be reported with 95% confidence intervals.
- The following outcomes will be described by arm as count and percentages **in patients discharge alive.** Those outcomes will not be compared between arms:
    - **Admission to rehabilitation through 3 months in patients discharge alive**
    - **Transfer to LTCF through 3 months** in patients discharge alive
    - **All-cause readmission to acute care setting in patients discharge alive**
    -
- The **quality of life 30 days and 90 days** will be described by arm as median and IQR **in patients discharge alive.** Quality of life will not be compared between arms

8.2.4 Assessment of statistical assumptions

The Cochran-Mantel-Haenszel method requires that stratification by centre is appropriate, with sufficient patient numbers per centre to provide reliable estimates. Since the study will include approximately 500 patients distributed across three centres, it is expected that the sample size per centre will be large enough to satisfy this requirement and provide stable stratified estimates.

Regression models (linear or logistic) assume independence of observations; homoscedasticity and normality of residuals for linear models; and linearity of the logit for logistic regression (when continuous predictors are included). Survival analyses assume non-informative censoring and proportional hazards over time. For linear models, the assumptions will be checked graphically (scatter plots, scale-location plots, residual-versus-fitted values plot). The proportionality of hazards will be graphically checked with the log-minus-log plot and regression coefficients based on categorizations of the continuous variable. The proportionality of log-odds will be checked with the regression coefficients of categorized variables. If significant violations of key assumptions are detected (e.g., non-normality of residuals, heteroscedasticity, or sparse data in logistic models), alternative methods (e.g., data categorization, exact methods, or non-parametric approaches) or sensitivity analyses will be considered and documented.

8.3 Interim analyses

There will be no interim analyses for efficacy or futility. An initial safety analysis was performed after 200 patients completed the 1-month follow-up, following which the Data and Safety Monitoring Board (DSMB) made the final decision to continue the study without modifications.

8.4 Missing data

Analyses will be conducted using a complete case approach, including only participants with fully observed data for the variables of interest, as the amount of missing data is expected to be low. The extent and reasons for missing data will be assessed and reported by study arm.

8.5 Safety evaluation

Safety analyses will consist of descriptive statistics by study arm for all reported adverse events (AEs), serious adverse events (SAEs), and other safety-related outcomes collected during the study period.

8.6 Statistical software

All statistical analyses will be conducted using R statistical software (version 4.2.2 or later).

9. Statistical deviation from the protocol

The following exploratory analysis, not specified in the protocol but added before the database was locked, will be conducted.

1. Studying in-hospital mortality was not prespecified in the protocol. This variable was finally retained due to its clinical relevance and availability in the collected data, providing complementary insight into short-term patient outcomes
2. Subgroup analyses according to
    - Patients with chronic pulmonary disease
    - Patients with obesity (BMI>=30)

Indeed, CT may be a better diagnostic strategy compared to others in those patients, and this could lead to recommendations for patients with a chronic pulmonary disease and for patients with obesity.

The following analyses were part of the initial protocol and will finally not be conducted:

1. Time to clinical stability was found to be difficult to compute reliably during SAP drafting and will therefore not be analysed

10. References

SOP “Plan Analyse Stat” _UAM_3 SOP-4, version 3.0, valid from 14.05.2024

R Development Core Team. 2008. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria

Panel of experts

LOw-dose CT Or Lung UltraSonography versus standard of care based-strategies for the diagnosis of pneumonia in the elderly: protocol for a multicentre randomised controlled trial (OCTOPLUS)

Administrative information
Version 1.2
Date 14 January 2026

Study information
Author Virginie Prendki
Brief Title CT Scan Compared to CXR and LUS in Pneumonia in the Elderly
Trial registration number NCT04978116
BASEC number 2019-01288

