OCTOPLUS: lOw-dose CT cOmPared to Lung UltraSonography vs standard care for the diagnosis of pneumonia in the elderly: a multicentre randomized controlled study

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Study Type:	Randomized Clinical trial
Study Categorisation:	Risk category according to HRA: A
Study Registration:	Intended registry: Clinicaltrials.gov, SNCTP
Study Identifier:	OCTOPLUS
Principal Investigator:	Dr Virginie Prendki, Division of Internal Medicine of the Aged, Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva Hôpital des Trois-Chêne, Chemin du Pont-Bochet 3, 1226 Thônex-Genève Switzerland Tel: +41795538308 Fax: +41223056115 Email: virginie.prendki@hcuge.ch
Sponsor	University Hospitals of Geneva Rue Gabrielle-Perret-Gentil 4 Geneva, Switzerland 1205 Represented by the Principal Investigator
Trial sites & investigators	Dr Virginie Prendki, Geneva Trois-Chêne Dr Jérôme Stirnemann, Geneva Cluse-Roseraie Pr Wolf Hautz, Bern Pr Enos Bernasconi , Lugano Pr Nicolas Garin, Rennaz
Methodological advisors	Dr Christophe Combescure
External monitor	Clinical Trials Unit, HUG
Investigational Product:	Diagnosis methods: CXR, LDCT and LUS in pneumonia
Protocol Version and Date:	V5.2 (05/10/2023)

Version Nr	Version date	Description, comments
1	03.07.2019	Initial version
2	20.11.2019	Corrected version after 1st review
3	25.01.2020	Corrected version after 2nd review
4	03.01.2021	Changes after SNF review and after SARS-CoV-2 pandemic
5	03.05.2021	Corrected version before launch of the study (safety, flow-chart, …)
5.1	31.05.2021	Correction in the inclusion criteria
5.2	05.10.2023	Change of monitoring plan for the Berne site

Signature Page(s)

Study number	The study will be registered on ClinicalTrials.gov
Study Title	OCTOPLUS: lOw-dose CT cOmPared to Lung UltraSonography vs standard care for the diagnosis of pneumonia in the elderly: a multicentre randomized clinical study

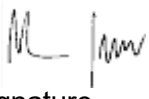
The Sponsor-Investigator and trial statistician have approved the protocol version V5.2 (05/10/2023) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Sponsor-Investigator:
Dr Virginie Prendki
Geneva/Thonex,
05 October 2023

Place/Date | Signature

Local site investigators

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Dr Jérôme Stirnemann Local investigator, Geneva Cluse-Roseraie	05 October 2023 Date	 Signature
Pr Wolf Hautz Local investigator, Bern	05 October 2023 Date	 Signature
Pr Enos Bernasconi Local investigator, Lugano	05 October 2023 Date	 Signature
Pr Nicolas Garin Local investigator, Rennaz	05 October 2023 Date	 Signature

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GLOSSARY OF ABBREVIATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CAP	Community-Acquired Pneumonia
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
CXR	*Chest x ray*
ED	*Emergency Department*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
GRL	*Genomic Research Laboratory*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
HUG	*Geneva University Hospitals*
ICH	*International Conference on Harmonisation*
ICU	*Intensive Care Unit*
LDCT	*Low dose CT scan*
LTCF	*Long-term care facility*
LUS	*Lung Ultrasound*
PACS	*Research picture archiving and communication system*
PI	*Principal Investigator*
QOL	*Quality of Life*
RCT	*Randomized-controlled trial*
SAE	*Serious Adverse Event*
SNF	*Swiss National Funding*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Dr Virginie Prendki, Division of Internal Medicine of the Aged, Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva Hôpital des Trois-Chêne, Chemin du Pont-Bochet 3, 1226 Thônex-Genève Switzerland Tel: +41795538308 Fax: +41223056115 Email: virginie.prendki@hcuge.ch
Study Title	lOw-dose CT cOmPared to Lung UltraSonography vs standard care for the diagnosis of pneumonia in the elderly: a multicentre randomized clinical study
Short Title / Study ID	OCTOPLUS
Protocol Version and Date	V5.2 (05/10/2023)
Study Registration	Clinicaltrials.gov; Swiss National Clinical Trial Portal
Study Category and Rationale	Risk category according to HRA: A
Background and Rationale	**Principal study: OCTOPLUS** Pneumonia is one of the leading causes of morbidity and mortality from infection in elderly patients, and is one of the first causes of antimicrobial therapy prescription. Its diagnosis is challenging, particularly in elderly patients, because of the lack of sensitivity and specificity of clinical signs and symptoms and because of the high incidence of differential diagnoses. Limitation of chest X-Ray (CXR) for this diagnosis have been abundantly documented. Hence, clinical studies are needed to improve diagnosis of pneumonia, leading to better management of the patients and more appropriate antimicrobial therapy prescription. We showed in a previous study that low-dose CT scan (LDCT) changed the probability of pneumonia in 45% of elderly patients (>65 years, median age 84 years) suspected of pneumonia according to clinical presentation and CXR (Prendki, Eur Resp J 2018). LDCT mostly helped the clinician to exclude a diagnosis of pneumonia. Another study showed a similar impact of CT in adult patients (>18 years, median age 65 years) consulting in the emergency department (ED) for a suspicion of pneumonia (Claessens, Am J Respir Crit Care Med 2015). Hence, CT-scan could contribute to a more accurate diagnosis of pneumonia in the emergency department setting. However, availability, costs, and associated irradiation are significant issues. Lung ultrasonography (LUS) is a promising diagnostic tool for the detection of pulmonary infiltrates, with a reported accuracy outperforming CXR (Nazerian, Am J Emerg Med 2015). As it is readily available at the bedside, use of ultrasonography by non-specialists in the emergency room has significantly increased. However, published studies have mainly been conducted by team experts in LUS, and generalizability of their results to less specialized settings is unwarranted. Finally, only a randomized-controlled trial (RCT) may establish if one diagnostic strategy leads to better or equivalent clinical

	outcomes while allowing a more judicious AT prescription. Such RCT has yet not been reported. In 2020, Coronavirus disease (COVID-19) has caused a pandemic threatening millions of people worldwide. Patients with SARS CoV-2 infection will be excluded from the trial if COVID diagnosis has been done by PCR or antigenic test within the past 3 weeks and before the arrival to the ED. **Ancillary study: GEROBIOTA** (GERiatric, Oral health assessment and oral microBIOTA): The burden of pneumonia in elderly and comorbid patients will increase in the coming years. Functional, cognitive impairments and malnutrition are frequently associated with pneumonia and its mortality in the elderly. Despite evidence of a link between oral health and the risk of pneumonia, the oral status is not yet routinely screened in elderly patients hospitalized for pneumonia. In the same line, aspiration, mostly due to oropharyngeal dysphagia is a frequent mechanism of pneumonia and is not routinely screened any either. Links have been highlighted between oral care and mortality from pneumonia (low level of evidence). Like in other organ systems, microbiota may have a major role in maintaining health in the airways and lungs, being involved in immunity and homeostasis, and preventing colonization by respiratory pathogens. Moreover inflammation, vaccinal response and genetic markers are other factors involved in the occurrence and the outcome of pneumonia. Long-term mortality and readmission were associated with persistent inflammation in patients hospitalized with sepsis.
Risk / Benefit Assessment	This study is carried out in an emergency situation and the expected results can only be achieved in an emergency situation. Indeed pneumonia is a major cause of morbidity and mortality and the patient's prognosis is engaged. Diagnosing and the decision of treating the patient consulting the ED must be performed within first hours (the international guidelines recommend treating the patient while he/she is still in the ED for a suspicion of pneumonia). -Risk of the CT: LDCT is well-tolerated and its mean radiation exposure is much lower than a full-dose CT scan (about 1mSv). -Risk of LUS: there will be many clinicians performing LUS at each site. LUS is known to have a fast-learning curve. To minimize heterogeneity between the clinicians and centres, standardization of LUS practice will be performed in all centres before the beginning of the study. -Risk of the blinding: blinding is one of the major challenges of the trial. It will be performed in each site using a research PACS thanks to radiologist engineering. To allow for compliance and smooth running of the study, all ED and radiology staff will be regularly informed regarding methods and stakes. As soon as the patient is included, the research staff will anticipate and inform the radiology staff who will take care of the patient, and the clinician to perform LUS about the necessity of blinding and the CRF to fill in. The research staff will be the only one able to provide the attending clinician with the result of the allocated imaging modality, and ensure that it is accessible in the patient's

	medical record. The two other imaging modalities will be concealed until day 5, and will only be accessible on the PACS. According to a predefined list of emergency findings, the radiologist interpreting CXR or LDCT or the clinician performing LUS will be able to immediately ask the investigator for unblinding. At day 5, the research staff will ensure that the two blinded imaging modalities are made accessible again to the treating clinician. The risk of a false negative (meaning a missed diagnosis of pneumonia) will be counterbalanced by the fact that the clinician will be allowed to prescribe antimicrobial therapy for another diagnosis than pneumonia. As patients with severe pneumonia will not be included, a delay of a few hours in the diagnosis of pneumonia is unlikely to lead to an unfavourable outcome. Indeed, a longer time to antibiotic administration was not associated with an unfavourable outcome in moderately severe Community-Acquired Pneumonia (CAP) in the literature (Garin et al). Finally, we estimated that risks inherent to the trial are minimal and inferior to the benefices of the study which could deliver key results which would provide long-term benefit to all patients with pneumonia.
Objective(s)	**Primary objective:** To assess the difference in diagnostic accuracy for patients with suspected pneumonia using LDCT compared to CXR. We hypothesize that it will be higher in LDCT than in CXR arm. **Main secondary objectives**: To evaluate whether a diagnostic strategy using LUS compared with CXR, and using LUS compared with LDCT leads to better diagnostic, therapeutic (antibiotic consumption at day 30), and clinical outcomes (time to clinical stability, length of hospital stay, admission to the intensive care unit, 1-month and 3-month mortality and readmission, and quality of life); cost outcomes; concordance between physicians at the ED and experts and the association of biomarkers and the presence of an infiltrate. **GEROBIOTA** To identify factors associated with the probability of pneumonia, the probability of aspiration pneumonia, 1 month and 1 year mortality, 1 year readmission and to create a biobank allowing the assessment of inflammation, immune status and genetic markers.
Endpoint(s)	**Primary outcome measure:** The primary outcome will be the difference in accuracy between LDCT and CXR, assessed at the end of the ED evaluation, using the expert panel as the reference standard, accuracy being computed as (true positive + true negative cases) / (true positive + true negative + false positive + false negative cases). **Main secondary outcome measures:** Diagnostic outcomes: • Proportion of patients with an adequate diagnosis using LUS compared to CXR • Proportion of patients with an adequate diagnosis using LUS compared to LDCT

