Study Protocol

Epidemiological Study of Community Acquired Pneumonia

Version 2.2

[redacted]

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1 Contents

2 Signatures of all Investigators

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[redacted]		[redacted]

Head of LCC (titel/name LCC-head in printed letters)	(signature/stamp)	date

3 Addresses of Participants

Central area

Local Clinical Center (LCC)

The LCCs taking part in CAPNETZ can differ because of the planned, long running period and through changing eventualities. The current LCCs and their addresses can be found at: https://www.capnetz.de/html/patients/locations.

If you have any further questions about the procedure of the study please contact the office of the CAPNETZ STIFTUNG at the Hannover Medical School, Tel.: (0511) 532 4447.

4 Synopsis

Acronym:	**CAPNETZ**: **C**ommunity **A**cquired **P**neumonia **NETZ**werk
Study aim:	Examination of prevalence, incidence and risk factors of community acquired pneumonia (CAP) and its interaction with comorbid diseases in a representative sample of outpatients and inpatients
Patients:	Male and female patients ≥ 18 years of age
Study design:	Prospective and observational study
Main objectives:	• Estimation of prevalence/incidence of CAP • Examination of the reciprocal relation between CAP and comorbidity • Evaluation of CAP in immunosuppressed patients • Determinants of CAP in HIV patients • Establishment of a database on antimicrobial resistance • Information concerning pathogens and pathogen/host interaction • Establishment of a genetic database concerning pathogens and strains of CAP patients
Study arms:	1) Outpatients or inpatients with CAP, without HIV infection 2) Outpatients or inpatients with CAP, with HIV infection 3) Outpatients or inpatients with CAP, with Immunosuppression
Interventions:	None prescribed or planned
Inclusion criteria:	• Age ≥ 18 • Radiological proof of pulmonary infiltrate (primarily chest x-ray or CT) • Signed informed consent
Further inclusion criteria (at least one should be fulfilled):	• Presence of cough • Presence of purulent sputum • Pathologic lung auscultation (crackles) • Fever
Exclusion criteria:	• Hospitalization longer than 48 hours prior to diagnosis of current pneumonia • Non-infectious infiltrate • Newly diagnosed, active pulmonary tuberculosis within the last 2 months
Study duration:	Unlimited, depending on funding possibilities (study duration according to funding duration)
Examination time points:	**Inpatients only:** Visit 1/baseline, visit 2 after 3-5 days, visit 3 after 7-10 days, telephone interviews after 4 weeks and after 6 months from inclusion date

Outpatients only:

Visit 1/baseline, telephone interviews after 4 weeks and after 6 months from inclusion date

Examinations:

Inpatients only:

- Baseline: anamnesis (incl. pneumonia-specific medication and co-mediation of chronic underlying diseases and comorbidities), physical examination, laboratory tests, chest x-ray, hospitalization within the last 3 months, for HIV patients with community acquired pneumonia an additional data entry form, for immunosuppressed patients an additional data entry form
- Visits after 3-5 and 7-10 days: patient's status assessment and medications, clinical stability criteria, complications, laboratory tests
- Visits after 28 days (by telephone): patient's status assessment and medications, complications, hospitalization
- Visits after 180 days (by telephone): survival status

Outpatients only:

- Baseline: anamnesis (incl. pneumonia-specific medication and co-mediation of chronic underlying diseases and comorbidities), physical examination, laboratory tests, chest x-ray, for HIV patients with community acquired pneumonia an additional data entry form, for immunosuppressed patients an additional data entry form
- Visits after 28 days (by telephone): patient's status assessment and medications, complications, hospitalization
- Visits after 180 days (by telephone): survival status

Number of patients: Approx. 500 per year

Number of study centers: Approx. 20-30

5 Summary

The aim of this study is to determine prevalence, incidence and risks for CAP outpatients and inpatients through

1. Establishment of a database on antimicrobial resistance, pathogens and pathogen/host interaction, chronic underlying diseases, course of the disease and risk identification
2. Establishment of a genetic database
3. CAP in immunosuppression as a sub-study
4. CAP in HIV as a sub-study
5. Investigation into the reciprocal relationship between CAP and comorbidity

Approx. 500 patients at the age of ≥ 18 years shall be included in a cohort-study through prospective observation. The medical histories and the medication anamnesis will be recorded by the beginning of the study, especially concerning the pneumological events and predefined comorbid diseases. Diagnosis is proven by detection of an infiltrate using imaging. Relevant vital parameters are measured and the acute course of the disease documented in detail. Additionally, biomaterials from the upper and lower respiratory tracts as well as blood and urine samples are taken.