OCTOPLUS expert panel method
Aim
Adjudication of the diagnosis of pneumonia in OCTOPLUS by experts.
A patient's diagnosis will be considered as accurate if the clinician's diagnosis and the panel of experts agree (true positive and true negative diagnoses).
What is the OCTOPLUS trial?
This is a multicentre randomised superiority clinical trial with three parallel arms comparing 3 diagnostic strategies for the pneumonia in patients >65y. Patients will be allocated in the ER to a strategy based on either chest-X ray (CXR), low-dose CT scan (LDCT) or lung ultrasonography (LUS), the CXR arm being the standard of care. All imaging modalities will be performed but the results of two of them will be masked during 5 days to the patients, the physicians in charge and the investigators according to random allocation. The primary objective is to compare the accuracy of LDCT versus CXR-based strategies.
http://dx.doi.org/10.1136/bmjopen-2021-055869

Description of the adjudication process/expert panel: modified Delphi methods with 3 rounds
A panel of experts (senior clinicians, including internists, geriatricians and radiologists), blinded to the allocation arm and the probability of pneumonia estimated by the treating clinician, will retrospectively rate the probability of pneumonia based on all available patient data present in the medical records, including the reports and images of the 3 imaging modalities: CXR, LDCT, and LUS. It will be centralized for all including centres and done as follows:
1st round. Each expert will individually assess for each patient the probability of pneumonia on a 5 Likert scale (very likely or confirmed, probable, possible, unlikely, excluded).
Patients with a very likely/confirmed, probable and possible probability of pneumonia will be considered as having a pneumonia. Patients with an unlikely or excluded probability will be considered as not having pneumonia; for these patients, an alternative diagnosis will be proposed by the panel.

For all cases, the panel will be asked to give a concomitant diagnosis (another pathology concurring to the symptoms presented, e.g. acute heart failure complicating an episode of pneumonia).
The panel of experts will also be asked to adjudicate the presence of aspiration pneumonia* and viral pneumonia.
2nd round. Pairs of experts will discuss discordant cases.
3rd round. In a plenary session and in the presence of an expert in thoracic imaging and an expert in LUS, all experts will achieve consensus on discordant cases. This final decision will serve as the reference diagnosis.
To promote agreement, the experts will be trained before the adjudication.

Methods

1/ Panel constitution

The experts will be randomly assigned to a pair. Each pair will include one expert from the study staff and a second expert not involved in the study.; The pair same pair will assess the patients on round one and two.
Both experts must be physicians in current clinical practice (at least part-time); they must be regularly confronted with patients with a suspicion of pneumonia; they must be board-certified in internal medicine, infectious disease, lung disease, intensive care medicine, or emergency medicine; and they must have at least 5 years of clinical experience.
Radiological experts who will attend the 3rd round of the adjudication will be board-certified in radiology and experienced in thoracic imaging. Ultrasonography experts will also be present, they will be board-certified.

2/ Information available to the panel

1st round: clinical results; biological tests; microbiological tests; imaging interpretation report (level of probability), data on evolution (length of hospitalization, antibiotic treatment, outcome).
2nd round: previous data + access to the raw images of CXR, CT and US.
3rd round: previous data and raw documents (physician notes, discharge letters, etc).

3/ Blinding of any index test

Not feasible in this study, but experts will be blinded to the randomization arm and to the diagnosis of clinician at the emergency room.
If the experts have been involved in routine clinical care, they will only adjudicate cases that they had not previously treated

4/Decision making process

a) Definition of CAP

« An acute illness with cough and at least one of new focal chest signs, fever >4 days or dyspnoea/tachypnoea, and without other obvious cause (…) supported by chest radiograph findings of lung shadowing that is likely to be new. In the elderly, the presence of chest radiograph shadowing accompanied by acute clinical illness (unspecified) without other obvious cause. » (Guidelines for the management of adult lower respiratory tract infections, Clin Microbiol Infect 2011 Nov;17 Suppl 6:E1-59. doi: 10.1111/j.1469-0691.2011.03672.x).

