Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

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PRESIDE

Prospective study of antimicrobial RESIstance in chronic lung DiseasE

Version 2 10/12/2024

MAIN SPONSOR: Imperial College London
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STUDY COORDINATION CENTRE: NA

IRAS Project ID: 346303
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Protocol authorised by:

Name & Role	Date	Signature

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Study Management Group

Chief Investigator: Dr Anand Shah

Co-investigators: Dr Aran Singanayagam, Dr Raju Misra

Statistician:

Study Management:

Study Coordination Centre *(may not be applicable)*

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator:
Address:
Tel:
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Registration:
E-mail:
Web address:

Clinical Queries

Clinical queries should be directed to Dr Anand Shah (s.anand@imperial.ac.uk) who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Imperial College - Research Governance and Integrity Team (RGIT) Website

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Funder:

European Respiratory Society

This protocol describes the PRESIDE study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

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GLOSSARY OF ABBREVIATIONS

AMR	Antimicrobial resistance
WGS	Whole genome sequencing

KEYWORDS

Antimicrobial resistance
Chronic lung disease

STUDY SUMMARY

TITLE PRESIDE: Prospective study of antimicrobial RESIstance in chronic lung DiseasE

DESIGN Prospective observational registry and cohort study

AIMS Understand role of antimicrobial resistance in individuals with chronic lung disease

OUTCOME MEASURES

1) Understand prevalence and burden of antimicrobial resistance in chronic lung disease
2) Understand antimicrobial susceptibility patterns of high-priority AMR pathogens in chronic lung disease
3) Analyse genotype-phenotype correlation of high-priority AMR pathogens in chronic lung disease
4) Understand effects of the resistome on chronic lung disease outcome
5) Analyse genomic transmission dynamics of high priority AMR pathogens in chronic lung disease

POPULATION Individuals with chronic lung disease

ELIGIBILITY Pathway 1:

- Any individual with chronic lung disease (e.g. COPD, bronchiectasis)
- Attending an outpatient clinic during the study sampling period.

Pathway 2:

- Age ≥18
- Presence of an underlying chronic lung disease (e.g. Bronchiectasis, COPD) stratified by colonisation status as detailed below.

DURATION 4 years

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1. INTRODUCTION

1.1. BACKGROUND

Antimicrobial resistance (AMR) refers to the ability of microorganisms like bacteria, viruses, fungi and parasites to resist the effects of antimicrobial drugs [1]. This phenomenon poses a significant challenge in the treatment of infectious disease, particularly in chronic lung diseases such as cystic fibrosis (CF), bronchiectasis (BE) and chronic obstructive pulmonary disease (COPD), in which patients' frequent exposure to antibiotics can drive the development and spread of AMR among respiratory pathogens [2]. AMR limits the effectiveness of standard antimicrobial agents, potentially resulting in treatment failure, prolonged illness and increased healthcare costs [1].

1.2. RATIONALE FOR CURRENT STUDY

AMR poses an escalating global health threat, contributing to difficult-to-treat infections associated with increased disease spread, disability and mortality, as well as a substantial economic burden [1]. The recent SARS-CoV-2 pandemic has significantly impacted antibiotic prescribing practices, resulting in a rise in inappropriate antibiotic use, often employed as a precautionary measure [3,4]

In chronic lung diseases, such as CF, BE or COPD, there is a higher risk of AMR due to the exposure to frequent or prolonged courses of antibiotics to treat recurrent respiratory infections and exacerbations, to reduce lung inflammation or to control chronic colonisations and suppress pathogens in chronic infections [2,5].

Most data on AMR in chronic lung diseases derive from retrospective data collected on a national basis [2], hence a prospective study is crucial to better understand and address AMR in chronic lung diseases. Prospective studies follow patients forward in time, collecting data on outcomes and allowing researcher to observe the natural history of AMR development, monitor trends and evaluate interventions.

This multicentre, prospective study, as part of the European Respiratory Society (ERS) Clinical Research Collaboration on Antimicrobial Resistance in Lung Disease (CRC – AMR Lung), aims to investigate the patterns of AMR in chronic lung diseases through a fully anonymous registry alongside a prospective sub-cohort study tracking individuals with chronic lung disease and known colonisation with high-priority AMR pathogens. This study will enable analysis of prevalence and burden of AMR within chronic lung disease alongside understanding the genomic drivers of resistance, genotype-phenotype correlation and transmission dynamics of AMR in chronic lung disease.

