Appendixes

Appendix 1 Baseline questionnaire (Adults with CVID/XLA)

Patient sticker:

Part A – for the patient to complete.

1. Do you take Steroids or any Immunosuppression treatment? *(Please circle)*

Yes No

- If YES what is it? ……

2. Do you frequently suffer from any types of infection? *(Please circle)*

Yes No

3. Are you on a long-term (prophylactic) antibiotic? *(Please circle)*

Yes No

- If YES, what is it? ……

4. How often do you take courses of antibiotics in a year (in addition to the long-term antibiotic if you are taking one)? *(Please tick one box)*

At least once a month ☐
Less that once a month but at least 6 times per year ☐
About 4 or 5 times per year ☐
About 2 or 3 times per year ☐
About once a year ☐
Less than once a year ☐

5. Approximately when did you last take a course of antibiotics (apart from the long-term antibiotic, if you are taking one)?

……

6. How often do you come for infusions? *(Please circle)*

Every 2 weeks Every 3 weeks Every 4 weeks Other (specify)……

Part B – to be completed by the doctor

Immunodeficiency diagnosis ……..

Other diagnoses ……..

……..

……..

……..

……..

Immunoglobulin product and dose …….

Year started immunoglobulin ……

Current medications …….

……..

……..

……..

……..

Confirm consented for research ☐

For the nurse / doctor:

Please tick if collected

Blood sample ☐
Sputum sample ☐
Serum sample ☐

Appendix 2 NTM-PD Study protocol

NTM-PD Study Protocol.docx

Appendix 3 Participant Information Sheet

(Version 2)

Investigating the severity of pulmonary Non-tuberculous Mycobacterial disease (Student Study)

We would like to invite you to participate in a research study that is part of a PhD Project. This study aims to identify measurable markers in blood or sputum of patients with pulmonary non-tuberculous mycobacterial (PNTM) infection that correlate with the extent of lung disease seen on a CT scan.

Please take time to read the following information carefully and discuss it openly.
Please feel free to ask us if anything is not clear or if you would like any further information.

Names of Investigators:
Miss. Meyad Alkarni (PhD Student), Dr. David Lowe (Consultant Clinical Immunologist), Prof. Marc Lipman (Consultant and Professor of Medicine)

What is the study about?

Non-tuberculous mycobacterial (NTM) infection is increasingly common. Unlike many other infections, these do not always need treatment: some people appear to spontaneously clear NTM, whilst others remain clinically stable, with no treatment over long periods of time. The need for drug therapy is usually determined by worsening symptoms and/or the findings from radiological tests. Unfortunately, standard chest x rays are not very sensitive at diagnosing NTM or detecting changes that are due to the infection. Therefore, more accurate computerized tomography chest scans (CT) have to be used as part of your routine care. The CT scan combines a series of X-ray images to provide more detailed information than plain X-rays. These procedures use ionising radiation to form images of your body and/or provide treatment and/or provide your doctor with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. The chances of this happening to you are the same whether you take part in this study or not as you will not be asked to have any more CT scans.

If drug therapy is needed, it has to be taken for several months and can have side effects in some people. NTM lung disease commonly occurs in people aged fifty or above, who may have other on-going conditions for which they need to take medication that can be affected by the treatments used for NTM. For all of these reasons, it would be of considerable clinical help to identify factors in a patient's blood or sputum (phlegm) samples that can indicate the presence of significant lung damage, and if so whether these factors might be able to predict which patients are likely to get future worsening lung disease (and so should start treatment earlier to try and manage this effectively). These factors may also allow us to monitor the disease without so many CT scans.

In this study, we are investigating whether a person's immune response markers in blood or sputum can discriminate between more and less severe disease on a CT scan; and whether the levels of these markers are different between people who go on to require treatment within the next 6 months, and those who remain stable without treatment.