	• Proportion of patients with an alternative diagnosis • Number of additional imaging studies and invasive procedures prescribed during the acute setting • Prevalence of unmasked imaging results (for an emergency finding) • Prevalence of incidentalomes Treatment outcomes: • Number of antibiotic free days at day 30 Clinical outcomes: • Time to clinical stability during the first 2 weeks • Length of hospital stay • Proportion of patients with an unplanned transfer to the ICU or operating room • Proportion of patients admitted to rehabilitation or long-term care facility (LTCF) days through 3 months • All-cause mortality through 1 month and 3 months • All-cause readmission to the acute care setting through 1 month and 3 months • Quality of life at admission, discharge and 3 months Agreement for the diagnosis of pneumonia between clinicians and a panel of experts Association between biological markers (C-reactive protein and procalcitonin) and the presence of an infiltrate Cost outcomes: Costs of care, physician, imaging, laboratory, treatment (including antibiotic therapy) and others per patient, health related quality of life until 3 months; unit of work consumption per hospital (number of minutes of care, physician, laboratory and imaging points) **Safety outcomes:** unplanned transfer to the ICU after initial admission; 1-month mortality. **GEROBIOTA** The probability of pneumonia/aspiration pneumonia according to the panel of experts; Proportion of patients admitted to rehabilitation or LTCF days through 3 months; all-cause mortality through one-year; all-cause readmission to hospital or LTCF through one-year.
Definitions	**-Reference diagnosis**: it will be done *a posteriori* by a panel of experts, including one radiologist, who will have access to all imaging studies (CXR, LUS, and LDCT), along with all clinical and biological data, including follow-up data up to one month after admission. They will give their probability of pneumonia, aspiration pneumonia, bacterial vs viral pneumonia or alternative diagnosis. -Time to clinical stability: number of days from admission to the first time all of the following parameters are above/under the threshold value and maintained for a minimum of 24 hours: heart rate <100 beats/min, systolic blood pressure >90 mmHg, temperature <37.8°C (axillary or tympanic), respiratory rate <24 breath/min, oxygen saturation >90% while breathing room air, or need for more than 28% fraction of inspired oxygen to maintain adequate oxygen saturation, resolution of delirium if present at admission)

	-Viral pneumonia: presence of an infiltrate on CT scan and a PCR positive for a virus -**Aspiration pneumonia**: compatible radiological findings witnessed aspiration or risk factors for aspiration
Study Design	**OCTOPLUS** is a Swiss multicentre superiority randomized clinical study with 3 parallel arms. Randomization will be 1:1:1 using randomly permutated block sizes and be stratified by centre. Patients will be either randomized into the CXR, the LDCT or the LUS arm. The 3 imaging modalities will be performed in the ED (and before the patient is discharged) for all included patients but only one will be available to the clinician according to the allocation arm. The concealed results of the imaging procedures will be unblinded at day 5. The duration of follow-up will be 3 months for OCTOPLUS. The panel of experts will provide their diagnosis *a posteriori*. An intermediate safety analysis will be performed after 200 patients have completed the 1-month follow-up. CIRCUS (**Calibration of reasoning confidence in uncertain situations)** is a substudy from OCTOPLUS which aims to understand which factors (of the physician such as experience or gender, of the patient such as urgency or presenting complaint and of the context such as daytime) affect physician confidence in their diagnosis (see appendix at the end of the protocol). **GEROBIOTA** is an observational substudy to OCTOPLUS. It will be performed in two academic hospitals and the duration will be one year. Comprehensive assessment of functional, cognitive, nutritional, oral health status and oral/respiratory microbiota will be done in order to identify factors associated with the diagnosis of pneumonia and its outcome. The creation of a biobank will allow the assessment of inflammation, vaccinal status and genetic markers. Identification of risk factors will pave the way for interventional studies aimed at reducing the onset and the recurrence of pneumonia. The reference diagnosis will be provided by the panel of experts: in addition to the probability of pneumonia, the experts will be asked to rate the probability of aspiration pneumonia. NB: only CXR will be billed to the participant, as this is the actual standard of care imaging
Statistical Considerations	**Methodology** Dr Christophe Combescure; Methodological support Unit, Clinical research center, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland, Email: christophe.combescure@hcuge.ch, Tel: +41 22 37 29 136 diagnosis of pneumonia (proportion of true positive plus true negative) will be higher in LDCT arm than in CXR arm. The null hypothesis that will be tested in the primary analysis is the equality of proportion of correctly classified patients in LDCT and CXR arm.

	The analysis will follow the intention to treat principle. A sensitivity analysis will be conducted on the per protocol population (i.e. excluding patients who have not received the allocated intervention, and patients who crossed over). Another sensitivity analysis will be conducted excluding patients who will have had CXR before LDCT and LUS. Subgroup analysis will be performed in patients aged over 80 years (versus less than 80 years) and in patients with positive PCR (i.e. virus detected, including SARS-CoV-2) at the beginning of the study (versus with a negative PCR). The diagnosis made by the panel of experts will be the reference diagnosis for calculation of the primary outcome in each arm, and to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values and likelihood ratios. The primary outcome in each arm will be compared to the two other ones.
Inclusion- / Exclusion Criteria	**Study population:** patients >65y with suspected CAP or nursing-home acquired (NHAP) pneumonia consulting to the ED. **Key inclusion criteria:** -presence of at least one respiratory symptom (new or increasing cough, purulent sputum, pleuritic chest pain, new or increasing dyspnea, respiratory rate >20/min, focal auscultatory findings or oxygen saturation <90% on room air). -AND at least one symptom or laboratory finding compatible with an infection (temperature >37.8°C or <36.0°C, C reactive protein (CRP) >10 mg/L, PCT >0.25µg/L, leukocyte count >10 G/L with >85% neutrophils or band forms) The presence of acute delirium or unexplained acute fall can substitute for the presence of either the respiratory or the infectious symptom in the oldest old group (patients ≥80y). **Key exclusion criteria:** patients for whom an immediate admission to the intensive care unit (ICU) is required; patients who were diagnosed with pneumonia in the past 3 months; patients who had positive PCR for SARS-CoV-2 and antigenic test within 3 past weeks; who were transferred from another hospital with a diagnosis of pneumonia; who already a thoracic imaging (CXR, CT scan or LUS) during the present episode; and who require an immediate contrast-enhanced CT; furthermore, patients with advanced care planning limiting therapy to comfort care only; prisoners; patients with known uncontrolled psychiatric disorders; and patients who were previously enrolled into the current study.
Number of Participants with Rationale	The number of patients has been computed based on the number of diagnoses of pneumonia correctly classified according to the panel of experts who had access to the results of LDCT in the PneumOldCT study (Prendki, Eur Resp J 2018 and unpublished data). Power calculation has not been performed for the LUS arm as there is too few data in the literature comparing directly LUS and LDCT. With an expected improvement of the diagnosis with LDCT in 16% of the patients, we calculated that 150 patients will be required in each arm to prove the superiority of LDCT over CRX with an alpha error =0.05 and a power of 0.9. Allowing for a 10% dropout after randomization, the plan is to enrol 165 in each arm, for a total of 495 patients.

	500 patients will be recruited for the study. For GEROBIOTA, sample size is based on the power calculation of the principal study.
Study Intervention	**OCTOPLUS** Performance of CXR, LDCT and LUS, in all patients during their time in the ED. CXR will be interpreted in real-time by the resident radiologist. LDCT (with no injection) will be interpreted in real-time by a senior radiologist LUS will be performed by another clinician than the one in charge of the patient; LUS practice of the former will be standardized before the launching of the study. **GEROBIOTA** **At admission**: -Microbiota samples (saliva and respiratory samples) before antibiotic administration at the ED if possible. They will be stored at -80. NB: respiratory samples will be those taken for routine methods including sputum, induced sputum, tracheal aspirate or broncho-alveolar lavage if done and still available - Biobank stored at -80 one saliva sample, serum (2 tubes), plasma EDTA (2 tubes), plasma citrate (2 tubes), PAX gene DNA (1 tube), PAX gene RNA (1 tube). During hospitalization: -Oral health examination by a medical dentist as soon as the patient is stabilized (≈30 min) -Geriatric assessment by the research staff during the first week of hospitalization (≈45min) **At discharge**: 2 tubes of serum, 2 tubes of plasma **Pneumoscope** Patients will also be proposed to participate to the Pneumoscope study. Registration of pulmonary sounds will be done with an intelligent stethoscope.
Control Intervention	LDCT (and LUS) will be compared to CXR, preferably with the patient standing and with two incidences, as recommended by international guidelines for the diagnosis of pneumonia.
Study procedures	**OCTOPLUS** The inclusions will be done on working days and hours. Performance of CXR, LDCT and LUS, in all patients during their time in the ED. CXR will be interpreted in real-time by the resident radiologist. LDCT will be interpreted in real-time by another radiologist. LUS will be performed by another clinician than the clinician in charge, and LUS practice of the former will be standardized before the launching of the study. After identification in the emergency department, included patients will be randomized 1:1:1 to one of the following three arms (stratified by participating center): -Only CXR (image and standardized report)) will be available to the clinician (control arm). LDCT and LUS will be performed but not available (clinician will be blinded to LDCT and LUS)

	-Only LDCT (image and standardized report) will be available to the clinician (first intervention arm). CXR and LUS will be performed but not available (clinician will be blinded to CXR and LUS) -Only LUS (image and standardized report) will be available to the clinician (second intervention arm). CXR and LDCT will be performed but not available (clinician will be blinded to CXR and LDCT) The blinding will be maintained during the first 5 days, and hence will not influence the diagnosis and the treatment of the patient. Before discharge of the ED, the clinician in charge will be asked to assess on a 3-level Likert scale the probability of pneumonia (high, intermediate, low level) while considering all available clinical and biological data, plus the imaging modality according to the randomization arm. He will document the intended treatment strategy (antibiotic prescription or not, which molecule, for which indication if not for pneumonia, intended duration). He will be allowed to prescribe antibiotic for another indication than pneumonia by documenting a principal alternative diagnosis (e.g. urinary tract infection, acute exacerbation of a chronic obstructive pulmonary disease, cardiac failure...) and strongly encouraged not to prescribe antibiotic for pneumonia if he rated a low probability of the disease. Patients will be followed-up daily during the hospitalization by research staff and by phone up to 3 months to assess readmission as well as mortality. A previously trained panel of experts will adjudicate the final diagnosis in all patients, having access to all data (clinical, CXR, LDCT and LUS and outcome data at day 28), while blinded to the allocation arm. Their diagnosis will be considered as the reference diagnosis. **Safety** Number of death and admissions to the ICU in each arm will be communicated to a dedicated data safety monitoring board after 200 inclusions for a safety interim analysis. **Blinding of the imaging modalities**: For each patient, the two blinded imaging modalities will be registered on a secured research picture archiving and communication system (PACS). The CRFs filled for these imaging modalities will be kept unavailable during the time of the blinding. **Unblinding:** The research staff will ensure that unblinding (of imaging and CRF) is done at day 5 and that all results are available in the electronic health record. Unblinding will be performed at the ED if the radiologist/clinician performing LUS diagnoses immediately life-threatening findings: pneumothorax, pleural effusion in large quantities (white lung) with mediastinal shift, complete atelectasis of one lung, indirect sign of aneurysmal rupture (haemomediastinum), massive pericardial effusion, tracheal foreign body, pneumoperitoneum, haemothorax, pneumomediastinum, suspicion of acute tuberculosis. Pulmonary embolism won't be excluded as LDCT will be performed without intravenous contrast.