Timely visits are carried out for all inpatients at the point in time of day 3-5 and day 7-10. During these visits, the status of the patients, the therapies concerning the current disease and the comorbid diseases are documented. Clinical stability criteria and complications are recorded. Chest x-ray or CT, if performed within the clinical routine, will be documented. Repeated blood samples are collected.

Further telephone interviews are carried out 28 and 180 days after inclusion. During every telephone interview, the specific medical history concerning the previous time period will be documented.

Furthermore, for patients in the HIV sub-study, specific HIV questions will be raised during the Baseline and the visits after 28 and 180 days.

For patients with immunosuppression specific questions will be raised during the Baseline and the visit after 28 days.

The study will be carried out according to the recommendations of “Good Epidemiological Practice” (GEP) by the “German Association of Epidemiology” (DAE) and the appropriate regulations of Good Clinical Practice (GCP) and the Helsinki Declaration.

6 Objectives

The objective of this study is the investigation of the prevalence, incidence and risk factors of community acquired pneumonia (CAP) and their interaction with comorbid diseases in an unselected group of adult patients under the care of GPs, specialists and inpatient treatment.

6.1 Primary Objectives

The main objectives are:

1. Estimation of prevalence/incidence of CAP
2. Improvement of diagnostic accuracy through integration of clinical and microbiological data
3. Documentation of comorbid diseases and analysis of their role as a risk factor
4. Investigation of the influence of CAP on the course of chronic underlying diseases
5. Investigation of HIV as a risk factor
6. Evaluation of importance, risk factors, spectrum of pathogens and course of community acquired pneumonia in patients with pre-existing congential, acquired or therapy-associated immunosuppression
7. Establishment of a central sample and strain biobank
8. Establishment of a central database concerning antimicrobial resistance
9. Information about pathogens and pathogen/host interaction
10. Establishment of a genetic database concerning pathogens and strains

6.2 Secondary Objectives

The secondary objectives are:

1. Central collection of clinical data on CAP
2. Improvement of prevention through evaluation of vaccination behavior
3. Timely identification of high-risk patients
4. Reduction of CAP morbidity (through improved CAP management and therapy of comorbid diseases)
5. Definition of risk factors for unusual pathogens or a severe course of CAP in patients with immunosuppression

6.3 Background

Community acquired pneumonia is a widespread and frequent disease. Approx. 350,000 patients with CAP are admitted to hospital every year (Struß R et al., Dtsch Arztebl Int. 2014 Jul 21; 111(29-30):503-8). Meaning that community acquired pneumonia patients are admitted to hospital more often than the more commonly known widespread diseases of heart attack (132,000 admissions) and stroke (162,000 admissions). The costs for the disease amount to more than 500 million Euro every year. Overall mortality still is 6-8 %. Community acquired pneumonia is therefore the sixth most often cause of death in Germany at present.

In spite of the importance of community acquired pneumonia there is still a huge lack of reliable data on the pathogen spectrum, the resistance profile of the pathogens and on the course of the disease. The

Federal Ministry of Education and Research recognized these deficits and initiated the excellence network for community acquired pneumonia, in short CAPNETZ, in the year 2001.

Since that time, CAPNETZ has networked various groups and organizations from all areas of medicine that are focusing on this disease in order to collect pneumonia-specific data.

Up to the end of 2018, approx. 13,000 patients with community acquired pneumonia have been included. All clinical and microbiological data have been collected and a central biomaterial as well as information database has been established. Among others, the following questions have been investigated und will be investigated:

1. How often do which pathogens cause community acquired pneumonia?
2. What is the resistance situation of pathogens in Germany?
3. Are there certain markers in blood, allowing a forecast about the severity of pneumonia?
4. Do existing official recommendations concerning the diagnosis and therapy of community acquired pneumonia have to be revised?
5. How can a better acceptance of vaccinations be achieved?
6. What causes bacteria to become invasive? Why can the endogenous immune system not prevent the disease?

Approximately 20% of all patients with CAP have underlying congenital, acquired or therapy-associated immunosuppression (di Pasquale et al., Clin Infect Dis 2019). There are still very few data about importance, risk factors, pathogen spectrum and course of CAP for this important patient group. Consequently, they are excluded from all national and international guideline recommendations for the management of CAP. Therefore, patients with immunosuppression are also to be evaluated within the established CAPNETZ study cohort in order to establish a database for future management recommendations.

The results of the CAPNETZ study are not only made available to their participants.
Researchers and research groups can apply for the use of clinical data and biomaterials for their current questions in CAP research and the research of other acute respiratory infections. In the past, through its research, the CAPNETZ FOUNDATION has set the basis for a widening understanding of pneumonia and has supported better and more comprehensive care of patients. Results of the CAPNETZ study impact the S3-guidelines for community acquired pneumonia.