Specifically, we will analyze neutrophils (immune white cells) which may be important in controlling these infections but could also damage the lungs; and antibodies, which might be important in defending the body against NTM infection. We will also look at people's genes to identify which of these are particularly active or inactive during NTM infection – and whether these can distinguish between people with more or less severe CT lung scan changes. Note that we will only be looking at which genes are 'turned on or off' in relation to your NTM infection (eg immune system genes, measured by something called RNA) and will not be looking at your genetics in general (i.e. we will not be looking at DNA). In future ethically approved research, we also intend to look at molecules in the urine using a similar approach.

Why have I been invited?

You have been invited to join this study because you have been recently or previously found to have a NTM organism in your sputum.

Do I have to take part?

No. It is up to you to decide if you want to take part. We will describe the study and go through this information sheet with you and you will be given at least 24 hours to decide whether you wish to participate in the study or not. If you agree to take part, we will then ask you to sign a consent form at the next scheduled appointment. You are free to withdraw at any time, without giving a reason. This will not affect any care or treatment you may be receiving.

What will happen in the study if I decide to participate in the study and how long will it last?

1. We will arrange an initial meeting to complete some documentation for the study.
   This will take at most 1 hour. At this initial appointment we will ask you to sign a consent form. We will then collect some details regarding your medical history and, if you have recently had a CT chest scan, ask you to complete questionnaires about your health. These include measures of quality of life which will take around 30 minutes and can be completed at home if you want. Please note that some of the questionnaires were designed for patients with chronic obstructive pulmonary disease (COPD) and bronchiectasis (widening of the breathing tubes) and will mention these terms. This does not mean that you have these conditions. However, we are using these because there are no validated questionnaires for people with NTM lung disease and we believe some of the COPD or bronchiectasis questions will be useful to inform us about your health status. If the questionnaires indicate significant anxiety or depression then we will contact you and, with your permission, inform your hospital team or GP who can arrange further assessment and treatment.

2. You will be asked to provide two sputum (phlegm) samples extra to your normal care, either at the first meeting (if you have had a recent CT chest scan) or close to the time of a CT chest scan that would be ordered in the future as part of your care by your doctors. If you cannot provide these spontaneously,

we will ask you to have a 'sputum induction' procedure. This may need to be done on a separate day from your usual clinic visit: in this case, we will reimburse you for reasonable travel. During this procedure, we will ask you to breathe in a fine mist (aerosol) of salt water. This will make you produce sputum which can be coughed out. Some people can find this uncomfortable, and we can stop at any time if you ask us to.

3. We will also take blood samples (up to 40 ml, equivalent to 8 teaspoons), extra to those collected for your normal care. These will be used to test for markers of infection, your body's response to infection and to exclude underlying problems with the immune system. This will include an HIV test as a standard of care if you have not recently had one. If the HIV test is positive, we will let your medical team know and they will contact you, explain the result and refer you on for specialist assessment and treatment. Again, these samples will be taken either at the first meeting or close to the time of your next CT scan if you have not recently had one.
4. When we take the sputum and blood samples, we will also ask you for a urine sample (20mls). This will be stored for future studies looking at your response to infection
5. An up to date spiral CT chest scan is needed for this study. We will use the data from your recent CT scan (or the next one your doctor orders as part of your routine care).
6. You will be seen at your regular scheduled follow up appointments that could be by phone or in the clinic as determined by your doctors. We will ask them to give us an update on your clinical status 6 months after we collect the samples.
7. If your doctors decide you require another CT scan within the next 18 months (or before the end of the study if this is sooner) then we may ask you to complete the questionnaires and donate further samples.

Are there any possible disadvantages or risks of taking part?

This is an observational study; it does not include any changes to your treatments or the care that your doctor recommends for your NTM infection other than taking the samples to do our research tests. Therefore, we don't anticipate any significant harm or risk. There is a small chance that our tests will identify a significant or treatable problem with your immune system. If this is the case, we will inform you and ensure that you receive the appropriate care and onwards referrals. We are unlikely to identify other significant health problems, but if this does occur we will inform you, your hospital medical team and, with your consent, your GP.

