



Improving the detection of active Tuberculosis in Accident and Emergency Departments

(ACE study, Work package 1)

A. Summary of the project

This study is focused upon early diagnosis, referral and treatment of active tuberculosis, which has two key components: 1) ensuring optimal outcome for individuals; 2) contributing to disease control in public health terms by preventing further spread.

A&E Departments are an important point of testing and referral for the client group that constitute those at greatest risk, as for many this will be their only interaction with the health service.

Currently, A&E Departments contribute about 20% of those diagnosed with TB. The majority of these individuals are most likely to have presented with symptoms indicative of disease, compared to those attending for other reasons that would have been unlikely to have been tested or referred.

This study will seek to evaluate specific measures currently being undertaken by Public Health England and the NHS to control TB as well as investigate whether case finding for active TB in A&E departments would improve TB control. This study is linked by the NIHR funded PREDICT study (Prognostic value of Interferon Gamma Release Assays in predicting active tuberculosis among individuals with, or at risk of, latent tuberculosis infection). The economic impact of these interventions will be evaluated, providing a measure of their value for money.

B. Planned Investigation

1.0 Background

Tuberculosis (TB) is a major cause of disease burden worldwide. The UK has seen a resurgence of TB since the late 1980s and there are currently over 8000 new cases each year (1). Most cases occur in major cities, particularly in London, and an increasing proportion occur in persons born abroad (currently two-thirds of TB cases and higher still in London) and other groups with specific risk factors. Control measures have traditionally relied on the prompt diagnosis of active TB cases and ensuring that patients complete their treatment.

The majority of TB cases in the UK arise due to reactivation of latent infection (1). Among immigrant groups, the infection is likely to have been acquired abroad whereas among the elderly UK-born population, the infection is likely to have been acquired in earlier years when TB was highly prevalent in the UK. TB causes significant morbidity in the UK. Identifying those in high risk groups such as drug users, those who have been in prison or been homeless, evaluating signs and symptoms of active TB and referring individuals for testing and management are key to disease control efforts. Early treatment may have the greatest impact by interrupting transmission. Between 2000-2009, active TB cases in England rose from 12.4 to 16 per 100,000 with over 8000 cases diagnosed annually, mostly among individuals from identified risk groups.

Diagnosis of TB is complex as it requires consideration of many factors. A potential mechanism to identify and test individuals at high risk of TB is to offer testing in A&E Departments. Of TB cases reviewed in a pan-London audit, 21% were diagnosed in A&E with less diagnostic delay compared to patients referred via other routes. If a successful system for undertaking testing in high risk groups attending A&E is developed, this would significantly improve the ability to diagnose a greater proportion of individuals at high risk of TB and complement current efforts to set up primary care based screening. Control of infectious diseases requires prompt, effective identification and treatment to safeguard health and prevent transmission.

1.2 National and International Guidelines and Policy Context

1.2.1 National Policy

The national policy for the control of tuberculosis is based on the action plan published in 2004 by the Chief Medical Officer, “Stopping TB in England” (2) with a major focus on the prompt identification of active TB cases and ensuring that they complete treatment (2). A new strategy would be launched by Public Health England in September 2014.

1.3.2 Guidelines

The national guidelines for the clinical and public health management of TB, developed by a group which included several of the co-applicants, were published by the National Institute for Health and Clinical Excellence (NICE) in March 2011 (3), and will be updated later in 2015. These guidelines include recommendations on the diagnosis and management of active and latent TB infection.

2.0 Objectives

2.1 Primary objectives

To evaluate the economic costs of screening patients at high-risk of active tuberculosis (TB) within hospital Accident and Emergency departments (A&E).

2.2 Secondary objectives

To measure the prevalence of active TB in high-risk patients attending A&E Departments.

3.0 Method

3.1 Design

3.1.1 Setting, population and disease burden

This prospective cohort study will recruit individuals 16 years or older, who are new entrants from high incidence countries in sub-Saharan Africa or Asia, bar former Soviet Union countries who have arrived in the UK within the past 5 years or those with social risk factors, such as drug use, been in prison or been homeless, who are at a higher risk of TB.

This is an observational study, which prospectively recruits participants at high-risk of TB testing, combined with health economics modelling. The prevalence of active TB will be measured by approaching attendees at three A&E Departments in England. The study areas have been chosen to include areas with a high burden of TB, both in and outside London, as well as being willing to participate. The areas covered by the Trusts involved provide services to areas of socioeconomic

deprivation and ethnic diversity reflecting the population of TB cases nationally. All study sites will be coordinated from PHE Colindale.