2. STUDY OBJECTIVES

Primary objective:

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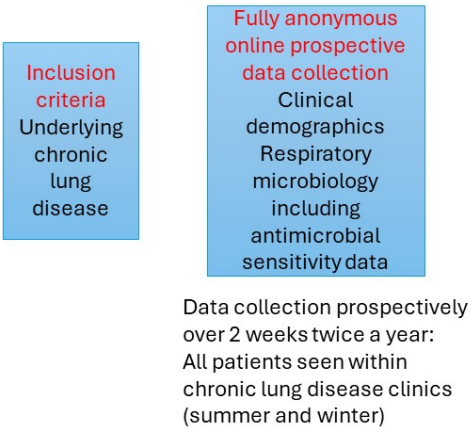
- Understand prevalence and burden of antimicrobial resistance in chronic lung disease

Secondary objectives:

- Understand antimicrobial susceptibility patterns of high-priority AMR pathogens in chronic lung disease
- Analyse genotype-phenotype correlation of high-priority AMR pathogens in chronic lung disease
- Understand effects of the resistome on chronic lung disease outcomes
- Analyse genomic transmission dynamics of high priority AMR pathogens in chronic lung disease

3. STUDY DESIGN

Pathway 1: Fully anonymous prospective registry:



Data will be collected from all participating centres over a two-week period during winter and summer of the same year. Patients with underlying chronic lung disease in an outpatient setting will be included and prospective data will be fully anonymised by the direct clinical care team prior to submission to a secure web-based database, Redcap. Anonymised data is data that has no code and cannot be linked back to a person (e.g. data without a code that cannot be linked back to a person). We will collect follow up variables every year for four years. We will aim to input data from ~800 patients within the UK annually.

Pathway 2:

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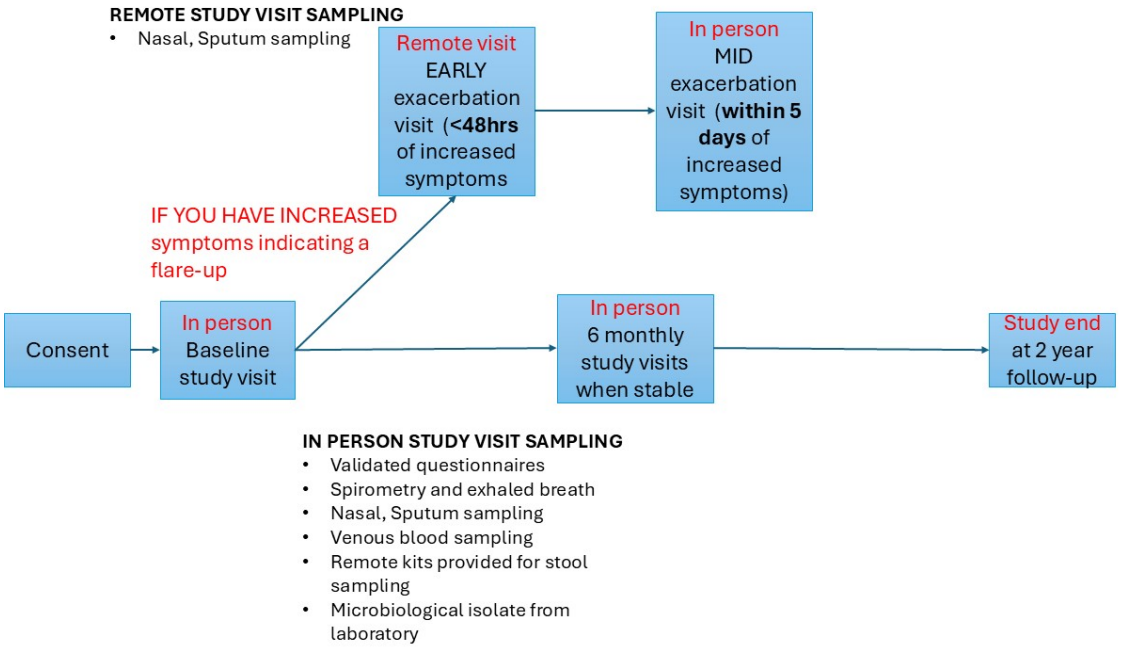