	In case of such finding, the radiologist interpreting CXR or LDCT and clinician performing LUS will call in emergency the investigator to be allowed to communicate the results to the clinician. In case of subsequent clinical deterioration, the clinician in charge of the patient may prescribe any new imaging deemed necessary: a new CXR for the diagnosis of heart failure; injected full-dose chest CT scan to eliminate a pulmonary embolism or to a suppurative complication. Nevertheless, the local investigator will be able to proceed to a deblinding in justified cases.
Study Duration and Schedule	3 years (2 years of recruitment plus 3 months of follow-up for OCTOPLUS and one year for GEROBIOTA) Planned 06/2021 of First-Participant-In Planned 12/2023 of Last-Participant-Out for OCTOPLUS Planned 09/2024 of Last-Participant-Out for GEROBIOTA
Investigator(s)	**OCTOPLUS** **Principal investigator** Dr Virginie Prendki; Division of Internal Medicine of the Aged, Department of Rehabilitation and Geriatrics, Geneva University Hospitals and University of Geneva (HUG), Hôpital des Trois-Chêne, Chemin du Pont-Bochet 3, 1226 Thônex-Geneva, Switzerland, Email: virginie.prendki@hcuge.ch, Tel: +41795538308 **Name(s) of all head investigator(s) of each site** - Geneva Trois-Chêne (HUG); Dr Virginie Prendki (see above) - Geneva Cluse-Roseraie (HUG): Dr Jérôme Stirnemann, Department of Internal Medicine, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Email: jerome.stirnemann@hcuge.ch, Tel: +41 22 372 9101 - Bern: Pr Wolf Hautz MME, Department of Emergency Medicine, Inselspital University Hospital Bern, Freiburgstrasse, 3010 Bern, Email: wolf.hautz@insel.ch, Tel: +41 31 632 4587 - Lugano: Pr Enos Bernasconi, Department of Infectious Diseases, Ospedale Regionale Civico, Via Tesserete 46, 6903 Lugano, Email: enos.bernasconi@eoc.ch, Tel: +41 91 811 60 22 - Rennaz: Pr Nicolas Garin, Department of Internal Medicine, Riviera-Chablais Hospitals, Route de Morgins, 1870 Monthey, Email: nicolas.garin@hopitalrivierachablais.ch, Tel: +41 24 468 8075 **CIRCUS** PI CIRCUS: Prof. Dr. Wolf Hautz, University of Bern Co-Investigators CIRCUS: Prof. Stefan Schauber, University of Oslo, Dr. Juliane Kämmer, Max Planck Institute for Human Development Berlin, Dr. Stefanie Hautz and Dr. Thomas Sauter, University of Bern **GEROBIOTA** Principal investigator: Dr Virginie Prendki Including centers: Geneva and Bern **Pneumoscope** Principal investigator: Pr Alain Gervaix Including center: Geneva.
Study Center(s)	Swiss multicenter study, total of 5 centers: Geneva Trois-Chêne, Geneva Cluse-Roseraie, Bern, Lugano, Rennaz (Hôpital Riviera Chablais).

Data privacy	Privacy and confidentiality of the patient's medical data will be maintained through the study. eCRFs and all other documents sent to the sponsor will be de-identified and carry only the numeric patient's identifier code. The study site will maintain the link between the patients' identifier code and their name. All electronic data will be password protected, and any paper documents will be stored in a locked cabinet. For monitoring, audits, and regulatory inspections, source data and documents will be made available, per routine protocols. Direct access to source documents will be permitted for purposes of monitoring, audits and inspections and should declare who will have access to protocol, dataset, statistical code, etc. during and after the study (publication, dissemination). The investigating team will provide direct access to all trial-related source data, documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities. The investigators will comply with the rules enacted by the Swiss Academy of Medical Sciences for biobanks, particularly concerning quality standards, data protection, transfer of samples and data. They will comply with the Swiss Human Research Act (HRA). Samples will be de-identified as soon as possible, but at the latest upon arrival of the sample in the biobank. Each sample will be coded, and access to personal data will be impossible without the code, which will be conserved separately. The code file will be kept by a designated member of the research staff, who will not be directly involved in research and analysis on the biobank samples. A specific consent form will be signed by the patient, allowing storage and re-use of his/her biological samples for research aims, including research on biomarkers and genetic polymorphisms associated with respiratory infection. The patient will be free to be included in the main cohort study, in both OCTOPLUS and GEROBIOTA or in none of them. He will be allowed to withdraw from participation at any moment.
Ethical consideration	**Reasons for inclusion of vulnerable participants**: elderly patients will be included. Although pneumonia is amongst the first causes of morbi-mortality and antibiotic prescription in elderly patients, clinical studies in this population are scarce, in part because informed consent is difficult to obtain due to acute confusion or permanent cognitive impairment. Diagnostic criteria need to be revised in this vulnerable population in order to improve antibiotic prescription and patient management. **Consent**: - The patient has his ability to consent in the emergency room: he signs the standard consent for participant. - The patient has not his ability to consent in the emergency room o he does not express either orally or by any particular behaviour his/her refusal of being part of the research project.

	○ a physician independent of the study will be sought to defend the interest of the patient (HRA 30-31) and sign the dedicated written confirmation Everything will be done to establish the will of the patient as soon as possible ○ the patient recovers his capacity during hospitalization : he signs the standard consent for participant. ○ the patient is known to no longer have the ability to consent or does not recover his ability to discern during hospitalization: the relative/legal representative sign the dedicated consent.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

By 2050 one in four persons in Europe and Northern America will be aged 65 years or over according to demographic projections (1). Pneumonia principally affects older people, with two thirds of patients hospitalized for pneumonia were more than 70 years old in a nation-wide German study (2). Accordingly, the burden of pneumonia on health and economic outcomes is expected to increase. Pneumonia is also the most frequent cause of antimicrobial therapy prescription in this population (3) (4). However, studies specifically investigating the elderly are scarce.

According to international guidelines, the diagnosis of pneumonia is based on clinical signs and symptoms and the presence of a new infiltrate on chest x-ray (CXR) (5) (6).The challenge in diagnosing pneumonia is to distinguish it from milder forms of respiratory infections, which do not require antibiotic treatment, and from other medical conditions. In fact, the clinical presentation of other common conditions in the elderly like acute heart failure, chronic obstructive pulmonary disease exacerbation, pulmonary embolism, lung cancer, non-infectious pneumonitis and non-respiratory sepsis overlaps with pneumonia. Signs and symptoms of pneumonia have poorer sensitivity and specificity in older patients, who also have a higher prevalence of abnormalities on CXR due to concomitant conditions, further compounding the diagnostic issues (7) (8) (9) (10) (11) (12).Indeed, more than one disease can simultaneously affect the same individual, with frequent comorbidities like heart failure exacerbating by infection (13) (14). Accordingly, it is not surprising that the specificity of an initial diagnosis of community-acquired pneumonia in hospitalized patients is low compared with the final diagnosis, with a positive predictive value of only 60% to 75% (15) (16). Misdiagnosis of pneumonia may translate into inappropriate antibiotic prescription, but also in harmful delays in the correct management of the real cause of patients' symptoms, an understudied issue. Finally, CXR also lacks sensitivity to detect pneumonia, which exposes patients to the risk of late initiation of appropriate antibiotic treatment (17).
Alternative imaging strategies have been proposed to surpass the acknowledged drawbacks of the current diagnostic work-up of pneumonia. The use of computed tomography (CT) scan is recommended by some authors if standard imaging is inconclusive (17) (18). In a cohort of 319 adult patients with suspected pneumonia at the emergency department (ED), Claessens et al reported that early CT scan changed the diagnostic classification of pneumonia in 59% of them with an increased probability of pneumonia in 19% (19). For 80% of the patients (i.e. 25% of the total population), modification of pneumonia probability was concordant with the final classification of an adjudication committee that used all available information, including follow-up data. The absolute Net Reclassification Improvement, which calculates the absolute number of patients correctly reclassified, was 60/319 (18%). Most appropriate modifications of pneumonia probability according to the reference diagnosis consisted in downgrading of the probability. The authors also demonstrated the feasibility of rapidly performing a CT scan in the emergency department settings for patients suspected of pneumonia. We obtained similar results with elderly patients in the PneumO-LD-CT cohort (20).The advantages of CT scan could be greater in elderly patients as it can be challenging to obtain good quality CXR and, as mentioned above, pneumonia can be difficult to distinguish from other frequent conditions. Native low-dose CT scan (LDCT) is appropriate to study the lung fields, is free of risks associated with contrast medium injection, and the irradiation burden is low. In the Netherlands, a cluster-randomized clinical trial is underway to determine the added value of LDCT in the diagnostic work-up of pneumonia to minimize selective antibiotic pressure while maintaining patient safety (ClinicalTrials.gov Identifier: NCT03360851). Nevertheless, neither CT scan nor LDCT have been directly compared to CXR in a randomized trial.

Lung ultrasonography (LUS) is another imaging modality under investigation for the diagnosis of pneumonia. LUS is increasingly available as a point-of-care, non-irradiating tool, often being performed directly at the bedside by trained emergency physicians. Diagnostic studies evaluating

LUS have reported a sensitivity of 80% to 90% and a specificity of 70% to 90% in diagnosing pneumonia, using various reference standards (diagnosis of pneumonia at discharge, or occasionally CT scan) (21) (22) (23) (24). In studies using CT scan as the reference standard, LUS showed a higher sensitivity than CXR, with similar specificity (24) (25). LUS was never compared with CXR or LDCT for the diagnosis of pneumonia in a randomized controlled study. Literature on its performance in elderly patients is scarce (26) (27).
Based on these premises, an LDCT or LUS-based work-up of suspected pneumonia may have significant advantages over standard CXR. Superior diagnostic accuracy of either modality can lead to better outcomes for patients through early appropriate management of the actual symptom-causing disease, but also to a more appropriate antibiotics use, a key issue in an era of growing bacterial resistance.
However, only a randomized trial comparing each diagnostic strategy head to head will allow for an unbiased assessment of each strategy's performance on a range of diagnostic, therapeutic and clinical outcomes.

Personal work
We assessed the impact of LDCT on the diagnosis of pneumonia in elderly patients in a prospective observational study, conducted at Geneva University Hospitals (20). We included 200 consecutive hospitalized patients, with a median age of 84 years and with suspicion of pneumonia. We showed that LDCT changed the presumptive diagnosis in a high proportion of patients (45%), with an upgrade in 15% of patients and a downgrade in 30% of patients. LDCT changed the probability of disease in more than 80% of the patients who had an intermediate probability of pneumonia after a standard work-up including CXR. After the use of an adjudication committee blinded to the results of LDCT as the reference diagnosis, the changes in clinician's probability matched the reference diagnoses in 68% of modifications (61/90) and in 31% of all patients (61/200). The absolute Net Reclassification Improvement was 16/200 patients (8%) (20). Correct reclassification was mainly observed in patients not having pneumonia according to the reference diagnosis, suggesting that LDCT will mainly reduce the overdiagnosis of pneumonia (28).
We explored strategies to guide LDCT indication in patients suspected of pneumonia, aiming to perform LDCT preferentially in patients with intermediate risk of pneumonia after standard work-up. We derived a simple prediction score to guide performance of LDCT in elderly patients with a suspicion of pneumonia in our cohort, and validated it in an independent cohort (29). This score, based on four readily available variables, would theoretically allow withholding LDCT in 46% of the patients, with moderate accuracy. In a similar approach, we validated a more complex algorithm in our cohort based on six variables, including the results of viral polymerase chain reaction of nasopharyngeal swabs derived from data obtained in a French cohort (30).