6.4 Project Structure and Legal Aspects (Sponsors)

The CAPNETZ FOUNDATION was founded in 2008 as a foundation for civil rights and fulfills solely and directly charitable purposes.

1. The foundation is listed in the foundation register of the state of Baden-Württemberg. The foundation headquarters is Ulm.
2. The financial year is the calendar year.

All details of the CAPNETZ FOUNDATION are regulated in the Statute of the Foundation.

6.4.1 Purpose, Tasks and Objectives of CAPNETZ

The purpose, tasks and objectives of CAPNETZ are:

1. Since 2008 the CAPNETZ FOUNDATION is responsible for the network and serves the establishment and continuation of the CAPNETZ network beyond the funding period of the BMBF from 2001-2011.
2. The purpose of the foundation is the support of science and research in the field of community acquired pneumonia and other acute diseases of the lower respiratory tract. This includes studies in the fields of basic research, microbiological research, and all forms of clinical studies (prevention, vaccination, diagnostic and therapeutic studies). Additionally, the foundation is to contribute towards improving the collaboration between leading research institutions in Germany (horizontal networking), speeding up the knowledge transfer from research to practice (vertical networking) and promoting the education of the general public about this disease. A key objective of the foundation is to significantly reduce morbidity and mortality of this disease through education, prevention and better understanding, thus also reducing the economic burden on the health system.

The CAPNETZ FOUNDATION shall continue its successful work of the past years and work on clinically relevant questions concerning the topic of inflammatory lung diseases. The foundation makes a relevant contribution to safeguarding the future for pneumonia research and it promotes synergies between different institutions and organizations. Current funds are raised from EU, federal, public and private funding, as well as from industry-funded clinical studies. Donations are also used for research purposes by the foundation.

6.4.2 Scientific Projects based on CAPNETZ Data and Biomaterials

Researchers who wish to carry out projects within the framework of the Foundation's objectives can apply for the use of clinical data from the CAPNETZ database as well as for biomaterials. This can be done using the CAPNETZ online portal.

To apply, a project outline must be submitted; the appropriate form is available online. Every submitted application which is approved by the executive board of the Foundation is supervised by a designated member of the board in order to support a successful completion. A timetable including milestones will be agreed with each applicant and retained in the project outline. If the applicant for important reasons cannot keep to the timetable, the board will be informed in writing immediately via the e-mail address vorstand@capnetz.de. The timetable can then be adjusted accordingly by the board. When considerable delays occur, projects can be stopped and additional work is no longer possible.

The CAPNETZ Office is responsible for the documentation and timely organization of the submitted research projects. On request, it provides assistance with the submission of projects.

When implementing scientific projects, the Publication Strategy of the CAPNETZ FOUNDATION is to be met. This strategy is available to the applicant.

6.4.3 CAPNETZ Office

The tasks of the CAPNETZ Office are:

1. The CAPNETZ Office is the central interface for internal and external data exchange and responsible for all network activities: planning, design and implementation in close communication with CAPNETZ participants. On the other hand, it is also responsible for ensuring a smooth flow of information within the network and serves as a contact and forwarder for questions, suggestions, or comments from the network and the general public to appropriate CAPNETZ members. The CAPNETZ Office is also responsible for the central CAPNETZ database in cooperation with the IT company 2mt Software Ltd. The CAPNETZ Office determines deadlines and forms for the archiving and deletion of stored data in accordance with the legal regulations.

2. The CAPNETZ Office is the formal and technical quality assurance entity in the network and responsible for data safety issues.

3. The CAPNETZ Office supports the board and the foundation's council in their tasks of coordination, implementation and quality assurance. Apart from the researchers and research groups, the CAPNETZ Office is also responsible for the compliance with the legal data protection regulations.

4. The CAPNETZ Office is responsible for the orderly financial management of CAPNETZ.

6.5 Members of the Network

6.5.1 Local Clinical Centers (LCCs)

The local Clinical Centers (LCCs) represent different geographical regions within Germany and other European countries. They are led by proven experts in the field of respiratory medicine. The LCC leads are named by CAPNETZ to coordinate local participating registered physicians, radiologists and microbiological laboratories.

Potential patients in the CAPNETZ study could be registered as an inpatient, as well as an outpatient of a clinical center or as an outpatient in practicing networks. Radiological diagnostics is performed in the framework of clinic routine with practicing radiologists or in the radiological department of the clinic. Radiological evidence of a pulmonary infiltrate is primarily found by conventional chest x-ray or via computed tomography of the thorax. The LCC's microbiological laboratories are responsible for processing of the patient samples, for routine diagnostics, for the preservation and dispatch of gained biomaterials to the CAPNETZ biobank. This is situated at the Hannover Medical School (Hannover Unified Biobank, HUB). A current overview of the LCCs network can be found at http://www.capnetz.de/html/patients/locations.