Pathway 2 is a prospective cohort study over a 2 year period recruiting individuals with underlying chronic lung disease (e.g. bronchiectasis, COPD) with colonisation with a high priority AMR pathogen. We will aim to recruit 170 patients within the UK stratifying by colonisation status as below:

- *Pseudomonas sp* (n=30)
- *Klebsiella sp* (n=20)
- *Haemophilus sp* (n=20)
- *E-coli sp* (n=20)
- *Stenotrophomonas sp* (n=20)
- *Staphylococcus sp* (n=20)
- *Other chronic colonisation* (n=20)
- *Not colonised with any bacterial pathogen (n=20)*

If study participants fulfil study entry criteria and consent in person, they will have an in-person baseline study visit where they will have spirometry, exhaled breath, blood, sputum, nasal sampling performed alongside validated questionnaires as well as being asked to return a remote stool sample within bespoke secure packaging. Bacterial isolates grown from respiratory sampling performed for clinical purpose will be retrieved from microbiology laboratories and stored for genomic and phenotypic further analysis. Clinical demographics will be retrieved from electronic health records and prior cross-sectional imaging pseudoanonymised and stored for radiological scoring. Further 6 monthly visits will be performed over a 2-year period during clinical stability with similar investigations performed. At 6 monthly intervals, further hospital environmental surveillance sampling will be performed with air and surface sampling within specific outpatient and inpatient environments (e.g. respiratory wards) using bespoke air sampling equipment (SAS and metagenomic air sampling) and surface standard swabs.

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Study participants will be asked to contact a study mobile phone number or email during self-reported exacerbations. At this point, further study visits will be performed. Within 48 hours of increased symptoms, participants will perform nasopharyngeal swabs and sputum sampling using bespoke sampling kits previously received and return within pre-paid secure packaging. They will then be asked to attend for an in-person study visit within 5 days of increased symptoms with similar sampling and investigation as baseline.

3.1. STUDY OUTCOME MEASURES

Primary endpoint:

- Prevalence of antimicrobial resistant specific high-priority AMR pathogens in chronic lung disease

Secondary endpoints:

- Antimicrobial susceptibility pattern of high-priority AMR pathogens in chronic lung disease
- Whole genome sequencing genotype-phenotype correlation of high-priority AMR pathogens in chronic lung disease
- Analysis of metagenomic resistome on exacerbation frequency and disease severity in chronic lung disease
- Genomic transmission dynamics of high priority AMR pathogens in chronic lung disease

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

Pathway 1 and 2: Presence of an underlying chronic lung disease

4.2. INCLUSION CRITERIA

Pathway 1:

- Presence of an underlying chronic lung disease (e.g. Bronchiectasis, COPD).
- Attending an outpatient clinic during the study sampling period.

Pathway 2:

- Age ≥18
- Presence of an underlying chronic lung disease (e.g. Bronchiectasis, COPD) stratified by colonisation status as below:
    - *Pseudomonas sp* (n=30)
    - *Klebsiella sp* (n=20)
    - *Haemophilus sp* (n=20)

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- *E-coli sp* (n=20)
- *Stenotrophomonas sp* (n=20)
- *Staphylococcus sp* (n=20)
- *Other chronic colonisation* (n=20)
- *Not colonised with any bacterial pathogen (n=20)*

4.3. EXCLUSION CRITERIA

Pathway 2:

- Inability to provide informed consent
- Pregnancy
- Medical instability preventing ability to attend for regular study visits at baseline.

4.4. WITHDRAWAL CRITERIA

As pathway 1 is a fully anonymised prospective registry with no identifiable information collected, no participant consent will be obtained.