There may be mild discomfort or bruising from the blood test. Blood will be taken by a suitably qualified person using procedures approved by the NHS Trust to ensure your safety and comfort.

If you require sputum induction with salt water (see point 2 in the previous section), this is a simple procedure. Some people can find it uncomfortable and there is a small risk of causing asthma-like symptoms such as chest tightness or wheezing which may need treatment by the clinical team. If this does occur, it usually only lasts for a few minutes and will settle quickly with treatments such as nebulisers with drugs that open up the airways and reverse the changes caused by the salt water.

Will information about me be passed on to anyone else?

All information collected about you during this study will be confidential. Your personal information will be stored with a study code and number in a secure place in UCL Institute of Immunity and Transplantation. No information that could identify you will be passed on to anyone outside of the research group.

Will my results be shared with the clinical team?

The results of the study data will not be fed back to your clinicians except in exceptional circumstances when the results need the attention of the clinical team. However, your doctors will of course have access to the results of CT scans and diagnostic blood tests performed within your hospital.

What will happen to the results of the research study?

We hope that the results of this study will help to improve care in the future. Some results may be presented at medical conferences or published in medical journals. You will not be identifiable from any published information. Participants who wish to be notified of the results will receive a lay summary of our findings by mail or e-mail as they wish by the end of the study. If you are interested to know more about the results, please let us know and we can provide you access to the final study report and all the scientific publications that are produced from this study by post or e-mail.

What will happen to the samples taken during this study?

This study will involve taking sputum (phlegm), urine and blood samples extra to normal care. Some of these samples will be tested immediately and some will be stored for later analysis. The stored samples will be anonymised (labelled with the study number only). These samples will be frozen and stored in UCL Centre for Clinical Microbiology and/or Institute of Immunity and Transplantation at Royal Free Hospital. If you give your consent any remaining biological samples collected in this study may be used for future ethically approved research. All samples will be disposed of in line with Human Tissue Act (2004) legislation.

What if things go wrong?

If you wish to complain about your treatment by members of staff due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you. Please ask your researcher if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, or if you have concern about any about any aspect of this study, you should ask to speak to a member of the study team who will do their best to answer your questions. If you remain unhappy or wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital Patient Advice and Liaison Service.

The patient advice and liaison service for the Royal Free Hospital in the hospital's main reception.

The service is open from 10am to 4pm, Monday to Friday, except Wednesday, when the service is open from 10.30am to 4pm.

7 August, 11 August, 14 August – closed

You can contact the team using the following details:

Tel: 020 7472 6446/6447; (020 7472 6445 - 24 hour answer phone)
Fax: 020 7472 6463

SMS: 447860023323 (Deaf, hard of hearing and hearing impaired patients only)
Email: rf.pals@nhs.net

What will happen if I don't want to carry on with the study?

If you wish to stop being part of this study, you can withdraw at any time without giving a reason. We will keep the information we already have up to that point. If you no longer want us to use any of your data for this study, please contact your clinician and we will delete your files. In this case, you will also have the right to request destruction of the biological samples collected from you. If, for some reason, you lose the ability to consent to the study (for instance if you are too unwell to consent) then we would withdraw you from the study although in this circumstance we would still use the information obtained whilst you retained the capacity to consent.

Finally, it is up to you to decide whether you want to be part of this study. If you do not want to be in this study, your usual NHS care will continue as normal. You can stop during the study at any time without giving a reason. Your doctor will still look after you as normal.

Insurance

The management of the research will be covered by UCL insurance for negligent harm.

Who is organizing, sponsoring and funding this study?

The study sponsoring by University College London UCL and fully funded to the PhD Student; Meyad Alkarni from her government – Royal Embassy of Saudi Arabia Cultural Bureau.

Who has reviewed this study?

This research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by London-Chelsea Research Ethics Committee.