6.5.2 Central CAPNETZ Biobank

The services of the Central CAPNETZ biobank at the Hannover Medical School can be summarized as follows:

Administration, quality management, sample shipping, processing and storage for scientific purposes of the CAPNETZ FOUNDATION.

Address:
Hannover Unified Biobank (HUB)
Medizinische Hochschule Hannover
CRC Hannover
Feodor-Lynen-Str. 15
30625 Hannover

The Management system of the biobank is certified by TÜV NORD according to DIN EN ISO 9001:2008.

7 Study Design

Currently there are approx. 13,000 patients in the prospective-observational study, the CAPNETZ study. The patients are individually followed-up (successively from the reference date 01.07.2002) for a time period of six months. The patients are identified in the outpatient or inpatient departments of the hospitals or practices and are recruited by their treating physicians (mainly specialists). All of the patients who fulfill the inclusion and exclusion criteria and who are verified as having newly acquired non-nosocomial pneumonia are invited to participate. No interventions are planned for this study; the physicians treat their patients as they usually do.

8 Patients

8.1 Sample size

It is planned that within the study duration from 01.01. 2020 approx. 500 patients will be included each year in order to obtain representative data for prevalence and incidence estimation.

8.2 Inclusion Criteria

The following inclusion criteria must be fulfilled:

- Age ≥ 18
- Radiological proof of pulmonary infiltrate (primarily by chest x-ray or CT)
- Signed informed consent

Further inclusion criteria (at least one must be fulfilled):

- Presence of cough
- Presence of purulent sputum
- Pathological lung auscultation (crackles)

- Temperature ≥ 38,3°C (rectal) or ≥ 37,8°C (axillary/oral/auricular/sublingual)

8.3 Exclusion Criteria

None of the following criteria may be fulfilled:

- Hospitalization longer than 48 hours prior to diagnosis of current pneumonia
- Non-infectious infiltrate
- Newly diagnosed, active pulmonary tuberculosis within the last 2 months

9 Patient Recruitment

The patients are included in the LCCs either as out- or inpatients.

The study begins with patient recruitment, whereby the inclusion and exclusion criteria of potential patients are tested. The maximum timeframe between presentation with CAP and inclusion as CAPNETZ patient is 48 hours. The study doctor informs a potential CAPNETZ patient about the CAPNETZ study and asks to sign the written informed consent. This includes a general declaration of consent to take part in the CAPNETZ study, as well as further consent for the use of blood samples for genetic examination (GENCAP).

After the patient's consent, he/she will be registered as a case in the CAPNETZ study. Using the identification data of the patient, the study doctor or a member of the study team will create a patient pseudonym using the CAPNETZ study online portal. The originals of the declaration of patient consent remain with the physician. The patient receives copies of the consent declarations.

Electronic data collection is performed by the study doctor and/or by the study personnel. After finalizing the data collection (recording the survival status after 6 months) and after ensuring the accuracy of the collected data the study documentation will be kept in the local clinical center for at least 10 years.

10 Study Implementation

The patients who fulfill the selection criteria and whose consent declaration has been handed in following previous information and advice now undergo a start-up examination (baseline) including medical history (Para. 13.1), medication anamnesis (Para. 13.2) and a short physical examination (Para. 13.4).

The obtained information and examination results as well as particulars about current therapy are documented.

Examinations for hospitalized patients:

Baseline:

During this visit, a patient anamnesis and the demographic data are recorded.

A physical examination is performed with recording of clinical parameters and vital signs and a medication anamnesis (pneumonia-specific medication and further concomitant medication). For immunosuppressed patients additional data concerning underlying immunosuppressive condition and medication for the last 3 months in relation to immunosuppressive therapy are recorded.

Furthermore, lung and respiratory diseases, further chronic underlying diseases as well as comorbidities, the hospitalization status and vaccination status are all recorded.

Additionally, the results of the clinical routine patient imaging, primarily chest x-ray or CT are documented. Results of clinical-chemistry and microbiological laboratory routine are recorded. Blood and urine samples as well as samples of the upper and lower respiratory tracts are taken for analysis of clinical-chemistry and microbiological laboratory parameters and for later preservation.

Visit after 3-5 days

During this visit, the health status of the patient along with medication anamnesis (antimicrobial/antiviral therapy), complications associated with community acquired pneumonia as well as clinical stability criteria are documented.