The steps of the study methodology are as follows:

1. When presenting at the A&E Department, potential participants will be given a flyer for the study by the reception staff during the routine checking in process.
2. After potential participants have been triaged by the clinic staff, they will be approached by the research nurse (RN). If participants are interested in the study or would like further information the research nurse will take them to a separate area, e.g. a side room, where they can speak privately.
3. The RN will explain the study, and give the potential participant a full information sheet to read and confirm that the participant is eligible to join the study as either:
 - aged 16 years or older, new entrant from a high incidence country (as per the defined study specific list) who has arrived in the UK within the past 5 years.
 - born in a high incidence country who entered the UK more than five years ago, but has spent more than one year (cumulative) in the past five years in a high incidence country.
 - UK born with a risk factor for TB defined as current or in the last five years a history of homelessness, problem drug use, alcohol misuse or imprisonment. These participants would be triaged directly to the symptom screen as outlined below.
4. If the potential participant wishes to join the study the RN will ask the individual to complete the written informed consent form.
5. The RN will then collect some baseline information from the participant; including details about recent illness that will help determine whether the participant should be investigated for active or latent TB. Where latent TB is indicated, the procedures set out in the linked ACE:LTBI study, based on the PREDICT study protocol, will be followed).
6. The participant will return to the A&E waiting room where they will be seen by the A&E staff as a part of the routine care offered to those attending A&E clinics.
7. If the participant is considered at high risk of active TB based on the baseline questionnaire (see below) they will be asked to produce a sputum sample. This sample will be sent to the hospital laboratory where it will be tested for the presence of Mycobacterium using GeneXpert MTB/RIF, a cartridge-based, automated diagnostic test.
8. If the participant is male, or female and not pregnant, they will be asked to attend the hospital radiology department where they will undergo a chest x-ray in order to see if any scarring is visible on their lungs.
9. After these procedures are complete the participant will leave the hospital.
10. If any test results indicate active TB, the patient's records and test results will be sent to the local NHS TB service for follow-up and treatment. All further care and communication with the patient will be carried out by the NHS TB service as part of the routine care of suspected TB cases.
11. We would systematically collect all chest x-ray films and the accompanying radiological reports for each case. We would use a computer software to assign a diagnosis to each film allowing us to investigate whether this automated algorithm developed by Bram van Ginneken (Radboud University Medical Center, Nijmegen, The Netherlands).

Permission to inform the GP is included in the consent form as per the NHS R&D Governance Framework. A letter detailing the test results will be sent to the participant and the participant's GP, if they are registered with a practice (Appendix 2).

Clinical outcome data will be collected from the NHS TB service by the RN on a routine basis until the end of the project.

Baseline TB symptom screen:

*If any patient has any of the above risk factors plus a fever or cough lasting longer than 2 weeks and any of the following symptoms (1):

- Blood in sputum
- Drenching night sweats
- Unexplained weight loss

Should be referred for investigation with Xpert and chest x-ray.

1. Adapted from Disharoon *et al* Developing an Emergency Department Tuberculosis Triage Screening. American Journal of Infection Control. 40. 2012. e31-e176

3.1.2 Recruitment and inclusion criteria

In order to assess their basic eligibility before directing patients to the research nurse, patients may be asked the following questions:

- If non-UK born, are they from a high TB prevalence country?
- How long they have lived in the UK?
- How often they have visited a high TB prevalence country and for how long in the last five years
- If UK or non-UK born, do they have the following risk factors currently or in the last five years: homelessness, imprisonment, problem drug use?

A study TB specialist or practice nurse will identify eligible persons and give them written information sheets (translated as appropriate). Written informed consent will be obtained (with the help of a translator where appropriate) from all patients willing to take part. The research nurse will complete a baseline assessment questionnaire including demographic and clinical information.

The inclusion criteria are:

1. Individuals aged 16 years or older
2. are a new entrant from a high incidence country and have arrived in the UK within the past 2 years.
or
were born in a high incidence country, entered the UK more than five years ago, but have spent more than one year (cumulative) in the past five years in a high incidence country.
3. Have social risk factors for TB including drug use, ever been in prison or ever been homeless, irrespective of place of birth.

The exclusion criteria are:

- Individuals who are under 16 years

- Individuals who were born in the UK or a low incidence country without a known risk factor as outlined in the inclusion criteria.
- Individuals who were born in a high incidence country who arrived in the UK more than 5 years ago and have not travelled since.