Local Data Protection Privacy Notice

Notice:

The controller for this project will be University College London (UCL). The UCL Data Protection Officer provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, or if you would like to contact us about your rights, please contact UCL in the first instance at data-protection@ucl.ac.uk

How will we use information about you?

- In this research study we will use information from you and your medical records. We will only use this information to do the research stated or to check your records to make sure that the research is being done properly
- People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.
- We will keep all information about you safe and secure.

(The paper documents containing information will be stored in locked offices by the local principal investigators, while the electronic data will have a code number, and will be stored in a folder with password protection).

- Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have unless you request otherwise (see above).
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to [data-protection@ucl.ac.uk.], or
- by ringing us on [020 7472 6141].

Thank you for taking time to consider this study. Please ask any questions and let us know if there are things that you do not understand, or if you would like more information. Please address any further questions to:

Dr David Lowe, Consultant Clinical Immunologist at the Royal Free Hospital.
Telephone number: 020 7830 2141 **Email address:** d.lowe@ucl.ac.uk
Prof. Marc Lipman, Respiratory Consultant at the Royal Free Hospital.
Miss. Meyad Alkarni (PhD Student, Div. of Infection and Immunity, UCL)
Email: Meyad.Alkarni.18@ucl.ac.uk
Telephone: 020 7472 6141 **Mobile**: 07387985702
10/04/2020

Thank you for taking the time to read this information sheet.

Please keep it for future reference.

Appendix 4 Consent Form

Investigating the severity of Non-tuberculous Mycobacterial Disease.

(Student Study)

Please initial box

Study UID: _____ Researcher: _____

1. I confirm that I have read the information sheet dated 23/07/2020 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the UCL Institute of Immunology and Transplantation, and the Respiratory/Infection research team from the Royal Free Hospital from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand that the biological samples taken from me as part of this research project (blood, sputum, urine) will be stored for analysis by UCL Institute of Immunity and Transplantation. ☐
5. I agree that the information and biological samples collected from me in the context of this study may be used to support other ethically approved research in the future, and may be shared anonymously with other researchers (optional). ☐ YES ☐ NO
6. I understand that my anonymized data will be stored on UCL computers and may be transferred to collaborators at UCL or other universities for analysis ☐
7. I agree to my General Practitioner being informed of my participation in the study. ☐
8. I understand that the information held and maintained by the research team (Chief Investigator, researcher, and research assistants) from Royal Free Hospital and other central UK NHS bodies may be used to help contact me or provide information about my health status. ☐
9. I agree that if I have other tests such as lung function tests and CT scans whilst I am in this study the research team may use this information. ☐
10. If I am required to have another CT scan for clinical reasons, I may be asked to provide further samples, but can refuse this request without providing any reason (optional). ☐ YES ☐ NO
11. I agree that if I lose capacity in the future to consent to continued participation in the study, the research team would retain the samples and personal data collected and continue to use it confidentially. ☐
12. I agree to take part in the above study. ☐
13. I wish to receive a summary of the results from the study and am happy to provide my contact details for this purpose (optional). ☐ YES ☐ NO

Name of Participant Date Signature

Name of Person taking consent Date Signature

Appendix 5 Ethics approval

264375_20.PR.0118_Letter_of_HRA_Approv

Appendix 6 Sponsorship Insurance

Gallagher

Insurance | Risk Management | Consulting

22nd July 2019

TO WHOM IT MAY CONCERN

We, the undersigned Insurance Brokers, hereby certify that the following described insurance:

VERIFICATION OF INSURANCE

Unique Market Reference:	B1262 FI0153319
Type:	Legal Liability and No Fault Compensation for Human Clinical Trials
Insured:	University College London
Period:	From: 1st August 2019 To: 31st July 2020 Both days inclusive at Local Standard Time.
Interest:	This Policy will indemnify/Cover the insured in respect of their Legal Liabilities arising out of the Insured's activities and as more fully disclosed within the Policy Wording.
Limit of Indemnity:	GBP 15,000,000 Any One Claim and GBP 15,000,000 in the Aggregate, including costs and expenses
Excess:	GBP 2,500 Each and Every Claim, other than United States of America Jurisdiction where USD 25,000 each and every Claim shall apply
Underwriter:	100.0000% Newline Syndicate 1218

This document is for information only and does not make the person or organisation to whom it is issued an additional Insured, nor does it modify in any manner the Contract of Insurance between the Insured and the Insurers. Any amendment, change or extension to such Contract can only be affected by specific endorsement attached thereto.