Results of clinical-chemistry laboratory routine are recorded and blood samples are taken for later preservation.

Visit after 7-10 days

During this visit, the health status of the patient, the medication anamnesis (antimicrobial/antiviral therapy), the complications associated with community acquired pneumonia and the clinical stability are recorded.

Results of clinical-chemistry laboratory routine are recorded and blood samples are taken for later preservation.

Telephone interview after 28 days:

During this interview, the health status of the patient, the medication anamnesis (antimicrobial/antiviral therapy), the hospitalization and the complications associated with community acquired pneumonia are recorded.

Telephone interview after 180 days (6 months):

During this interview, the survival status of the patient is documented.

HIV patients

HIV patients with community acquired pneumonia are questioned additionally regarding HIV-specific parameters during the baseline visit, after 28 as well as 180 days. The visits after 3, 7, 28 and 180 days are carried out as for other CAP patients.

Immunosuppressed patients

If patients with community-acquired pneumonia are immunosuppressed, specific parameters during Baseline Visit as well as Visit after 28 days are asked. The visits after 3, 7, 28 and 180 days are carried out as for other CAP patients.

Examinations for outpatients:

Baseline:

During this visit, a patient anamnesis and the demographic data are recorded.

A physical examination is performed with recording of clinical parameters and vital signs and a medication anamnesis (pneumonia-specific medication and further concomitant medication). For immunosuppressed patients additional data concerning underlying immunosuppressive condition as well as medication for the last 3 months in relation to immunosuppressive therapy are recorded.

Furthermore, lung and respiratory diseases, further chronic underlying diseases as well as comorbid diseases, the hospitalization status and vaccination status are all documented.

Additionally, the results of clinical routine patient imaging, primarily chest x-ray or CT are documented. Blood and urine samples as well as samples from the upper and lower respiratory tracts are taken for analysis of clinical-chemistry and microbiological laboratory parameters and for later preservation.

Telephone interview after 4 weeks:

During this interview, the health status of the patient, the medication anamnesis (antimicrobial/antiviral therapy), the hospitalization and the complications (associated with community acquired pneumonia) are recorded.

Telephone interview after 6 months after inclusion:

During this interview, the survival status of the patient is documented.

HIV patients

HIV patients with community acquired pneumonia are questioned additionally regarding HIV-specific parameters during the baseline visit, after 28 as well as 180 days. The visits after 28 and 180 days are carried out as for other CAP patients.

Immunosuppressed patients

If patients with community-acquired pneumonia are immunosuppressed, specific parameters during Baseline Visit as well as Visit after 28 days are asked. The visits after 28 and 180 days are carried out as for other CAP patients.

Remarks:

Patient therapy lies exclusively with the physician treating the patient. In the framework of the study further biomaterials are taken in addition to the samples for the clinical routine diagnostics (see 13.6).

The samples collected in the study are shipped to the local laboratory, processed there and aliquoted. Part of the biomaterials is used in routine diagnostics and for pathogen determination. The remaining part is frozen, temporarily stored and quarterly sent to the central CAPNETZ biobank at the Medical School in Hannover.

11 Methods

11.1 Data Collection

The data collected for every patient are documented in the provided Case Report Forms (CRFs) resp. in the web-based CAPNETZ database. The study personnel receive personalized access (see 12.1). The study physician ensures whether the electronic CRFs in the database have been filled out correctly and promptly. In case data is missing the study physician or the study personnel must state whether this data is not available, not recorded or not applicable to this special case.

If after checking documented data in the database the data subsequently needs to be corrected for completeness or plausibility, electronic queries will be sent to the study center using the web-based study portal.

11.2 Data Security – Data Protection Requirements

The following describes the data protection requirements which are necessary for collecting and storing personal data in CAPNETZ.

The data to be collected are personal-related data. They are separated into personally identifying data and medical (non-identifying) data.

The data protection aspects of the EU General Data Protection Regulation (GDPR), which came into force on 24.05.2016 with a transition period until the end of 2018, are taken into account.

According to Article 4 / Number 1 GDPR, the term “personal data” refers to all information that relates to an identified or identifiable natural person. All personal data are stored and processed exclusively in pseudonymized form, which it is impossible to confirm the identity of the patient.

Pseudonymization is “the processing of personal data in such a way that the personal data can no longer be assigned to a specific person concerned without the use of additional information if this additional information is stored separately and meet the technical and organizational measures. It ensures that the personal data can not be assigned to an identified or identifiable natural person” (Reference: Article 4 Number 5 GDPR).