3.1.3 Test results and further action

Clinicians will be informed of all test results by the testing laboratory. Subsequent action after testing will follow existing NICE guidance. If any test results, or the chest x-ray are indicate for active TB, the patient's records and test results will be sent to the patient, the patient's GP and the local NHS TB service for follow-up and treatment. All further care and communication with the patient will be carried out by the NHS TB service as part of the routine care of suspected TB cases.

3.1.4 Follow-up

All participants will be followed for an average of 24 months (between 18 and 36 months) from the date of diagnosis using a number of approaches:

- A search of national enhanced TB surveillance reports,
- A search of national database of culture proven TB.
- Local TB service clinic records.

The use of these data sources enables comprehensive national follow-up of participants. This should minimise loss due to transfer of care to other centres by patients or physicians. The follow up will be undertaken by the study coordinator, administrator and database manager in collaboration with participating centres and coordinated from the PHE Centre for Infections.

3.2 Data Collection

Data gathered directly from the participant will be collected by trained research nurses using paper based forms. Follow up data are collected either directly from the TB clinic or through the web-based national surveillance system, supplemented by clinic and primary care record. The web based TB surveillance system already holds demographic, clinical and microbiological details of all TB cases in England and Wales. All data will be imported into a purposely built section of the PREDICT study database maintained at the Respiratory Disease Department of the PHE. This unit has considerable experience of data management and holds the national enhanced tuberculosis and mycobacterial laboratory databases.

Data items to be collected from participants include age, gender, country of birth and date of entry to the UK for non UK born persons, ethnicity, duration of residence in the UK, current employment, the time interval between the most recent suspected exposure date and the date of diagnosis in the source case, details of any previous contact tracing, history of previous TB including treatment, BCG vaccination status (scar and record), vitamin D status, associated medical diagnoses or use of immunosuppressive agents, drugs used for the treatment of latent infection and simple measures of compliance with, and adverse effects of, chemoprophylaxis (i.e. treatment of latent infection), and pregnancy status.

3.3 Outcome measures and definitions

3.3.1 Primary Outcome:

- a) Confirmation of active TB (Incident Rate Ratios) in Accident and Emergency departments. Cases of active tuberculosis will include a) culture confirmed cases with a microbiological diagnosis (isolation of *M. tuberculosis* in the presence of clinical disease) and b) clinically diagnosed cases (signs and symptoms of TB with radiological or histological evidence of tuberculosis). Cases will include all diagnosed individuals reported to the national surveillance system, national microbiological database or diagnosed at participating clinics.
- b) Cost per QALY.

3.3.2 Secondary Outcome:

We will investigate the diagnostic accuracy of the symptom tool, Xpert test and radiology by calculating sensitivity and specificity of each approach in this context.

3.4 Analysis Plan

Statistical analysis: Following descriptive analyses, a multivariable Poisson regression model will be built in a forward stepwise manner to identify risk factors for the primary and secondary outcomes. We will also investigate the diagnostic accuracy of the computer aided diagnostic tool by comparing outcomes derived by the algorithm with culture confirmed tuberculosis and clinically diagnosed tuberculosis. We will present sensitivity, specificity, predictive values and diagnostic odds ratios.

3.4.1 Sample size

It is estimated that on average, 2 participants will be screened each day at each of the three sites for a total of 40 weeks, resulting in a sample size of 1,200. Assuming a detection rate of 2%, we would expect to identify 20 cases of active TB with a 95% confidence interval of 12 to 31 based on a Poisson distribution.

3.4.2 Measuring effectiveness

Prevalence will be calculated for active TB and a multivariable Poisson regression model will be built in a forward stepwise manner to identify risk factors for the primary and secondary outcomes.

3.4.3 Measuring costs

The full cost of detecting cases of TB in Accident and Emergency departments will be calculated. Costs considered will include staff, accommodation and testing costs. Costs of treating active TB will come from literature and other studies.

3.4.3 Decision-analytic modelling

Decision analytic models will be developed to calculate cost per QALY for detecting each case within Accident and Emergency. Modelling will be used to calculate numbers of transmission events averted – and consequent costs and QALY losses averted – by averting active disease. Cost effectiveness will be estimated according to standard the National Institute for Health and Clinical Excellence (NICE) methods. The analysis will be conducted from an NHS perspective with a 15 year time horizon. All costs and outcomes will be discounted at 3.5% per annum. Probabilistic sensitivity analysis will be used to investigate the impact of uncertainty over model parameters, and the value of collecting additional information. Deterministic sensitivity analysis will also be used to test the impact of structural uncertainty over modelling assumptions (e.g. the time horizon).