Should the above mentioned Contract of Insurance be cancelled, assigned or changed during the above policy period in such manners as to affect this document, no obligation to inform the holder of this document is accepted by the undersigned or by the Insurers. The information provided is correct at the date of signature.

Authorised Signatory
Arthur J Gallagher

Appendix 7 Demographic data

Patient number :		Day _____

DEMOGRAPHICS										
Gender		☐ Female		☐ Male						
Age (years)		☐☐								
ETHNICITY		Which ethnic group does participant belong to? Please select **ONE** option from A-E (✓)								
A	***WHITE***	White Britis h	☐	White Irish	☐	White (Other background)	☐			
B	***MIXED RACE***	White & Black Caribbean	☐	White & Black African	☐	White & Asian	☐	Other mixed background	☐	
C	***ASIAN OR ASIAN BRITISH***	Indian	☐	Bangladeshi	☐	Pakistani	☐	Other Asian background	☐	
D	***BLACK OR BLACK BRITISH***	Caribbean	☐	African	☐	Black (Other background)	☐			
E	***OTHER ETHNIC GROUP***	Chinese	☐	Any other ethnic group	☐	Not stated	☐			

Appendix 8 QOL-B (NTM module) questionnaire

QOL-B - NTM *QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS – NTM MODULE*

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have bronchiectasis. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Section I. Quality of Life

Patient code: _____

Please check the box indicating your answer.

*During the past **week**, to what extent have you had difficulty:*	**A lot of difficulty**	**Moderate difficulty**	**A little difficulty**	**No difficulty**
1. Performing vigorous activities, such as gardening or exercising	☐	☐	☐	☐
2. Walking as fast as others (family, friends, etc.)	☐	☐	☐	☐
3. Carrying heavy things, such as books, groceries, or shopping bags.....	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐
*During the past **week**, indicate how often:*	**Always**	**Often**	**Sometimes**	**Never**
5. You felt well.....	☐	☐	☐	☐
6. You felt tired	☐	☐	☐	☐
7. You felt anxious	☐	☐	☐	☐
8. You felt energetic	☐	☐	☐	☐
9. You felt exhausted.....	☐	☐	☐	☐
10. You felt sad……..	☐	☐	☐	☐
11. You felt depressed.....	☐	☐	☐	☐

Are you currently on any treatments (such as oral or inhaled medications, PEP or Flutter® device, chest PT, or Vest) for bronchiectasis?

☐ Yes ☐ ***No (Go to Question 15 on the next page)***

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for bronchiectasis make your daily life more difficult?

1. Not at all
2. A little
3. Moderately
4. A lot

13. How much time do you currently spend each day on your treatments for bronchiectasis?

1. A lot
2. A moderate amount
3. A little
4. Almost none

14. How difficult is it for you to fit in your treatments for bronchiectasis each day?

1. Not at all
2. A little
3. Moderately
4. Very

Continue to Next Page

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?

1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

*Thinking about your health during the past **week**, indicate the extent to which each sentence is true for you.*	**Completely true**	**Mostly true**	**A little true**	**Not at all true**	
16. I have to limit vigorous activities, such as walking or exercising	☐	☐	☐	☐	
17. I have to stay at home more than I want to.....	☐	☐	☐	☐	
18. I am worried about being exposed to others who are sick.....	☐	☐	☐	☐	**Doesn't apply**
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity).....	☐	☐	☐	☐	☐
20. I lead a normal life	☐	☐	☐	☐	
21. I am concerned that my health will get worse	☐	☐	☐	☐	
22. I think my coughing bothers others	☐	☐	☐	☐	
23. I often feel lonely	☐	☐	☐	☐	
24. I feel healthy	☐	☐	☐	☐	
25. It is difficult to make plans for the future (vacation, attending family events, etc.) ..	☐	☐	☐	☐	
26. I feel embarrassed when I am coughing……..…...	☐	☐	☐	☐	

***Please circle the number or check the box indicating your answer*.**

During the past week:

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?