GEROBIOTA
Comorbidities, functional and cognitive impairments and malnutrition are frequently associated with pneumonia of the elderly and its mortality (31) (32) (33). Despite evidence of a link between oral health and the risk of pneumonia, the oral status is not yet routinely screened in elderly patients hospitalized for pneumonia (34) (35). In the same line, aspiration, mostly due to oropharyngeal dysphagia, is a frequent mechanism of pneumonia and is not routinely screened any either (33) (36). Links have been highlighted between oral care and mortality from pneumonia (low level of evidence) (34). A new tool allows to describe the oral function of the elderly, classifying the patient into four different stages: healthy state, oral frailty, oral hypofunction and oral dysfunction (37). Like in other organ systems, microbiota may have a major role in maintaining health in the airways and lungs, being involved in immunity and physiologic homeostasis, and preventing colonization by respiratory pathogens (38) (39). An imbalanced oropharyngeal and respiratory microbiota is known to raise the susceptibility to pneumonia (40). Moreover, inflammation, vaccinal response, and genetic markers are other factors involved in the occurrence and the outcome of pneumonia. Long-term mortality and readmission are associated with persistent inflammation in patients hospitalized with sepsis (41). The links between inflammation, poor response to vaccination and microbiota need to be further investigated (42)

(43). At last, genetic variants of the FER gene (encoding protein-tyrosine kinases) and interferon regulatory factor 5 are associated with susceptibility to and severity of pneumonia (44) (45).
In GEROBIOTA, we aim to identify factors associated with the diagnosis of pneumonia in the elderly and its recurrence, the most important being oral hypofunction and the presence of particular oral/respiratory microbiota. A biobank (including serum, plasma and saliva) at admission and discharge will allow the assessment of inflammation, immune, and genetic markers.

We described the risk factors for pneumonia in the elderly patients in two narrative reviews (one being under review), highlighting the relevance of oral health and microbiota (46) (47).The Division of Gerodontology is currently undertaking a pilot study to validate the oral hypofunction tool (37). The Genomic Research Laboratory, which has expertise in the application of metataxonomic and metagenomic tools from sample preparation to data analysis, showed that oropharyngeal and tracheal microbiota cluster close to salivary and throat microbiota (48) (49) (50). In a recent work, metataxonomic data from oropharyngeal secretions and endotracheal aspirate samples obtained from intubated patients showed that bacterial diversity, and intra and inter-individual similarity decreased over time, while the abundance of several taxa changed significantly. Overall microbiota profiles of oropharyngeal secretions, and the abundance of certain bacterial taxa in oropharyngeal and tracheal secretions at baseline correlated with the later development of ventilator-associated pneumonia during intubation (51).

Risk category
The risk category of the study according to ClinO, Art. 61 is classified A, because CXR, LDCT and LUS are prescribed everyday in clinical practice and very often at the ED. The irradiation induced by a low-dose CT scan is low, about 1 mSv and under the Swiss annual irradiation) and there is no intravenous injection.

3. STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

Overall aim: To compare the diagnostic, therapeutic and clinical outcomes of three diagnostic strategies based on CXR (standard care), low-dose CT scan (LDCT) or lung ultrasonography (LUS) in elderly patients with suspected community or nursing-home acquired pneumonia in the ED.

Primary objective: To evaluate whether a diagnostic strategy using LDCT compared with CXR leads to a more accurate diagnosis in suspected pneumonia.

Secondary objectives:
Diagnostic objectives:
- To assess the difference in diagnostic accuracy for patients with suspected pneumonia using LUS compared to CXR, and using LUS compared to LDCT
- To assess sensitivity and specificity of CXR, LDCT and LUS; the number of additional imaging studies and invasive procedures prescribed during the acute setting; the imaging studies needing unmasking in emergency; the incidentalomes.

Treatment objectives: to assess whether there is a difference between the diagnostic strategies in:
- Antibiotic consumption up to one month

Clinical objectives: to assess whether there is a difference between the diagnostic strategies in:
- Time to clinical stability
- Length of hospital stay

- Unplanned transfer to the intensive care unit or operating room
- Admission to rehabilitation/long-term care facility (LTCF) up to 3 months
- All-cause mortality up to 3 months
- All-cause readmission up to 3 months
- Quality of life at admission, discharge and 3 months

Cost outcomes
Diagnosis concordance between physicians at the ER and experts
The association of biomarkers and the presence of an infiltrate.

GEROBIOTA objectives
To identify factors associated with the probability of pneumonia, and aspiration pneumonia, 1 month and 1 year mortality, 1 year readmission and to create a biobank allowing the assessment of inflammation, immune status and genetic markers.

3.2 Primary and secondary endpoints

Primary outcome measure:
The primary outcome will be the difference in accuracy between LDCT and CXR, assessed at the end of the ED evaluation, using the expert panel as the reference standard, accuracy being computed as (true positive + true negative cases) / (true positive + true negative + false positive + false negative cases).

Main secondary outcome measures:
Diagnostic outcomes:
- Difference in accuracy between LUS and CXR, assessed at the end of the ED evaluation, using the expert panel as the reference standard
- Sensitivity, specificity of CXR, LDCT and LUS
- Number of additional imaging studies and invasive procedures prescribed during the acute setting
- Prevalence of viral pneumonia
- Prevalence of unmasked imaging results (for an emergency finding)
- Prevalence of incidentalomes

Treatment outcomes:
- Number of antibiotic free days at day 30

Clinical outcomes:
- Time to clinical stability during the first 2 weeks (number of days from admission to the first time all of the following parameters are above/under the threshold value and maintained for a minimum of 24 hours: heart rate <100 beats/min, systolic blood pressure >90 mmHg, temperature <37.8°C (axillary or tympanic), respiratory rate <24 breath/min, oxygen saturation >90% while breathing room air, or need for more than 28% fraction of inspired oxygen to maintain adequate oxygen saturation, resolution of delirium if present at admission)
- Length of hospital stay (in the ED and in the acute setting)
- Proportion of patients with an unplanned transfer to the ICU
- Proportion of patients admitted to rehabilitation or LTCF days through 3 months
- All-cause mortality through 1 month and 3 months
- All-cause readmission to the acute care setting through 1 month and 3 months
- Quality of life at admission, discharge and 3 months **(**measured by EQ-5D-3L and a CAP score questionnaire)
- Interagreement rate for the probability of pneumonia between physicians participating to the trial and a consensus of experts in chest imaging, for each method

- Association between biological markers (CRP and PCT) and the presence of an infiltrate

Cost outcomes:
Costs of care, physician, imaging, laboratory, treatment (including antibiotic therapy) and others per patient, health related quality of life until 3 months; unit of work consumption per hospital (number of minutes of care, physician, laboratory and imaging points)

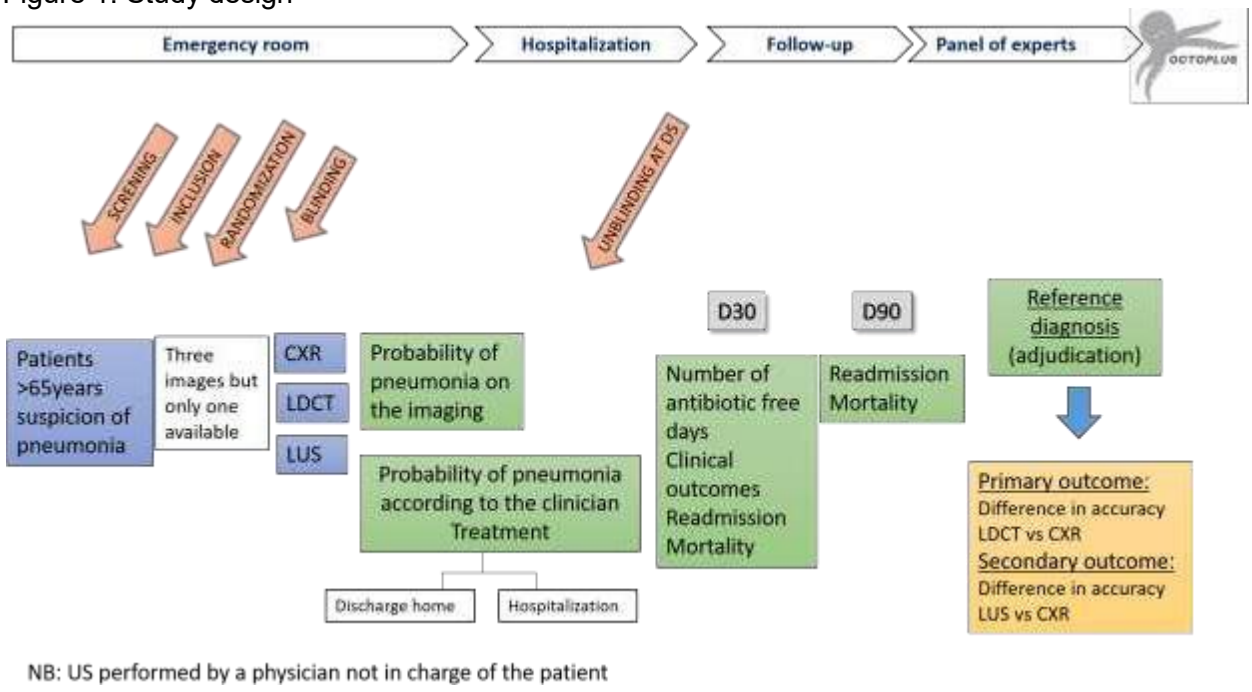
Safety outcomes: unplanned transfer to the ICU; 1-month mortality.

GEROBIOTA:
The probability of pneumonia/aspiration pneumonia according to the panel of experts, all cause 1 month and 1 year mortality, 1 year readmission for pneumonia.

3.3 Study design

This is a Swiss multicentre superiority randomized clinical study with 3 parallel arms. Randomization will be 1:1:1 using randomly permutated block sizes and be stratified by centre. Patients will be either randomized into the CXR, the LDCT or the LUS arm. The 3 imaging modalities will be performed in all included patients but only one will be available to the clinician according to the allocation arm. The concealed results of the imaging procedures will be unblinded at day 5. The duration of follow-up will be 3 months for OCTOPLUS. The panel of experts will provide their diagnosis a posteriori. An intermediate safety analysis will be performed after 200 patients have completed the 1-month follow-up.

Figure 1: Study design



NB: US performed by a physician not in charge of the patient

Known or potential problems associated with the trial design:
-Insufficient **recruitment**: given the case load of the participating centres and the required sample size, this scenario is unlikely.
-**Risk of the CT**: LDCT is well-tolerated and its mean radiation exposure is much lower than a full-dose CT scan (about 1mSv) (52). In a previous study, a mean (sd) radiation exposure of 1.5 (0.47) mSv was measured, which can be compared to the mean (sd) exposure of conventional CXR of 0.05 (0.03) mSv (20).