In the case of the CAPNETZ project, pseudonymized means that only a number or a combined number / letter code is used instead of names or initials. The procedure is as follows:

- Pseudonyms must be generated using the identifying data. They must be clear and cryptographically secure. Here, clearness means that the identifying data at another point in time and at a different site depict the same pseudonym. Cryptographically secure means that reversing the pseudonym to identifying data should not be possible.
- The collection of data on different input devices (PC, Laptop etc.) has to occur safely. The security of electronic transmission is considered accomplished if the authenticity of the communication partners, the integrity, confidentiality and access control of the data are guaranteed.

- Pseudonyms must in substantiated seldom case at least be manually traceable. For example, this is useful to find patients who are already recorded in the study database for further queries especially in the context of incidental findings.
- Non-electronic data, some medical samples or image material are also pseudonymized and stored securely after they have been collected and recorded.

12 Safe Data Collection

12.1 Basic Considerations

The transmission of electronically recorded data as well as login or registration of users is carried out through a secure internet connection (SecureHTTP “HTTPS”). HTTPS technology provides a secure connection for data transmission. The authenticity of the CAPNETZ server is proven by a server side certificate. The transmission of data is in encoded form

Users who whether reading or writing have access to CAPNETZ data must authenticate themselves via user names and passwords. Secure passwords are guaranteed by password rules (minimum length, special characters should be included).

The CAPNETZ internet portal is based on the web-based information and content management system (WebSpirit from the company 2mt Software Ltd).When designing the system, the requirements of GCP regulations, GDPR and CFR21 parts 11 and 820 were taken into account. . It has an access control system which can restrict access to certain functions and areas for users or user groups (therefore meaning readable or writeable data).The case data set is pseudonymized. Pseudonyms are generated from the identifying data in the user’s web browser so that the identifying data does not leave the study center. The pseudonymization may only be performed by certain user groups (study personnel of the study centers), who previously should authenticate themselves in the login area.

12.2 Quality of the Data to be collected

The recording of a new case in the CAPNETZ database requires different types of data which are variously recorded and at various times.

- Patient master data so called identifying data
- Anamnestic and clinical examination results
- Biomaterials

Patient master data, as well as anamnestic and clinical examination results are recorded electronically via the CAPNETZ internet portal. Identifying patient data are only used to calculate the pseudonym and are not saved.

Anamnestic and clinical examination results collected are text-based and are only saved in connection with the previously generated patient pseudonym.

Biomaterials from patients include blood, urine and respiratory samples. These samples are pseudonymized by the study personnel, provided with a barcode and frozen locally in the study centers. At periodic intervals these samples are sent to the central CAPNETZ Biobank Hannover for the further preservation. The assignment to a case is possible only using a pseudonym or a barcode.

12.2.1 Online Data Collection

The process of online data collection occurs as follows:

1. First the study physician resp. the study personnel authenticate themselves by using a user name and password. Identifying data is entered encrypted and transmitted to the web server. The server then transfers the identifying data to the pseudonymization function.
2. The pseudonymization function gives the identifying data a secret key and calculates the pseudonym using a non-linear Secure Hash function.
3. The calculated pseudonym is returned to the web browser of the requesting user as output.
4. The collection of treatment data can now be done using the pseudonym as identification.

12.2.2 Additions to Pseudonymization

Identifying Data

The following are defined as patient identifying data:

- Forename
- Surname
- Surname at birth
- Date of birth
- Place of birth
- Mother's maiden name
- Address
- Telephone number

These data serve apart from surname, the address and the telephone number (which can be changed at a later date) as (identifying) entries for the pseudonymization function. Surname, address and telephone number are needed for the case of a return of the patient's pseudonym. The study center makes itself a handwritten note on a separate form.

Identifying data cleansing

In order to make different entries clearer, the module of the pseudonymization function before pseudonymization cleanses the entries of the identifying data.

Pseudonym Creation

A highly non-linear (and therefore irreversible) mathematical hash function is used as the pseudonymization function (RIPE-MD). The identifier calculated by the hash function in the web browser, which represents the pseudonym, is transmitted to the server. There it is assigned to a random eight-digit number. The number is provided with a ninth check digit and divided into three triplets for better readability. The generated identifier is a key for further data entries or changes of the treatment data and it is used as an externally visible pseudonym.

An example of such a pseudonym is: *123-456-789.*

Duplicate pseudonyms

Duplicate pseudonyms can be generated if the identifying data are identical (i.e. a patient is included once again). It is almost impossible that the pseudonymization function generates the identical pseudonym for different data entries. The identifying data are so chosen that there cannot be practically two people with identical values. If it should happen that a pseudonym appears twice, the study personnel will be informed that this pseudonym already exists. If it occurs that this person is not identical to the person whose data were already recorded, an alternative pseudonym can be determinated by contacting the CAPNETZ Data Center.