E. Expected output of the research

A comprehensive report will be prepared. This will include recommendations to the DH regarding an economic analysis of the cost effectiveness of identifying active TB cases within Accident and Emergency departments. The report will summarise findings particularly relevant to UK tuberculosis control policy.

In addition to a formal report to the DH, the research will be disseminated through peer reviewed publications, conference presentations and engagement with policy makers (Department of Health and the PHE), patients and the public (via local clinical networks in London, community-based programmes working with at-risk for TB populations and voluntary sector agencies such as TB Alert).

F. Project time table including milestones

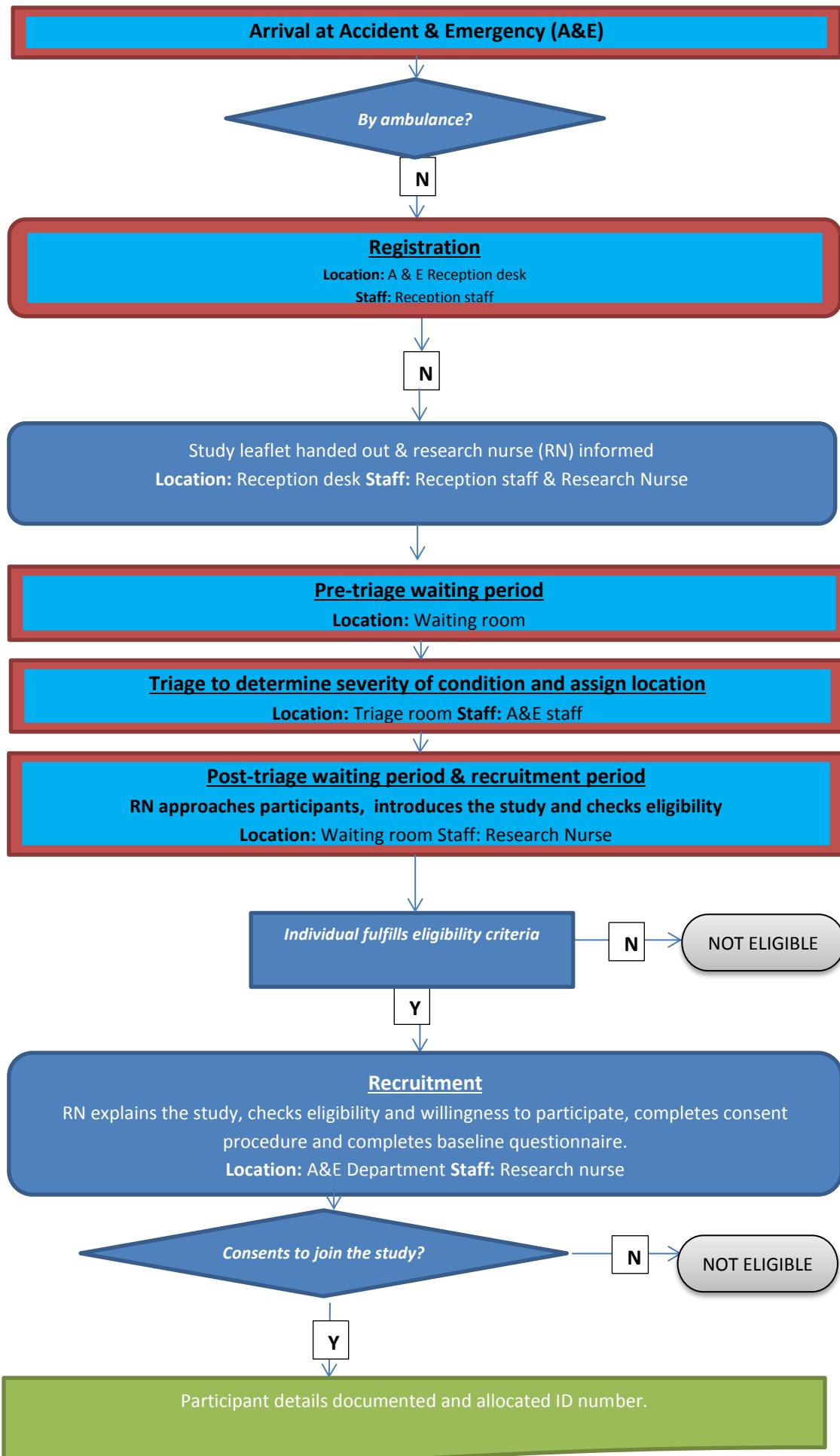