-**Risk of LUS**: there will be many clinicians performing LUS at each site. LUS is known to have a fast-learning curve. To minimize heterogeneity between the clinicians and centres, standardization of LUS practice will be performed in all participating centres before the beginning of the study.
-**Risk of the blinding**: blinding is one of the major challenges of the trial. It will be performed in each site using a secured research picture archiving and communication system (PACS) thanks to radiologist engineering. To allow for compliance and smooth running of the study, all ED and radiology staff will be regularly informed regarding methods and stakes. As soon as the patient is included, the research staff will anticipate and inform the radiology staff who will take care of the patient, and the clinician to perform LUS about the necessity of blinding and the CRF to fill in. The research staff will be the only one able to provide the attending clinician with the result of the allocated imaging modality, and ensure that it is accessible in the patient's medical record. The two other imaging modalities will be concealed until day 5, and will only be accessible on the PACS.
According to a predefined list of emergency findings, the radiologist interpreting CXR or LDCT or the clinician performing LUS will be able to immediately ask the investigator for unblinding.
At day 5, the research staff will ensure that the two blinded imaging modalities are made accessible again to the treating clinician.
-**The risk of a false negative** (meaning a missed diagnosis of pneumonia) will be counterbalanced by the fact that the clinician will be allowed to prescribe antimicrobial therapy for another diagnosis than pneumonia. As patients with severe pneumonia will not be included, a delay of a few hours in the diagnosis of pneumonia is unlikely to lead to an unfavourable outcome. Indeed, a longer time to antibiotic administration was not associated with an unfavourable outcome in moderately severe CAP (53).
-The **panel of experts**: we already used the Delphi method with a panel of experts for the reference diagnostic in our previous study. The panel of experts will be composed by board-certified specialists in infectious diseases, respiratory diseases, internal medicine and radiology. All will be senior attending physicians with expertise in caring for patients with pneumonia. They will be previously trained for the diagnosis of pneumonia using international and Swiss guidelines. They will have access to all imaging studies, to avoid any potential incorporation bias.
-**Coordination**: as this is a multicentre and multidisciplinary trial, particular emphasis will be put on coordination.

Finally, we estimated that risks inherent to the trial are minimal and inferior to the benefices of the study which could deliver key results which would provide long-term benefit to all patients with pneumonia.

Sequential realization of the 3 imaging modalities may delay the final working diagnosis of the physician in charge. However, this delay will be minimized by the research staff, who will make any effort to guarantee quick delivery of all diagnostic procedures. As severe pneumonia will not be included, a delay of at most a few hours before adequate treatment is not expected to have a negative impact on patients' evolution (54). All imaging must be done before leaving the ED. A transfer from one ED to another is not considered as an exit from the ED (e.g. a transfer of the 3-Chêne to Cluse-Roseraie for Geneva)

Methods of minimising bias:
-Stratified randomization will be used in this study.
-Allocation sequence
Participants will be randomized 1:1:1 to either the CXR, the LDCT, or the LUS arm as per a computer-generated randomization schedule stratified by study centre using investigator blinded randomly permuted blocks of varying size.
-Concealment mechanism
Patients will be randomized via eCRF directly.
-Implementation

An independent statistician will create confidential randomization lists for each site. The lists will be given to the data-manager to implement the randomization list in the eCRF. Each site will have a dedicated research staff responsible for approaching patients attending the ED regarding inclusion in the study. The triage nurses and the physician working at the ED will also be asked to help the study team by alerting the research staff to the presence of any potential participant. The site's coinvestigator(s) will also be on hand to answer any additional questions the patient might have. If the patient agrees to participate in the study, the patient's written informed consent will be obtained and the study coordinator randomized the patient directly through the eCRF. The research staff will keep the "crosswalk", a table linking the participant's randomization number with his/her identifying data, in a locked document.

3.4. Study intervention

CXR, LDCT and LUS are prescribed at ED for the diagnosis of pneumonia, but have never been compared to each other in a randomized trial.
NB: only the first imagery made accessible to the participant will be billed
Experimental interventions
LDCT will be performed at the radiology unit of the ED. There will be no administration of intravenous contrast. Interpretation will be done in real-time by a radiologist who will record his probability of pneumonia on a specific CRF.
LUS will be performed at bedside in the ED by a physician trained in point-of-care LUS for pneumonia, and different from the treating clinician. He/she will also record his probability of pneumonia.
As with all ultrasound examinations, it will be important to standardize the examination procedure for LUS to minimize the influence of setting and examiner. Standardization will be performed among centres, before the beginning of the study. The ultrasound and educational experts, experienced as directors of Point-of-Care Ultrasound Certification (POCUS) courses and approved instructors of thoracic ultrasound, will supervise this standardisation procedure.
Control intervention
The control diagnostic procedure will be CXR, preferentially standing, and with 2 incidences, which is the recommended and most commonly used diagnostic imaging technique for pneumonia in guidelines (5) (6) (55). A radiologist other than the one who interpreted LDCT will evaluate the CXR and rate his/her probability of pneumonia and fill in a specific CRF.

Patients who already had CXR, LDCT and LUS prior to randomization will be excluded.

Registration of pulmonary sounds will be done in a securized Cloud with an intelligent stethoscope in the Pneumoscope study (protocol in appendix).

4. STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

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. and at least one sign or laboratory finding compatible with an infection (temperature >37.8°C or <36.0°C, CRP >10 mg/L, PCT >0.25µg/L, leukocyte count >10G/L with >85% neutrophils or band forms) will be required
   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 and before the arrival to the ED
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 enrollment into the current study

Reasons for inclusion of vulnerable participants:
Patients over 65 years of age presenting to the ED with a suspicion of pneumonia will be included, even if the potential benefit is not restricted to elderly patients. As pneumonia is a common pathology in elderly patients, our study will frequently include vulnerable participants, e.g. participants incapable of judgment or participants under tutelage (of note, one third of the patients of the PneumO-LD-CT cohort had dementia or delirium and consent was obtained from next of kin). We think it is meaningful to study this population because overdiagnosis of pneumonia and over-prescription of antibiotics in the elderly is likely. Moreover, although being more affected by the disease, elderly patients are often excluded from clinical trials in part because informed consent is difficult to obtain due to delirium or permanent cognitive impairment. This results in guidelines and recommendations being developed on a younger and healthier population, although they are mainly used for elderly patients. Diagnostic criteria need to be revised in this vulnerable population in order to improve antibiotic prescription and patient management.

4.2 Recruitment, screening and informed consent procedure

Recruitment:
Patients will be recruited at their admission to the ED during the triage process. Inclusions will be done on working days and hours.
The participating sites will identify all eligible patients. The investigator and the research staff will approach each potential patient and inquire about their interest and eligibility in participating in this study. This inquiry will include screening questions to confirm eligibility as well as a description of the study and responsibilities for participating. All enrolled patients should be followed up within the study, except if their participation is prematurely terminated.
The recruitment period will be up to 2 years, during which 500 patients are planned to be enrolled, which means between 1 to 2 patients per site and per week. If the enrolment goals are not met, the study will be extended until achievement. The recruitment is competitive between the sites.

Emergency situation (HRA, Art. 30-31 and OClin Art. 15)
This study is carried out in an emergency situation and the expected results can only be achieved in an emergency situation. Indeed pneumonia is a major cause of morbidity and mortality and of antibiotic prescription in hospitalized patients whom prognosis is engaged. Making the diagnosis and the decision of treating the patient consulting the ED must be performed within first hours (the international guidelines recommend treating the patient while he/she is still in the ED for a suspicion of pneumonia).

Description of the informed consent process (HRA, Art. 7, 16, and 18, 42; ClinO, Art. 7 - 9) including time for consideration given to the participants:
The investigators will explain to each participant/or their representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant or their representative will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment. The participant or his/her representative will be informed that the medical records may be examined by authorised individuals other than their treating physician.

Consent:

- The patient has his ability to consent in the emergency room: he signs the standard consent for participant.
- The patient has not his ability to consent in the emergency room
    - he does not express either orally or by any particular behaviour his/her refusal of being part of the research project.
    - a physician independent of the study will be sought to defend the interest of the patient (HRA 30-31) and sign the dedicated written confirmation

Everything will be done to establish the will of the patient as soon as possible

- the patient recovers his capacity during hospitalization : he signs the standard consent for participant.
- the patient is known to no longer have the ability to consent or does not recover his ability to discern during hospitalization: the relative/legal representative sign the dedicated consent.

CIRCUS: an information letter will be given to the clinican in charge of the patient at the ED (appendix).

GEROBIOTA
The patient will be able to participate to **GEROBIOTA** in Geneva and Bern. He will also be asked to give his consent to participate to the **biobank**.

Pneumoscope
The patient will be able to participate to **this ancillary study** when included in Geneva.

4.3 Study procedures

3 years (2 years of recruitment plus 3 months of follow-up for OCTOPLUS and one year for GEROBIOTA), inclusions on working days and hours (see Figure 1)
CXR will be interpreted in real-time by a first radiologist and a CRF will be filled in, including the probability of pneumonia.
LDCT will be interpreted in real-time by another radiologist and a CRF will be filled in, including the probability of pneumonia. Both will be blinded to the other's interpretation.
LUS will be performed by another clinician than the one in charge of the patient, and his practice of LUS will be standardized before the launching of the study.
After identification in the ED, included patients will be randomized 1:1:1 to one of the following three arms (stratified by participating center):
-Only CXR (image and CRF) will be available to the clinician (control arm). LDCT and LUS will be performed but not available (clinician will be blinded to LDCT and LUS)
-Only LDCT (image and CRF) will be available to the clinician (first intervention arm). CXR and

LUS will be performed but not available (clinician will be blinded to CXR and LUS)
-Only LUS (image and CRF) will be available to the clinician (second intervention arm). CXR and LDCT will be performed but not available (clinician will be blinded to CXR and LDCT)
The blinding will be maintained during the first 5 days, and hence will not influence the diagnosis and the treatment of the patient.
Before discharge of the ED, the clinician in charge will be asked to assess on a 3-level Likert scale the probability of pneumonia (high, intermediate, low level) while considering all available clinical and biological data, plus the imaging modality according to the randomization arm.
He will document the intended treatment strategy (antibiotic prescription or not, which molecule, for which indication if not for pneumonia, intended duration).
He will be allowed to prescribe antibiotic for another indication than pneumonia by documenting a principal alternative diagnosis (e.g. urinary tract infection, acute exacerbation of a chronic obstructive pulmonary disease, cardiac failure...) and strongly encouraged not to prescribe antibiotic for pneumonia if he rated a low probability of the disease.
Patients will be followed-up daily during the hospitalization by research staff and by phone up to 3 months to assess readmission as well as mortality.
A panel of experts will adjudicate the final diagnosis in all patients, having access to all data (clinical, CXR, LDCT and LUS and outcome data at day 28), while blinded to the allocation arm. Their diagnosis will be considered as the reference diagnosis.

Safety: Number of death and admissions to the ICU in each arm will be communicated to a dedicated data safety monitoring board after 200 inclusions for a safety interim analysis.

Blinding of the imaging modalities: For each patient, the two blinded imaging modalities will be registered on a secured PACS. The CRFs filled for these imaging modalities will be kept unavailable as well as images until day 5.

Unblinding: The research staff will ensure that unblinding of imaging and CRFs is done at day 5 and that all results are available in the electronic health record.