1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

	Always	**Often**	**Sometimes**	**Never**
28. How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?	☐	☐	☐	☐

Continue to Next Page

Section II. Respiratory Symptoms

Please check the box indicating your answer.

*Indicate how you have been feeling during the past **week:***	**A lot**	**A moderate amount**	**A little**	**Not at all**
29. Have you felt congestion in your chest?	☐	☐	☐	☐
30. Have you been coughing during the day?	☐	☐	☐	☐
31. Have you had to cough up mucus?.....	☐	☐	☐	☐

32. Has your sputum been mostly:

☐ Clear ☐ Clear to yellow ☐ Yellowish-green
☐ Brownish-dark ☐ Green with traces of blood ☐ Don't know

*How often during the past **week:***	**Always**	**Often**	**Sometimes**	**Never**
33. Have you had shortness of breath with greater activity, such as housework or yardwork?.....	☐	☐	☐	☐
34. Have you been wheezing?.....	☐	☐	☐	☐
35. Have you had chest pain?.....	☐	☐	☐	☐
36. Have you had shortness of breath when talking?	☐	☐	☐	☐
37. Have you woken up during the night because you were coughing? ……..	☐	☐	☐	☐

NTM Module:
We would like your feedback on the following

Please circle the number indicating your answer. Please choose only one answer for each question.
Thinking about your health over the last week:

38. To what extent do side effects from NTM medications make your daily life more difficult?
1. Not at all
2. A little
3. Moderately
4. A lot

39. How do you feel about eating?
1. Just thinking about food makes you feel sick
2. You never enjoy eating
3. You are sometimes able to enjoy eating
4. You are always able to enjoy eating

Please select a box indicating your answer.

*Thinking about your health during the past **week**, indicate the extent to which each sentence is true for you.*	**Completely true**	**Mostly true**	**A little true**	**Not at all true**
40. I have to force myself to eat	☐	☐	☐	☐
41. I think I am too thin.....	☐	☐	☐	☐
42. I think I look different from others my age	☐	☐	☐	☐
43. I feel bad about my physical appearance.....	☐	☐	☐	☐
44. I think I am too heavy……	☐	☐	☐	☐
45. I have to use the bathroom frequently……	☐	☐	☐	☐

*Indicate how you have been feeling during the past **week:***	**A lot**	**A moderate amount**	**A little**	**Not at all**
46. Have you had eating problems?	☐	☐	☐	☐
47. Have you had trouble gaining weight?.....	☐	☐	☐	☐
48. Have you felt feverish (sweating, chills)?……..….....	☐	☐	☐	☐
49. Have you had problems sleeping?……..….	☐	☐	☐	☐

Continue to Next Page

*Indicate how you have been feeling during the past **week:***	**A lot**	**A moderate amount**	**A little**	**Not at all**
50. Have you had pain?……..….	☐	☐	☐	☐
51. Have you felt bothered by cold weather?……..…. ...	☐	☐	☐	☐
52. Have you had sensitivity to smell?……..….	☐	☐	☐	☐
53. Have you had sensitivity to taste?……..….	☐	☐	☐	☐
54. Have you had a bad taste in your mouth due to sputum?……..…. ...	☐	☐	☐	☐
55. Have you experienced problems with memory?……..….....	☐	☐	☐	☐