12.3 Returning the Pseudonyms

The return of a patient's pseudonym can only occur with the full agreement of the patient.

CAPNETZ can send a pseudonymized written enquiry to the study doctor at the study center, who forwards it to the patient. The study documents are archived for at least 10 years in the study center in accordance with the GCP regulation § 13 (10). The patient will have the discretion to contact CAPNETZ. CAPNETZ has therefore no possibility to annul the pseudonym actively.

13 Examinations

13.1 Medical History

The medical history is documented at the beginning of the study by questioning the patient. The anamnesis includes the following diseases, symptoms and personal circumstances:

- Comorbid diseases especially chronic respiratory diseases and special risk factors (smoking status, i. e. non-smoker, ex-smoker or current smoker, as well as if necessary the number of pack years)
- Tumor diseases, differentiated according to the affected organ system

- Miscellaneous comorbidities
- For immunosuppressed patients: data for underlying immunosuppressive condition

13.2 Medication Anamnesis

The taking resp. prescription of antimicrobial drugs for the treatment of current pneumonia is recorded at the beginning of the study. Past antibiotic therapies within the last 4 weeks are documented. Possible further concomitant drug therapy is also inquired about. For immunosuppressed patients data concerning medication for the last 3 months in relation to immunosuppressive therapy are also recorded.

13.3 Vaccination Status

Vaccinations against seasonal influenza during the last 12 months are recorded as well as pneumococcal vaccination within the last 5 years and whooping cough (pertussis) vaccination.

13.4 Physical Examination

The physical examination at the beginning of the study includes the following:

- Body weight and height
- Blood pressure and heart frequency
- Breathing frequency
- Body temperature

13.5 Clinical Symptoms

The following clinical symptoms are recorded:

- Mental confusion
- Angina pectoris
- Lower leg edema

13.6 Laboratory

In the framework of clinical routine diagnostics, examinations are carried out with regard to the disease (e. g. physical examination, x-ray of the lungs or various laboratory tests). The results are recorded in the CAPNETZ study database. Furthermore, samples from patient's upper and lower respiratory tracts as well as urine and blood samples are taken, if this has not already been routinely undertaken, and if necessary examined and preserved. Sampling should as far as possible be linked with medically necessary collection. Basically, urine, serum, plasma, EDTA whole blood (for possibly additional genetic analyses), sputum as well as nasal/throat swabs should be taken. If a bronchoalveolar lavage (BAL) is performed during the treatment, this will also be recorded in the CAPNETZ study with the results of the locally performed diagnostics and the biomaterial preserved.

For microbiological diagnostics, the local microbiological laboratory should carry out the following examinations:

- Aliquoting and preservation of serum and plasma samples
- Cultural examination as well as other local diagnostics of respiratory tract and blood samples in local laboratory
- Performance of pneumococcal and legionella antigen detection tests in urine samples
- Taking and shipping of respiratory tract samples (as e. g. nasal/throat swabs) to external laboratories for further diagnostics
- Histological examination when performing a lung biopsy
- Preservation of respiratory tract, blood and urine samples at -80 °C as well as quarterly shipping of the samples

All steps from sample collection, transport to laboratories and further processing up to shipping to the central sample database are consistently regulated by Standing Operating Procedures (SOPs).

14 Statistical Evaluation

In order to describe the demographic/epidemiological data, standard procedures of descriptive statistics are applied. According to scientific questioning further biometric analyses can follow (see 6.4.2).

15 Ethics

15.1 Ethics Committee

Epidemiological studies are subject to the basic ethical principles of human research in the same way as clinical trials. The study is carried out according to the guidelines of Good Clinical Practice (GCP) and the Helsinki Declaration. The study protocol and any subsequent changes to the study protocol have to be reviewed by an Ethics Committee. The CAPNETZ Office is responsible for obtaining approval of the Ethics Committees for the individual study centers.

15.2 Informed Consent

Every patient is informed that taking part in the study is voluntary and that they may end their participation at any time. Patients are informed about the planned investigations as well as the reason and the objectives of the study. His/her declaration of consent confirms that participation is voluntary. The patient must give his/her declaration of consent prior to inclusion in the study. The declaration of consent can, if the condition of the patient requires, also be made orally so long as a third party witnesses this. In this case the witness must sign an informed consent. The signed informed consent form is kept by the study physician. The patient may revoke his/her declaration of consent at any time without giving reasons.