Unblinding will be performed **in emergency** at the ED if the radiologist/clinician performing LUS diagnoses immediately life-threatening findings: pneumothorax, pleural effusion in large quantities (white lung) with mediastinal shift, complete atelectasis of one lung, indirect sign of aneurysmal rupture (haemomediastinum), massive pericardial effusion, tracheal foreign body, pneumoperitoneum, haemothorax, pneumomediastinum, suspicion of acute tuberculosis (NB: pulmonary embolism won't be excluded as LDCT will be performed without intravenous contrast).

In case of such finding, the radiologist interpreting CXR or LDCT and the clinician performing LUS will call in emergency the investigator to be allowed to communicate the results to the clinician.
In case of subsequent clinical deterioration, the clinician in charge of the patient may prescribe any new imaging deemed necessary: a new CXR for the diagnosis of heart failure; injected chest CT scan to eliminate a pulmonary embolism or a suppurative complication.
Nevertheless, the local investigator will be accessible and able to proceed to a deblinding in justified cases.

GEROBIOTA

At admission:
-Microbiota samples (saliva and respiratory samples) before antibiotic administration at the ED if possible. They will be stored at -80.
NB: respiratory samples will be those taken for routine methods including sputum, induced sputum, tracheal aspirate or broncho-alveolar lavage if done and still available

-Blood: Serum (2 tubes), plasma EDTA (2 tubes), plasma citrate (2 tubes), PAX gene DNA (1 tube), PAX gene RNA (1 tube).

During hospitalization:
-Oral health examination by a medical dentist as soon as the patient is stabilized (≈30 min)
-Geriatric assessment by the research staff during the first week of hospitalization (≈45min)

At discharge: 2 tubes of serum, 4 tubes of plasma

Table 1: Timeline of patient enrolment/allocation, interventions, and assessments

Study periods	Screening	Inclusion	Discharge from the ED	Discharge from the acute setting	1 month	3 months	Reference diagnosis
Visit	1	2	3	5	6	7	8
Time (day)	From the ED admission until the ED discharge (D0).			d15	d30	d90	
Windows (days)	NA	NA	NA	-2/+5	-2/+10	-2/+15	NA
Patient/representative IC or independent physician	x						
In-/exclusion criteria	x						
Randomization		x					
Demographics		x					
Medical history		x					
Physical examination	x						
Vital signs Time to clinical stability	x	x	x	x			
Laboratory tests	x						
CXR, LDCT, LUS		x					
Main diagnosis, other diagnosis, and therapeutic outcomes before ED discharge			x				
No. of days of AT prescription Other diagnosis outcomes				x			
Clinical outcomes (safety outcomes)				x	x	x	
QoL questionnaire		x		x		x	
Panel of experts							x

AT = antimicrobial therapy, CXR = chest x-ray, ED = emergency department, IC = informed consent, LDCT = low-dose computed tomography, LUS = lung ultrasonography, QoL = quality of life

Table 1 bis: GEROBIOTA

Study period	Inclusion	Hospitalization	Discharge	1-year
Biobank	x		x	

Geriatric and oral health assessment		x (once)		
Phone call				x

Table 2 : Interventions in both studies

OCTOPLUS	GEROBIOTA
CXR, LDCT and LUS	Blood (30 ml), saliva, respiratory samples (biobank) at admission
Follow-up during the hospitalization by the research staff	Oral health assessment and Geriatric assessment during hospitalization
Phone call at 1 and 3 months	Saliva and blood (6 tubes) (biobank) before discharge
	Phone call at 1 year

Measures taken to reduce biases:

-**Blinding of patients, attending physicians, investigators**:

-the clinician in charge will know the allocation arm but will be blinded to the results of the two other exams

-the radiologist interpreting LDCT will not have access to CXR and LUS

-the clinician performing LUS will have access to the electronic file (including clinical data) but not to CXR and LDCT

-the participants will be blinded, meaning they will know their diagnosis but not the allocation arm

-the panel of experts will be blinded to the arm of allocation and to the probability of pneumonia according to the clinician to perform the final review

-the investigators will be blinded to the allocation arm

-**Blinding of outcomes assessment and data analysis**:

Clinical data on all included patients will be collected by the study personnel and recorded in the CRF and database. HUG data managers experienced in generating blinded reports will then provide data exports to a blinding outcomes accessor and a blinded data analyst. These exports will contain recoded study identification numbers and no information on diagnostic assignments allowing for both fully blinded outcomes assessment and data analysis. For analyses, data management will be asked to export data with only coded treatment group labelling.

-**Blinding of the imaging results**:

As explained above, these blinded results will be available on a research PACS until day 5, when the research staff will proceed to unblinding.

4.4 Withdrawal and discontinuation

Withdrawal:

If a patient wishes to withdraw consent, the investigator will be informed, and the patient will be excluded from the study without any consequence on his care.

As the validity of the clinical trial or its results could be distorted in essential points by the destruction of biological material and personal health-related data, their use in the clinical trial will allowed despite the refusal of the patient. Since pneumonia is very frequent in elderly patients and since this population is very rarely included in clinical trials, we think it is very important to carry out this trial and not to destroy data which would be valuable for further elderly patients having pneumonia.

In case of protocol violation, the patient will stay in the randomized arm for the intention to treat analysis and will be excluded from the arm for the per protocol analysis. If the patient gets lost to follow-up, the data will be censored after the last visit. In case of death, the civil registry will be consulted regarding the information on mortality.

Death of the patient:

In case of death before obtaining provisional consent, there will be no inclusion.
In case of death of the person after provisional consent, it will be verified whether the patient has issued Advance Directives authorizing the use of data or biological materials for research purposes. If this is not the case, the consent of the representative will be necessary.

5. STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Methodology
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We hypothesize that the proportion of patients with a correct diagnosis of pneumonia (proportion of true positive plus true negative) will be higher in LDCT arm than in CXR arm. The null hypothesis that will be tested in the primary analysis is the equality of proportion of correctly classified patients in LDCT and CXR arm.
The analysis will follow the intention to treat principle. A sensitivity analysis will be conducted on the per protocol population (i.e. excluding patients who have not received the allocated intervention, and patients who crossed over). Another sensitivity analysis will be conducted excluding patients who will have had CXR before LDCT and LUS.
The diagnosis made by the panel of experts will be the reference diagnosis for calculation of the primary outcome in each arm, and to determine diagnostic accuracy expressed as sensitivity, specificity, predictive values and likelihood ratios. The primary outcome in each arm will be compared to the two other ones.

Primary analysis
The reference diagnosis will be positive (respectively “negative”) if the panel of experts rates the probability of pneumonia diagnosis “intermediate” or “high” (respectively “low”) on the Likert scale. The clinician’s diagnosis will be positive (respectively “negative”) if the clinician rates the probability of pneumonia diagnosis “intermediate” or “high” (respectively “low”) on the Likert scale. We will assume an adequate diagnosis classification, if the clinician’s diagnosis and the reference diagnosis (panel of experts) agree (true positive and true negative diagnoses). The proportions of correctly classified patients in the LDCT and CXR arms will be calculated with 95% Clopper-Pearson confidence intervals (CIs), and will be compared with a logistic regression model adjusted for sites to account for the stratified randomization. The statistical test will be two-sided and the significance threshold will be 0.05.

Secondary analyses
1) The proportion of adequate diagnoses in the LUS arm will be also calculated with the 95% Clopper-Pearson CI, and will be compared with the CXR arm using a logistic regression model adjusted for sites.
2) Similarly, the proportion of adequate diagnoses in the LUS arm will be compared with the LDCT arm.
3) The sensitivity (proportion of positive diagnoses among patients with a positive reference diagnosis) and specificity (proportion of negative diagnoses among patients with a negative reference diagnosis) will be also calculated with 95% Clopper-Pearson CIs in each arm. The

sensitivity between the LUS and CXR arms and between the LUS and LDCT arms will be compared using a logistic regression model adjusted for sites.
4) Positive and negative predictive values, and likelihood ratios will be calculated with 95% Clopper-Pearson CIs in each arm.
5) As a sensitivity analysis, the primary and secondary analyses 1) to 4) will be repeated, whereby only the level “high” on the Likert scale is regarded as positive diagnosis (clinician’s diagnoses and reference diagnoses).
6) Treatment outcomes: The cumulative incidence of antibiotic free patients will be investigated over 30 days by using a non-parametric competing risk model with death before antibiotic intake as a competing event and will be compared between arms. Comparisons will be stratified on sites.
As a sensitivity analysis, this analysis will be repeated excluding exacerbation of COPD, where the need for antibiotic therapy is still debated.
7) Diagnosis outcomes: We will describe each of the alternative diagnoses by frequencies in each arm, and the percentage of patients with an alternative diagnosis consistent between radiologists and experts will be evaluated. 95% Clopper-Person CIs will be reported. The proportions of imaging results needing unmasking and of additional radiological studies (and invasive procedures) during the 2 first weeks will be also reported with their 95% Clopper-Pearson CIs. A post-hoc procedure will be applied for pairwise comparisons.
8) Clinical outcomes: We will use Kaplan Meier’s estimates to evaluate the time to clinical stability over 15 days in each arm, and a log-rank to compare them. Patients who die in the first 2 weeks will be censored at day 15 (i.e. considered has never reaching clinical stability). The Mann-Whitney test will be used to compare the length of hospital stay between the groups. The proportion of patients with an unplanned transfer to the ICU or operating room will be reported by arm and compared between the arms using a logistic regression model adjusted for sites. All-cause mortality during the 3-month follow-up will be investigated with Kaplan Meier’s survival curves, and compared between the arms using a log-rank test stratified on sites. Readmissions during the 3-month follow-up will be investigated using survival models with competing risk. Death before readmission will be the competing event.
9) Cost outcomes: Mean cost per patient will be assessed and compared between arms using multiple linear regression models adjusted for sites. Reweighted estimators will be used to account for censoring.
10) Interagreement rate for the probability of pneumonia rated on a 3-level Likert scale: the agreement between raters participating to the trial and a consensus of two experts will be investigated by using kappa statistics.
11) The association between biological markers (CRP and PCT) and infiltrates will be assessed by differences in the mean levels of markers between patients with and without infiltrates and tested by using t test. Transformations on markers will be applied if needed. Multiple linear regression models will be used for adjustment. Similar methods will be used to investigate the association between markers and the probability of pneumonia rated on the 3-level scale. The analyses will be conducted for each arm.

Interim and safety analyses
There will be no comparative analysis for efficacy or futility. An initial safety analysis will be performed after 200 patients have reached the 1-month follow-up. The study’s data manager will ensure that the data will be exported with “scrambled” allocation labels and that study investigators do not have access to the data. The results will be transmitted to the principal investigators and the safety monitoring board. The latter will be free to lift the blind if deemed necessary, and will be asked to make the final decision on the continuation of the study without modification, or terminating the study.

Sub-group analyses
The primary analysis and the secondary analyses related to the assessment of diagnostic performances (secondary analyses 1) to 4)) will be conducted in sub-groups of patients: 1)

patients aged less than 80 years versus patients aged over 80 years, 2) patients with a positive PCR (i.e. detection of a virus) at the beginning of the study versus patients with a negative PCR.