*How often during the past **week:***	**Always**	**Often**	**Sometimes**	**Never**
56. Have you been constipated?	☐	☐	☐	☐
57. Have you had acid reflux?.....	☐	☐	☐	☐
58. Have you felt bloated?.....	☐	☐	☐	☐
59. Have you had problems with gas?	☐	☐	☐	☐
60. Have you had diarrhea?.....	☐	☐	☐	☐
61. Have you had abdominal pain?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

Appendix 9 Modified MRC breathlessness scale

Modified MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yards or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Appendix 10 EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

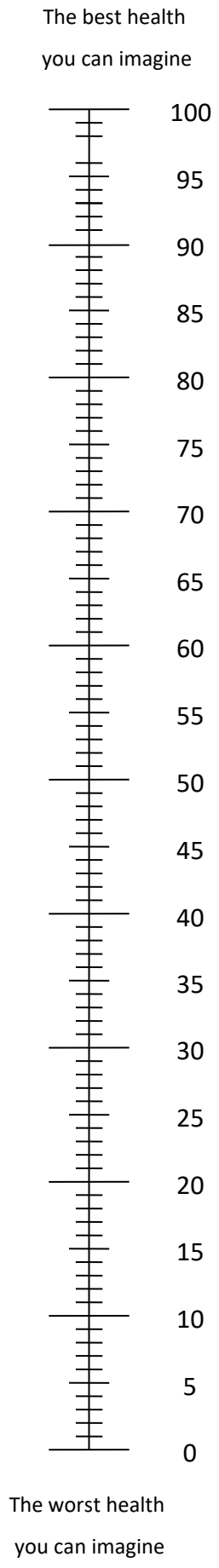
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Health Status Measures

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 11 COPD Assessment Test (CAT)

Your name:_____

Today's date:_____

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional to measure the impact that COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score can be used by you and your healthcare professional to help improve the management of your COPD and gain the greatest benefit from the treatment.

For each item below, place a mark (X) in the box that best describes your current situation. Please ensure that you only select one response for each question.

Example: I am very happy | 0 | **X** 1 | 2 | 3 | 4 | 5 | I am very sad

I never cough	0	1	2	3	4	5	I cough all the time	
I have no phlegm (mucus) on my chest at all	0	1	2	3	4	5	My chest is full of phlegm (mucus)	
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight	
When I walk up a hill or a flight of stairs I am not out of breath	0	1	2	3	4	5	When I walk up a hill or a flight of stairs I am completely out of breath	
I am not limited to doing any activities at home	0	1	2	3	4	5	I am completely limited to doing all activities at home	
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not confident leaving my home at all because of my lung condition	
I sleep soundly	0	1	2	3	4	5	I do not sleep soundly because of my lung condition	
I have lots of energy	0	1	2	3	4	5	I have no energy at all	

SCORE

TOTAL SCORE

A COPD assessment test was developed by an interdisciplinary group of international COPD experts with support from GSK. GSK's activities in connection with the COPD assessment test are monitored by a supervisory council that includes external, independent experts, one of which is chair of the council.

Appendix 12 GAD-7 Anxiety Scale

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✓" to indicate your answer"*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Column totals: ___ **+** ___ **+** ___ **+** ___

= Total Score _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
☐	☐	☐	☐

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc.

Appendix 13 PHQ-9 Depression

PHQ-9 Depression

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(Use "✓" to indicate your answer)

	Not at All	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving .around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Column totals ___ **+** ___ **+** ____ **+** ___

= Total Score _____

Scoring notes

- ***GAD-7 Anxiety Severity*.**

This is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of “not at all,”
“several days,” “more than half the days,” and “nearly every day,” respectively. GAD-7 total score for the seven items ranges from 0 to 21.

Scores represent: **0-5 mild 6-10 moderate 11-15 moderately severe anxiety 15-21 severe anxiety.**

- ***PHQ-9 Depression Severity***

Scores represent**: 0-5 = mild 6-10 = moderate 11-15 = moderately severe 16-20 = severe depression**

Appendix 14 Protocol of KAPA RNA HyperPrep Kit with RiboErase (HMR) Globin

Sequencing Methods

KAPA RNA HyperPrep Kit with RiboErase (HMR) Globin

--UCL-GENOMICS--

UCLG

Library preparation

Total RNA quantification and integrity was confirmed using Agilent's 4200 Tapestation (Standard Total RNA assay). RINs values were confirmed to be in the range of 3.0-9.0, indicating variable integrity RNA suitable for library prep with ribosomal RNA and globin depletion.