For pathway 2:
Patients may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally authorised representative
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being

In all cases, the reason for withdrawal will be recorded on the case report form and in the subject's medical records. Subjects will be closely monitored by the research team. This is defined further in the section on 'Serious Adverse Events'.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. As the

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study is solely observational, exacerbations solely related to the underlying chronic lung disease will not be included as adverse events within the study.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs
All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs
An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to chronic lung disease and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the South Yorks Rec where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
Chief Investigator: Dr Anand Shah – s.anand@imperial.ac.uk

Please send SAE forms to: RGIT@imperial.ac.uk
Tel: 020 7589 5111 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Pathway 1:
Prospective data collection will occur twice a year over a two-week period capturing attendees to chronic lung disease clinics in that period. No participant identifiable information will be recorded with a e-CRF capturing baseline demographics, medical history, clinical characteristics, treatment regimens, and microbiological findings and inputted into a secure online Redcap database.

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The end of the last 2 week period will be defined as the end of the study for pathway 1.

Pathway 2:
After providing informed consent, participants will undergo a baseline assessment followed by 6 monthly sampling over a 2 year period. Clinical assessments will include validated symptom scores (e.g. CAT score, SGRQ, BHQ) alongside spirometry and exhaled breath sampling.

Sampling will consist of:
- Blood tests (venous blood up to 40mls)
- Nasal sampling: nasopharyngeal swabs, nasosorption, nasal brushes (see details below)
- Sputum
- Stool (remote collection)

Participants will be asked by the investigating team to report any symptoms of exacerbation to a study contact mobile number and email rapidly. Increased symptoms consistent with an exacerbation will trigger further remote and in person study visits as described above. Any incidental findings will be directed to the participant's clinical care team, general practitioner or the Emergency Department, depending on acuity. The date of the last participant's last visit will mark the end of the study. At the end of the study, samples collected will be retained by the study team pending ethical approval for use in further studies.

Sampling methodology in study:

Venous Blood: Venous blood (40mls) will be taken at baseline and at 6 monthly intervals over the study period and during in person study visits within 5 days of increased symptoms in keeping with an exacerbation.

Spirometry and exhaled breath sampling:
Spirometry will be performed according to guidelines (joint American Thoracic Society / European Respiratory Society) using a MicroLab spirometer (CareFusion, UK). The best of three tests will be recorded. FeNO will be performed using a NIOX VERO machine, according to the manufacturer's instructions. Subjects will be advised not to consume a caffeinated drink, or eat for at least one hour before

Nasopharyngeal swabs and Nasosorption: Nasopharyngeal swabs will be performed from each nostril 6 monthly and during exacerbation study visits and added to viral buffer for storage or postal return to the study team. In addition nasorption which is a minimally invasive technique which samples nasal (i.e. upper airway) mucosal lining fluid through avoidance of significant analyte dilution (inherent with lavage). Nasosorption will be performed at baseline and during in person study visits. In brief, two strips of Synthetic Absorptive Matrix (SAM) (Leukosorb, Pall Life Sciences, UK) measuring 7mm x 35mm will be placed inside the participant's nostrils for 2 minutes to obtain samples of nasal lining fluid. This is a painless, minimally

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invasive procedure that will not require any local anaesthetic. Each piece of SAM will be placed in a single labelled Spin-X Centrifuge Tube with Filter (Sigma-Aldrich) containing an assay buffer. This will be transported to the lab on ice for initial processing and transferred to -80°C pending analysis for interferons by multiplex immunoassay.

Nasal brushings: Nasal brushings will be performed using cytology brushes (CONMED, USA). Patients will additionally be asked to blow their nose first. A brush will be inserted into one nostril with the bristles in contact with the medial inferior turbinate. Nasal cells will be collected by a few backward–forward and rotatory movements of the brush. This will then be withdrawn from the nostril and clipped into a tube containing RNA preservative. The procedure will be repeated in the other nostril with a second brush. Cells will be removed from the brushes and stored in an RNA buffer at -80°C pending RNA extraction and analysis.

Remote stool analysis: Participants will be asked to provide stool samples using bespoke remote stool collection (Genotek) which can be posted back to the study team in secure packaging for storage and further analysis of the stool microbiome. This will happen at each in person study visit.

The last study visit of the last participant will be defined as the end of study for Pathway 2

7. STATISTICS AND DATA ANALYSIS

Pathway 1:
Prospective fully anonymised registry data collection. Statistical analysis will include prevalence of high priority AMR pathogens in chronic lung disease stratified by underlying disease and specific antibiotic resistance. Multivariate analysis will be used to analyse clinical variates associated with AMR.