15.3 Incapacitated Patients

The CAPNETZ study is not an intervention study. Therefore, it appears justified to begin the study even if the patient is incapacitated if this complies with the patient's assumed intention. If a patient is incapacitated whether through being unconscious or other medical measures (e. g. strong analgesics or narcotics) his/her data will be temporarily recorded.

The following procedure should be carried out with this group of patients

- If a patient is incapacitated he/she is temporary observed and his/her biological samples are collected and preserved as quickly as possible
- The study personnel tries to obtain consent to participate in the study from his/her legal guardian
- If a patient regains his/her ability to give consent, he/she will be informed and the consent will be obtained afterwards
- If a patient died and the study personnel did not obtain consent or in the case when consent could not be obtained afterwards or if a patient refuses to be included in the study, the biological samples, which were taken and preserved before, will be destroyed. The personal data as well as data, which were already collected, will be deleted or destroyed and no longer used. All related study documents will be destroyed and no data will be saved.

- The study personnel documents the procedure described above in a separate form for each of these patients.

Patient's Representative

A representative declaration of consent must, in any case, be preceded by information on the content, procedure, benefits and risks of the planned study, analogously to those patients who are competent of making a declaration, so that the representative can decide, in the patient's interest, on granting or refusal of the consent. Possible decision makers are the guardian court, legally appointed representatives or guardians as well as persons authorized by the patient to manage their affairs and patient's relatives. In this case the representative must give their consent to the study.

16 General Regulations

16.1 Guidelines

The following guidelines are taken from data protection conditions and must be fulfilled by all project participants:

Patient Information

The patient, whose data are to be recorded in the CAPNETZ study must be informed using a patient information sheet about the storage and use of data.

Informed Consent

The patient must agree to his/her pseudonymized personal and medical data by signing the informed consent. These are handed over, signed and collected by the respective study physician of the clinic or practice and, if necessary, by a specific study physician. The data of a patient may not be recorded before the return of the signed informed consent. The informed consent is kept in the study documents. The patient will receive a copy for his/her records.

Agreement with Study Centers

All study centers that participate in the CAPNETZ studies conclude a study center contract with the CAPNETZ FOUNDATION. In this contract, study centers are obliged to inform all potential patients, and to perform and document the examinations according to the study plan as well as to keep all essential clinical trial documents for at least 10 years after the end or the termination of the study. Furthermore, regulations for remuneration and sample shipment are agreed upon.

Approval of the Ethics Committee

The required ethics approval is obtained before the beginning of the study from the responsible Ethics Committees of all the LCCs.

Web-Browser

The Web-browser used must support server-side certificates. Here, the free web-browser Mozilla is recommended.

16.2 Monitoring

Monitoring visits may be carried out during the study in cooperation with the study physicians. The purpose of these visits is to ensure compliance with the study plan and to check the plausibility and completeness of the patient's case report forms.

16.3 Data Archiving

The CAPNETZ Office and the foundation's council archive the study database for at least 10 years. Patient's declarations of consent and the most important study documents are kept in the patient files by the study physicians after completion of the study for a period of at least 10 years (§ 13 paragraph 10, GCP-V). Other regulations for the storage of medical records remain unaffected.

16.4 Study Plan Amendments

Every additional research aspect is formulated as a change to the study plan (amendment). The modified study plan is also sent to the Ethics Committees involved for re-evaluation.

16.5 Final Report and Publication

The members of the board and the Foundation's Council are authorized to use the data for publication and/or presentation in scientific media and/or congresses.

Every publication or presentation which is created after application for use of clinical data and/or biomaterials (see 6.4.2.), requires approval of the board. The guidelines for the use of data and biomaterials from the CAPNETZ study are laid down in the CAPNETZ FOUNDATION's publication strategy. These are made available to all applicants.

In case the parties cannot agree regarding the interpretation of the data, diverging opinions will be fairly and amply considered in the publication or presentation. A multi-center study, which is based on the cooperation of all participants, includes any publication of the results by the participants.

Abbreviations

AMG	Arzneimittelgesetz (German Drug Law)
BAL	Bronchoalveolar Lavage
CAP	Community Acquired Pneumonia
CRF	Case Report Form
CT	Computer Tomography
DAE	Deutsche Arbeitsgemeinschaft Epidemiologie (German Association of Epidemiology)
DIN	Deutsches Institut für Normung (German Institute for Norms)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GmbH	Gesellschaft mit beschränkter Haftung (Limited Company)
HIV	Human Immune-deficiency Virus
HUB	Hannover Unified Biobank
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
ISO	International Organisation for Norms
LCC	Local Clinical Center
SOP	Standard Operating Procedure
TÜV	Technischer Überwachungsverein (Technical Inspection Association)