3 mains components:
-Acute illness (<21 days).
-Respiratory and infectious findings (or geriatric syndrome in the elderly): cough, dyspnoea, expectorations, chest pain, fever/hypothermia, tachypnoea, hypoxemia.
CAVE In elderly patients, delirium, falls (geriatric syndromes) may reveal an infection. (DOI:10.1016/j.ejim.2025.02.025)
-Radiologic demonstration of an invasion of lung parenchyma.

Additionally: not explained by another process (caution with acute exacerbation of COPD; acute decompensated heart failure; pulmonary embolism; lung cancer; diffuse lung disease; large pleural effusion with atelectasis), but concomitant diagnoses are possible.

Supporting information:
Elevated CRP (> 30 mg/L); elevated procalcitonin not required because we aim to include viral pneumonia; leukocytosis, neutrophilia, leukopenia.
Identification of a bacterial pathogen known to cause pneumonia thanks to blood cultures, respiratory samples, urinary antigens (*Streptococcus pneumoniae*, streptococci other than *S. pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, Legionella spp, *Moraxella catarrhalis*, *Chlamydia psittaci* or *Chlamydia pneumoniae*, *Coxiella burnetiid, P. jirovecii* in immunocompromised patients.
Caution with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other as Enterobacteriaceae (can be a contamination, but can be causative agent of CAP in elderly patients)).
Identification of viruses on naso/oropharyngeal swabs.

b) ***Format of the result****: Likert scale with 5 levels*

Pneumonia very likely or confirmed *(more than 90% of probability)*
Typical clinical and radiological presentation but no pathogen identified or pathogen not specific to pneumonia (e.g. S. aureus; streptococci other than pneumoniae)
Typical pathogen identified with any acute lung infiltrate.

Pneumonia probable *67-90% of probability)*
Imaging suggestive of pneumonia, but a chronic lung condition or heart failure is also present; however, pneumonia probably explains most of the clinical findings

Pneumonia possible *(34-66% of probability)*
Imaging compatible with pneumonia, but another disease could as well explain the findings (acute heart failure with moderate inflammatory biomarkers; known diffuse lung disease with acute symptoms and worsening radiology, known lung cancer with acute symptoms and worsening radiology). However, most clinicians would probably choose to treat with antibiotics.

Pneumonia unlikely *(10-33% probability)*
Imaging compatible with pneumonia, but another disease may better explain the image (pulmonary embolism with lung infarction; large atelectasis with few findings of acute infection).

Pneumonia excluded *(less than 10% of probability):*
No infiltrate on all imaging studies
Faint infiltrate or imaging suggestive of an acute lung condition (heart failure, nodules / mass…), AND another disease is evident (abdominal or urinary sepsis; acute heart failure; cancer)
Response to antibiotic treatment should be considered with caution because of frequent concomitant treatment in that population (diuretics, bronchodilators, corticosteroids
The five levels will then be reduced to three (1 and 2: high probability; 3: intermediate probability; 4-5: low probability), to concord with the protocol. The diagnostic threshold will separate 1-3 from 4-5.
If pneumonia is rated as excluded or unlikely, the experts will be asked to propose an alternative diagnosis for the symptoms of the patient: congestive heart failure, exacerbation of COPD, other

non-pneumonic respiratory infection (acute bronchitis), pulmonary malignancy, interstitial lung disease, pneumothorax, other

If pneumonia is rated as possible, probable or very likely, the experts will be asked two further questions:

- 'Do you think it is aspiration pneumonia (Y/N)
- "Do you think it is a viral pneumonia (i.e. without bacterial superinfection Y/N) if pneumonia is possible, probable or certain?

5/ Validity and reproducibility of the diagnosis: agreement between groups of experts will be assessed in a random sample of patients

Nota bene:

This document was first submitted on Clinical Trial on May 2025.

It is re-submitted on January 2026 with no major modification except for the Official Title of the study, NCT number, and date of the document, added as required.