5.2. Handling of missing data and drop-outs

Some patients will be discharged from the ED, but they won't be considered as dropout patients as the diagnosis of pneumonia will be made before the discharge, and follow-up will be done by phone. Missing data that cannot be avoided will be excluded from the primary analysis (complete case analysis) and signalled as such. In addition, multiple imputation will be performed if more than 10% of data of the outcome are missing.

6. REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP.

6.2 (Serious) Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it. According to the local regulation (Clin O Art.39), no documentation of the AE is planned in this study.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)
All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study. If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days (only 7 days for a death). If the SAE potentially attributable to the intervention occurs at one of the study sites, the coordinating Investigator reports the events to the Ethics Committee concerned, within 15 days (only 7 days for a death).

Reporting of death, no attributable to the intervention (see ClinO Art.40)
Only death attributable to the intervention will report to the Ethics Committee via BASEC within 7 days. All deaths due to another cause will be reported in the annual report.

6.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).
In international multicentric studies the ASR/DSUR contains information from all sites including information from sites outside of Switzerland. The Sponsor-Investigator distributes the ASR/DSUR to all the participating Investigators.

6.4 Radiation

If the permitted dose guidance value (5 mSv per year if no direct benefit is expected for the participants) is exceeded at any time, the local Investigator notifies the Ethics Committee via BASEC within 7 working days of it becoming known (see ClinO, Art. 44).
The dose expected for LDCT is 1 to 1.5 mSV (see paragraph 3.3 with references on risk of CR, page 17).

6.5 Pregnancy

NA

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.
Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).
A list of all non-substantial amendements will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,

- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).
Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

6.8 Insurance

In the event of study-related damage or injuries, the liability of the institution HUG provides compensation, except for claims that arise from misconduct or gross negligence.

7. FURTHER ASPECTS

7.1 Overall ethical considerations

Ethical conduct of the study
The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH and the Swiss Law and Swiss regulatory authority's requirements. The Competent Ethics Committee will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.
Participant privacy and confidentiality
The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files. For data verification purposes, authorized representatives of the Sponsor (-Investigator), an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.
Early termination of the study
An initial safety "checkpoint" analysis will be performed after 200 patients have reached the 30-day follow-up.
The Sponsor-Investigator may terminate the study prematurely if there is evidence of benefit or harm of the experimental intervention according to the advice of Safety Monitoring Board.
The safety outcomes in each arm will be transmitted to the Safety Monitoring Board who will decide if the study has to be stopped prematurely in case of higher risk of transfer to intensive care unit (ICU) or mortality in a study arm compared with the two other arms (members of the Safety Monitoring Board will be blinded to the allocation arm).
About **vulnerability of the population**, please see paragraph 4.1

7.2 Risk-benefit assessment

This study will not have an immediate benefit to the study participant, but its results should benefit future patients.
Pneumonia is the leading cause of morbidity and mortality from infection in elderly patients, and one of the main causes of antibiotic prescription. Its diagnosis is, however, particularly challenging in elderly patients, because of the lack of sensitivity and specificity of clinical signs, symptoms and CXR findings, and because of the high incidence of alternative diagnoses. Hence, new

strategies are needed to improve the diagnosis of pneumonia, leading to patient management and more appropriate use of antibiotics in an era of increasing antibiotic resistance.
An LDCT or LUS-based work-up of suspected pneumonia may have significant advantages over standard CXR. Superior diagnostic accuracy of either modality can lead to better outcomes for patients through early appropriate management of the actual symptom-causing disease, but also to a more appropriate antibiotics use, a key issue in an era of growing bacterial resistance.

8. QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

The quality of the clinical investigation is derived from the quality of the investigation planning and reliability of the results. Sponsor's quality assurance policies and guidelines apply to the planning, selection of investigators and participating clinics, contracts, monitoring, recording of data and its analysis, documentation and archiving, evaluations, and reporting of the entire clinical study. This clinical study is conducted in accordance to the ICH-GCP guidelines.
Prior to recruiting the first patient, the study site PI, Subinvestigators, and Study Coordinator(s) will undergo a defined training program. This will occur during an investigator meeting prior to recruitment start. The training includes explanations of the procedures, inclusion and exclusion criteria, the CRFs, and general aspects of GCP. The training will be performed by the principal investigators. A training record is maintained for all study site personnel involved in study-specific activities. In the case of a change in the study site personnel, the new staff will be retrained.
All research team members will have current GCP or equivalent training/certification.
The Study Coordinator with primary responsibility for managing the study at each study site will be provided with comprehensive training on the study procedures, duties and responsibilities of the Study Coordinator.

The PI at each study site will be responsible for the supervision of the study and will provide direction and training to all other research personnel, as necessary.
A double data entry will be performed.

Independent data review will be done through an independent Safety Monitoring Board and a trial monitoring.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files will be done on such occasions. All involved parties will keep the participant data strictly confidential.

8.2 Data recording and source data

For each participant a CRF will be maintained. It will not identify participants by their name or birth date, but will provide appropriate coded identification.

This study will use REDCAP®, an encrypted, web-based platform for clinical trials used widely in Switzerland and abroad. Data from source documents will be entered directly into the CRF with restricted access to research associates and other members of the research staff, as prospectively determined by principal investigators in coordination with data management.
REDCAP has built-in safeguards with pre-defined ranges and other rules for all data values; the CRF will be constructed with these rules well before study launch to allow for careful validation (repeated testing with mock participants) by members of the central and peripheral study sites.
Source data (demographic data, visit dates, participation in study and Informed Consent Forms, randomization number, all the outcomes, results of relevant examinations, see CRF in appendix) will be available at the site to document the existence of the study participants. They will include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

Only routinely collected data is part of participant file but it may be transferred to the participant's CRF under the condition that, in this case, the CRF will no longer be considered as source data. After database lock, data will be fully anonymized and registered in a FAIR-compliant repository (see data management plan).

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

Privacy and confidentiality of the patient's medical data will be maintained through the study. CRFs and all other documents sent to the sponsor will be de-identified and carry only the numeric patient's identifier code. The study site will maintain the link between the patient identifier code and the patient's names.

All electronic data will be password protected, and any paper documents will be stored in a locked cabinet. For monitoring, audits, and regulatory inspections, source data and documents will be made available, per routine protocols.
Direct access to source documents will be permitted for purposes of monitoring, audits and inspections and should declare who will have access to protocol, dataset, statistical code, etc. during and after the study (publication, dissemination).

The investigating team will provide direct access to all trial-related source data, documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

Biobank

PAX gene RNA and DNA will be taken for the biobank performed at inclusion and coded genetic data will be used when the material will be used at the end of the study.
Biological material in this study will be not identified by participant name but by a unique participant number. Biological material will be appropriately stored in a restricted area only accessible to the authorized personnel.

If biological material or data collected during the study are to be shipped outside the study site, include the receiver address, the responsible person to whom the materials or data are sent, the purpose of shipment, if applicable, temperature control and how participant confidentiality is guaranteed. Biological material or genetic data can only be sent abroad in the scope of the research study, if the participant involved has given his or her consent to do so upon having been sufficiently informed. Non-genetic health-related personal data can be sent abroad for research if the requirements of Swiss data protection law are met (FADP, Art. 6).

8.4 Retention and destruction of study data and biological material

All study data will be conserved for 10 years after study termination or premature termination of the clinical trial. They will be stored in a locked storage cabinet in the principal investigator's office. They will be destroyed afterwards and this will be documented

The investigators will comply with the rules enacted by the Swiss Academy of Medical Sciences for biobanks, particularly concerning quality standards, data protection, transfer of samples and data. They will comply with the Swiss Human Research Act.

Samples will be reversibly de-identified as soon as possible, but at the latest upon arrival of the sample in the biobank. Each sample will be coded, and access to personal data will be impossible without the code, which will be conserved separately. The code file will be kept by a designated member of the research staff, who will not be directly involved in research and analysis on the biobank samples.

A specific consent form will be signed by the patient, allowing storage of his/her biological samples for research aims, including research on biomarkers and genetic polymorphisms associated with respiratory infection. The patient will be free to be included in the main cohort study, in GEROBIOTA and the biobank. He will be allowed to withdraw from participation at any moment. If a person included in a clinical trial in an emergency situation dies without consent or refusal in accordance with Article 15, the biological materials and personal health data collected may only be used if that person has consented to the use of his or her biological materials and personal health data for research purposes in an advance directive or otherwise. If there is no expression of will, the use of biological materials and personal health data is only permitted with the consent of relatives or a trustworthy person designated by the data subject.

Data handling for the GEROBIOTA nested study

Included case patients will continue to be identified by their OCTOPLUS study randomization number. This code will be used to label the samples that will be transferred to the Genomic Research Laboratory (GRL), where DNA extraction and metagenomic analysis will be performed. Saliva and respiratory samples will be stored at GRL at -80°C in the secured (locked) deep-freezers (24/7 monitoring system) in HUG to maintain pre-set temperatures and respond quickly to emergencies such as temperature out of range. Biological materials will be destroyed 10 years after termination of metagenomic analysis following HUG's routine destruction procedure for biological samples.

Coded raw metagenomic data and result files (obtained by data analysis) will be kept for at least 10 years on a Genomic Research Laboratory server (separate from the RedCAP database) with an appropriate system for backup generation. If a central (HUG) data storage system (appropriate for metagenomic data) becomes available, the raw data will also be directly submitted to this facility. Access to metagenomic data on these servers will be restricted by entering a user name and password of GRL investigators. GRL investigators involved in the project will not have any access to the electronic patient's files on the HUG intranet - they will not be able to associate metagenomics data with patient's identity.

In line with SNSF policies and general principles of fair data sharing, publication of metagenomics results will require depositing the raw sequence data into a public sequence database. Before deposition to a database, any sequence read matching the human genomic sequence will be removed. Sequence file names and metadata that will be deposited will not contain any direct identifier or strong indirect identifier (e.g., name, initials, address, e-mail, phone number) and will contain only a minimum of indirect identifiers (sex, age [years], diagnosis, symptoms, treatment details).

9. MONITORING AND REGISTRATION

External monitoring will be performed according to the ICH Good Clinical Practice (GCP) by local CTU for Geneva and Lugano sites. Following a Monitoring Plan and written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. For the Bern site, internal monitoring will be carried out according to the same monitoring plan
The investigating team will provide direct access to all trial-related source data, documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

According to international guidelines, the risk of monitoring is considered to be low.
The source data/documents will be accessible to monitors and questions will be answered during monitoring.

Registration will be done in the Swiss National Clinical trial Portal (SNCTP via BASEC). In addition, the study will be registered in Clinical Trial Gov.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

A funding has been obtained from the Swiss National Science Foundation, la Ligue Pulmonaire Genevoise and the Nakao foundation.

Blinded scanners and ultrasounds performed at the ED will be paid by the funding of the study in order to avoid costs for health insurance and insurance companies.

An agreement will be done between HUG and external sites (Bern, Lugano and Rennaz).

Trial results will be disseminated on several levels. Healthcare professionals, hospital administrators and policymakers will be alerted to the trial's findings by means of publication in a peer-reviewed, high-impact journal with an international readership and presentation of data at international conferences. Trial findings will be integrated into national and international guidelines. As described in the data management plan, data will be shared according to FAIR data principles and thus in a FAIR-compliant data repository. The study protocol will be provided as part of the online supplement to the main publication reporting the trial's results. As described above and in the data management plan, data will be stored in a FAIR-compliant data repository. Statistical code for the study's analyses will be kept in code logs and do files and can also be shared upon request.