For each sample, 200ng of total RNA were processed using the KAPA RNA HyperPrep Kit with RiboErase (HMR) Globin for Illumina® Platforms (Roche p/n KR1520) according to manufacturer's instructions.

Briefly, rRNA and globin mRNA transcripts were depleted from total RNA by hybridization to complementary DNA oligonucleotides, followed by treatment with RNase H and DNase to remove the rRNA and mRNA duplexed to DNA oligonucleotides. The depleted RNA was fragmented using chemical hydrolysis (heat and divalent metal cation) and primed with random hexamers. Strand-specific first strand cDNA was generated using Reverse Transcriptase in the presence of Actinomycin D. This allows for RNA dependent synthesis while preventing spurious DNA-dependent synthesis. The second cDNA strand was synthesised using dUTP in place of dTTP, to mark the second strand. The resultant cDNA is then "A-tailed" at the 3' end to prevent self-ligation and adapter dimerisation. Full length xGen adaptors (IDT), containing two unique 8bp sample specific indexes, a unique molecular identifier (N8) and a T overhang are ligated to the A-Tailed cDNA. Successfully ligated cDNA molecules were then enriched with limited cycle PCR (13 PCR cycles). The high-fidelity polymerase employed in the PCR is unable to extend through uracil. This means only the first strand cDNA is amplified for sequencing, making the library strand specific (first-strand).

Sequencing

High yield, adaptor-dimer free libraries were confirmed on the Agilent TapeStation 4200 (High Sensitivity Agilent DNA 1000 assay). Samples were quantified using the Qubit High Sensitivity DNA assay and normalised to 10nM. An equal volume of each library was pooled together and re-quantified by Qubit. Samples were sequenced on the NovaSeq instrument (Illumina, San Diego, US) using the SP 100cycle kit at a concentration of 275pM, using a 56bp single read run with corresponding 8bp dual sample index and 8bp unique molecular index reads.

Appendix 15 CT scan scoring system

Patient ID								
Patient name								
Predominant phenotype	Fibrocavitary Nodular bronchiectatic Mixed Other (free text)							
Date of scan								
	Bronchiectasis extent	Bronchiectasis severity	Tree-in-bud	Nodules	Cavitating nodules	Severe cavitation	Consolidation	Aspergilloma
RUL								
LUL								
RML								
Lingula								
RLL								
LLL								
Total								
Overall change from prior	Better Worse Unchanged Mixed response							

30 **72**

CT scoring matrix.
The features are scored per lobe as follows:
Bronchiectasis extent: 0 = none; 1 = 1 bronchopulmonary segment, 2 = >1 bronchopulmonary segments, 3 = >2 bronchopulmonary segments
Bronchiectasis severity: 0 = none, 1 = mild (1-2x diameter of accompanying artery), 2 = severe (>2x diameter of accompanying artery)
Tree-in-bud opacification: 0 = none, 1 = mild, 2= moderate, 3 = severe
Nodules: 0 = none, 1 = 1 nodule, 2 = 2-4 nodules, 3 = >4 nodules
Cavitating nodules: 0 = no, 1 = yes; Severe cavitation: 0 = no, 1 = yes
Consolidation: 0 = none, 1 = mild, 2 = moderate, 3 = severe
Aspergilloma: 0 = no, 1 = yes.

Nodules were only counted if >5mm diameter, Severe cavitation was defined as the pattern of cavitation classically seen in tuberculosis. Adapted from Zoumot *et al.* **[1]**

Appendix 16 Review Article

The roles of neutrophils in non-tuberculous mycobacterial pulmonary disease