Pathway 2: We are deliberately recruiting individuals with chronic lung disease colonised with AMR specific pathogens that are likely to suffer from exacerbations per year. Although exacerbation frequency may vary from year to year, given that our study design will also capture ‘unreported’ exacerbations, we would anticipate that the majority subjects will have two exacerbation episodes per year. This would equate to a total of 300 exacerbation episodes over the study period alongside 600 steady-state visits which will be a sufficient number to measure our primary and secondary endpoints.

Similar cohort size analysis using genomic, protein and microbiome analysis have yielded significant insight into genome-phenotype associations, effects of resistome on outcome alongside disease pathogenesis and correlation with disease severity and progression. Multivariate analysis will be used to identify clinical variates associated with exacerbation frequency with student t test, spearmans correlation and random forest analysis used to determine genomic, microbial and immune associations with exacerbation frequency, severity and symptom scores.

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Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the South Yorks Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Pathway 1: As a fully anonymised prospective registry with no participant identifiable information collected, study consent will be not be required. However, we will use posters to highlight the study during periods of recruitment and also use the National Data Opt-Out dataset to confirm the participants have not refused the use of their data in this way.

Pathway 2: Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

Pseudonymised data is data that can be linked back to a person (e.g. coded data). It is considered both personal and identifiable data. Anonymised data is data that has no code and cannot be linked back to a person (e.g. aggregated data for publication, data without a code that cannot be linked back to a person)

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Pathway 1: Data will be fully anonymised

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Pathway 2: Data will be pseudonymised

Data will be kept in either fully anonymised (Pathway 1) or pseudoanonymised from and stored with secure online databases (Redcap)

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

European Respiratory Society are funding this study.

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Anand Shah at Imperial College London as CI..

(delete once inserted) CI to include study specific reporting requirements/notification responsibilities for the study

10. PUBLICATION POLICY

The participating investigators will have the right to publish the study data. Participants will be notified of the outcome of the study, if they have requested this. It is anticipated that the data will be widely disseminated in the medical and scientific community and, if of public interest, via the media department at Imperial College London.

11. REFERENCES

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Appendix 1:
Data collection as part of pathway 1 (fully anonymised registry)
Date of enrollment

Reason for the visit (routine control/acute exacerbation of chronic disease/ pneumonia, IV antimicrobial or immune modulatory therapy/other: specify)

Age (free text)

Sex (male/female)

Ethnicity

Smoking history (active/former/never) (if active or former: n years, n cigarettes)

Alcohol consumption (yes/no/unknown) (if yes: standard unit drink or gr/day)

Years of education (free text)

LUNG DISEASE

Non- CF Bronchiectasis

Cystic Fibrosis (if yes: mutation 1, mutation 2 as free text)

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COPD (if yes: AATD yes/no?)

Year of diagnosis

MICROBIOLOGICAL HISTORY

History of TB

History of NTM-PD

History of Pseudomonas

Inhaled antibiotics (if yes: which one)

Chronic macrolide (if yes: dose and frequency)

Oral antibiotics (eg for NTM PD)

Acute course of antibiotics in the last 30 days?

COMORBIDITIES

Cardiovascular disease

Hypertension

Stroke

Dementia

Chronic aspiration

GERD

HIV infection

AIDS

Active solid tumor

History of neoplasia

Active haematologic neoplasia

Asplenia

Aplastic anemia

Liver disease

Chronic renal failure

Diabetes Mellitus

Rheumatic disease

CLINICAL CHARACTERISTICS

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Dyspnoea (yes/no)

mMRC (0->4)

Cough (y/n)

Sputum (y/n) -> if yes: colour, quantity

Number of exacerbations not requiring hospitalization in the previous year

Number of exacerbations requiring hospitalization in the previous year

THERAPY

ICS

LABA

LAMA

SABA

SAMA

Oral steroids

PPI

Chemotherapy

Immunosuppressants

CFTR Modulators (if CF. If yes: which one(s))

MICROBIOLOGICAL CHARACTERISTICS

Microbe

Kind of respiratory sample

Antibiogram information

Pertinent resistance mechanisms (if tested, e.g. ESBL, CPE)

Action taken (none, antibiotic prescription)

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