The investigators declare no conflict of interest (independence, intellectual, financial, proprietary etc.).

11. REFERENCES

1. Kucera J. Vieillissement actif. wwwbfsadminch/bfs/fr/homehtml. 2008.
2. Ewig S, Klapdor B, Pletz MW, Rohde G, Schutte H, Schaberg T, et al. Nursing-home-acquired pneumonia in Germany: an 8-year prospective multicentre study. Thorax. 2012;67(2):132-8.
3. Chami K, Gavazzi G, Carrat F, de Wazieres B, Lejeune B, Piette F, et al. Burden of infections among 44,869 elderly in nursing homes: a cross-sectional cluster nationwide survey. J Hosp Infect. 2011;79(3):254-9.
4. Wroe PC, Finkelstein JA, Ray GT, Linder JA, Johnson KM, Rifas-Shiman S, et al. Aging Population and Future Burden of Pneumococcal Pneumonia in the United States. Journal of Infectious Diseases. 2012;205(10):1589-92.
5. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007;44 Suppl 2:S27-72.
6. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2011;17 Suppl 6:E1-59.
7. Albaum MN, Hill LC, Murphy M, Li YH, Fuhrman CR, Britton CA, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. Chest. 1996;110(2):343-50.

8. Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, et al. The management of community-acquired pneumonia in the elderly. European journal of internal medicine. 2014;25(4):312-9.
9. Fernandez-Sabe N, Carratala J, Roson B, Dorca J, Verdaguer R, Manresa F, et al. Community-acquired pneumonia in very elderly patients: causative organisms, clinical characteristics, and outcomes. Medicine. 2003;82(3):159-69.
10. Haga T, Fukuoka M, Morita M, Cho K, Tatsumi K. Computed Tomography for the Diagnosis and Evaluation of the Severity of Community-acquired Pneumonia in the Elderly. Intern Med. 2016;55(5):437-41.
11. Loeb MB, Carusone SB, Marrie TJ, Brazil K, Krueger P, Lohfeld L, et al. Interobserver reliability of radiologists' interpretations of mobile chest radiographs for nursing home-acquired pneumonia. Journal of the American Medical Directors Association. 2006;7(7):416-9.
12. Metlay JP, Schulz R, Li YH, Singer DE, Marrie TJ, Coley CM, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Archives of internal medicine. 1997;157(13):1453-9.
13. Aliberti S, Brambilla AM, Chalmers JD, Cilloniz C, Ramirez J, Bignamini A, et al. Phenotyping community-acquired pneumonia according to the presence of acute respiratory failure and severe sepsis. Respiratory research. 2014;15:27.
14. Black AD. Non-infectious mimics of community-acquired pneumonia. Pneumonia (Nathan). 2016;8:2.
15. Chandra A, Nicks B, Maniago E, Nouh A, Limkakeng A. A multicenter analysis of the ED diagnosis of pneumonia. The American journal of emergency medicine. 2010;28(8):862-5.
16. Kanwar M, Brar N, Khatib R, Fakih MG. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. Chest. 2007;131(6):1865-9.
17. Syrjala H, Broas M, Suramo I, Ojala A, Lahde S. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1998;27(2):358-63.
18. Waterer GW. The Diagnosis of Community-acquired Pneumonia. Do We Need to Take a Big Step Backward? American journal of respiratory and critical care medicine. 2015;192(8):912-3.
19. Claessens YE, Debray MP, Tubach F, Brun AL, Rammaert B, Hausfater P, et al. Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. American journal of respiratory and critical care medicine. 2015;192(8):974-82.
20. Prendki V, Scheffler M, Huttner B, Garin N, Herrmann F. Low-dose computed tomography for the diagnosis of pneumonia in elderly patients: a prospective, interventional cohort study. Eur Resp J. 2018;51(5).
21. Llamas-Alvarez AM, Tenza-Lozano EM, Latour-Perez J. Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. Chest. 2017;151(2):374-82.
22. Xia Y, Ying Y, Wang S, Li W, Shen H. Effectiveness of lung ultrasonography for diagnosis of pneumonia in adults: a systematic review and meta-analysis. J Thorac Dis. 2016;8(10):2822-31.
23. Liu XL, Lian R, Tao YK, Gu CD, Zhang GQ. Lung ultrasonography: an effective way to diagnose community-acquired pneumonia. Emergency medicine journal : EMJ. 2015;32(6):433-8.
24. Nazerian P, Volpicelli G, Vanni S, Gigli C, Betti L, Bartolucci M, et al. Accuracy of lung ultrasound for the diagnosis of consolidations when compared to chest computed tomography. The American journal of emergency medicine. 2015;33(5):620-5.
25. Amatya Y, Rupp J, Russell FM, Saunders J, Bales B, House DR. Diagnostic use of lung ultrasound compared to chest radiograph for suspected pneumonia in a resource-limited setting. Int J Emerg Med. 2018;11(1):8.
26. Staub LJ, Mazzali Biscaro RR, Kaszubowski E, Maurici R. Lung Ultrasound for the Emergency Diagnosis of Pneumonia, Acute Heart Failure, and Exacerbations of Chronic

Obstructive Pulmonary Disease/Asthma in Adults: A Systematic Review and Meta-analysis. The Journal of emergency medicine. 2019;56(1):53-69.
27. Ticinesi A, Lauretani F, Nouvenne A, Mori G, Chiussi G, Maggio M, et al. Lung ultrasound and chest x-ray for detecting pneumonia in an acute geriatric ward. Medicine. 2016;95(27):e4153.
28. Garin N, Marti C, Scheffler M, Stirnemann J, Prendki V. Computed tomography scan contribution to the diagnosis of community-acquired pneumonia. Curr Opin Pulm Med. 2019;25(3):242-8.
29. Garin N, Marti C, Carballo S, Darbellay Farhoumand P, Montet X, Roux X, et al. Rational Use of CT-Scan for the Diagnosis of Pneumonia: Comparative Accuracy of Different Strategies. Journal of clinical medicine. 2019;8(4).
30. Loubet P, Tubiana S, Claessens YE, Epelboin L, Ficko C, Le Bel J, et al. Community-acquired pneumonia in the emergency department: an algorithm to facilitate diagnosis and guide chest CT scan indication. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2019.
31. Riquelme R, Torres A, El-Ebiary M, de la Bellacasa JP, Estruch R, Mensa J, et al. Community-acquired pneumonia in the elderly: A multivariate analysis of risk and prognostic factors. American journal of respiratory and critical care medicine. 1996;154(5):1450-5.
32. Janssens J-P, Krause K-H. Pneumonia in the very old. The Lancet Infectious Diseases. 2004;4(2):112-24.
33. Ortega O, Martin A, Clave P. Diagnosis and Management of Oropharyngeal Dysphagia Among Older Persons, State of the Art. Journal of the American Medical Directors Association. 2017.
34. Sjogren P, Wardh I, Zimmerman M, Almstahl A, Wikstrom M. Oral Care and Mortality in Older Adults with Pneumonia in Hospitals or Nursing Homes: Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society. 2016;64(10):2109-15.
35. Kossioni AE, Hajto-Bryk J, Maggi S, McKenna G, Petrovic M, Roller-Wirnsberger RE, et al. An Expert Opinion from the European College of Gerodontology and the European Geriatric Medicine Society: European Policy Recommendations on Oral Health in Older Adults. Journal of the American Geriatrics Society. 2018;66(3):609-13.
36. Makhnevich A, Feldhamer KH, Kast CL, Sinvani L. Aspiration Pneumonia in Older Adults. Journal of hospital medicine. 2019;14(7):429-35.
37. Minakuchi S, Tsuga K, Ikebe K, Ueda T, Tamura F, Nagao K, et al. Oral hypofunction in the older population: Position paper of the Japanese Society of Gerodontology in 2016. Gerodontology. 2018;35(4):317-24.
38. Faner R, Sibila O, Agusti A, Bernasconi E, Chalmers JD, Huffnagle GB, et al. The microbiome in respiratory medicine: current challenges and future perspectives. The European respiratory journal. 2017;49(4).
39. Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nature reviews Microbiology. 2017;15(5):259-70.
40. de Steenhuijsen Piters WA, Huijskens EG, Wyllie AL, Biesbroek G, van den Bergh MR, Veenhoven RH, et al. Dysbiosis of upper respiratory tract microbiota in elderly pneumonia patients. Isme j. 2016;10(1):97-108.
41. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. American journal of respiratory and critical care medicine. 2008;177(11):1242-7.
42. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. Seminars in immunology. 2018;40:83-94.
43. Ciabattini A, Olivieri R, Lazzeri E, Medaglini D. Role of the Microbiota in the Modulation of Vaccine Immune Responses. Frontiers in microbiology. 2019;10:1305.
44. Rautanen A, Mills TC, Gordon AC, Hutton P, Steffens M, Nuamah R, et al. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. The Lancet Respiratory medicine. 2015;3(1):53-60.
45. Wang X, Guo J, Wang Y, Xiao Y, Wang L, Hua S. Genetic variants of interferon regulatory factor 5 associated with the risk of community-acquired pneumonia. Gene. 2018;679:73-80.

46. Chebib N, Muller F, Prendki V. [Pneumonia of the elderly and its link to oral health]. Rev Med Suisse. 2018;14(626):2007-11.
47. Chebib N CC, Malézieux-Picard A, Parent T, Roux X, Fassier T, Müller F, Prendki V. Pneumonia prevention in the elderly patients: the other sides. Aging and Clinical Experimental Research 2019.
48. Lazarevic V, Gaia N, Girard M, Francois P, Schrenzel J. Comparison of DNA extraction methods in analysis of salivary bacterial communities. PloS one. 2013;8(7):e67699.
49. Leo S, Gaia N, Ruppe E, Emonet S, Girard M, Lazarevic V, et al. Detection of Bacterial Pathogens from Broncho-Alveolar Lavage by Next-Generation Sequencing. International journal of molecular sciences. 2017;18(9).
50. Lazarevic V, Gaia N, Emonet S, Girard M, Renzi G, Despres L, et al. Challenges in the culture-independent analysis of oral and respiratory samples from intubated patients. Frontiers in cellular and infection microbiology. 2014;4:65.
51. Emonet S, Lazarevic V, Leemann Refondini C, Gaia N, Leo S, Girard M, et al. Identification of respiratory microbiota markers in ventilator-associated pneumonia. Intensive care medicine. 2019;45(8):1082-92.
52. Larke FJ, Kruger RL, Cagnon CH, Flynn MJ, McNitt-Gray MM, Wu X, et al. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. AJR Am J Roentgenol. 2011;197(5):1165-9.
53. Garin N, Felix G, Chuard C, Genne D, Carballo S, Hugli O, et al. Predictors and Implications of Early Clinical Stability in Patients Hospitalized for Moderately Severe Community-Acquired Pneumonia. PloS one. 2016;11(6):e0157350.
54. Lee JS, Giesler DL, Fine MJ. Duration of Antibiotic Therapy for Community-Acquired Pneumonia in the Era of Personalized Medicine. Jama. 2016;316(23):2544-5.
55. Eccles S, Pincus C, Higgins B, Woodhead M. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. Bmj. 2014;349:g6722.