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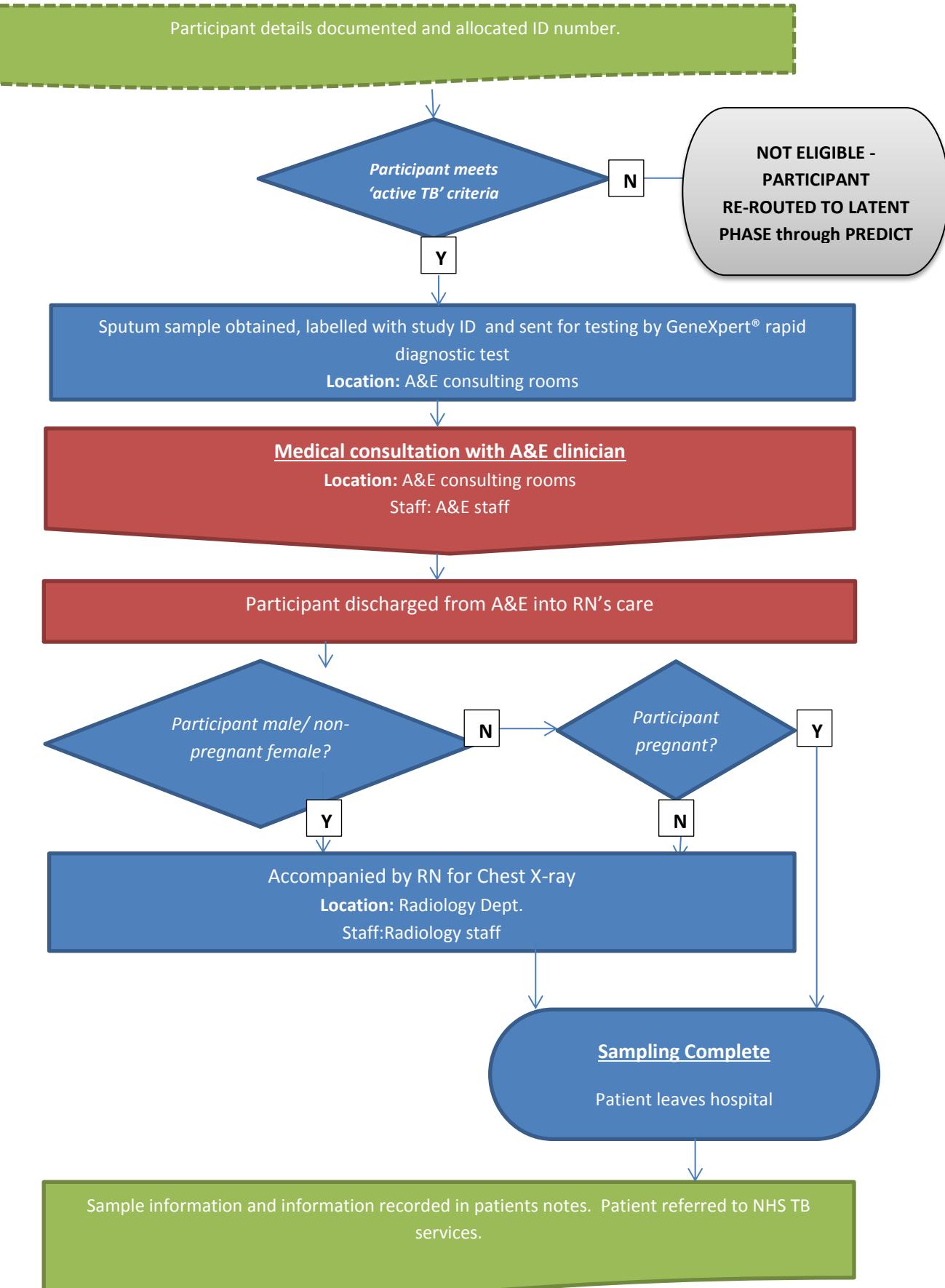
Year	2014				2016					2017				
Month (2 months)	2	4	6	8	22	24	26	28	30	32	34	36	38	
PRE STUDY PROCESSES		★												
• Ethics application														
• Purchase of equipment/materials for study			★											
• Staff recruitment				★										
• Organisation of recruitment of participants					★									
• Organisation of databases and data collection														
RECRUITMENT AND FOLLOW UP			★											
• Recruitment											★			
• Laboratory assays			★											
• Follow up												★		
DATA CLEANING AND ANALYSES													★	
• Data cleaning														
• Statistical analysis											★			
• Economic analysis											★			
REPORTING														
• Preparation of final report for HTA and paper writing												End		

References

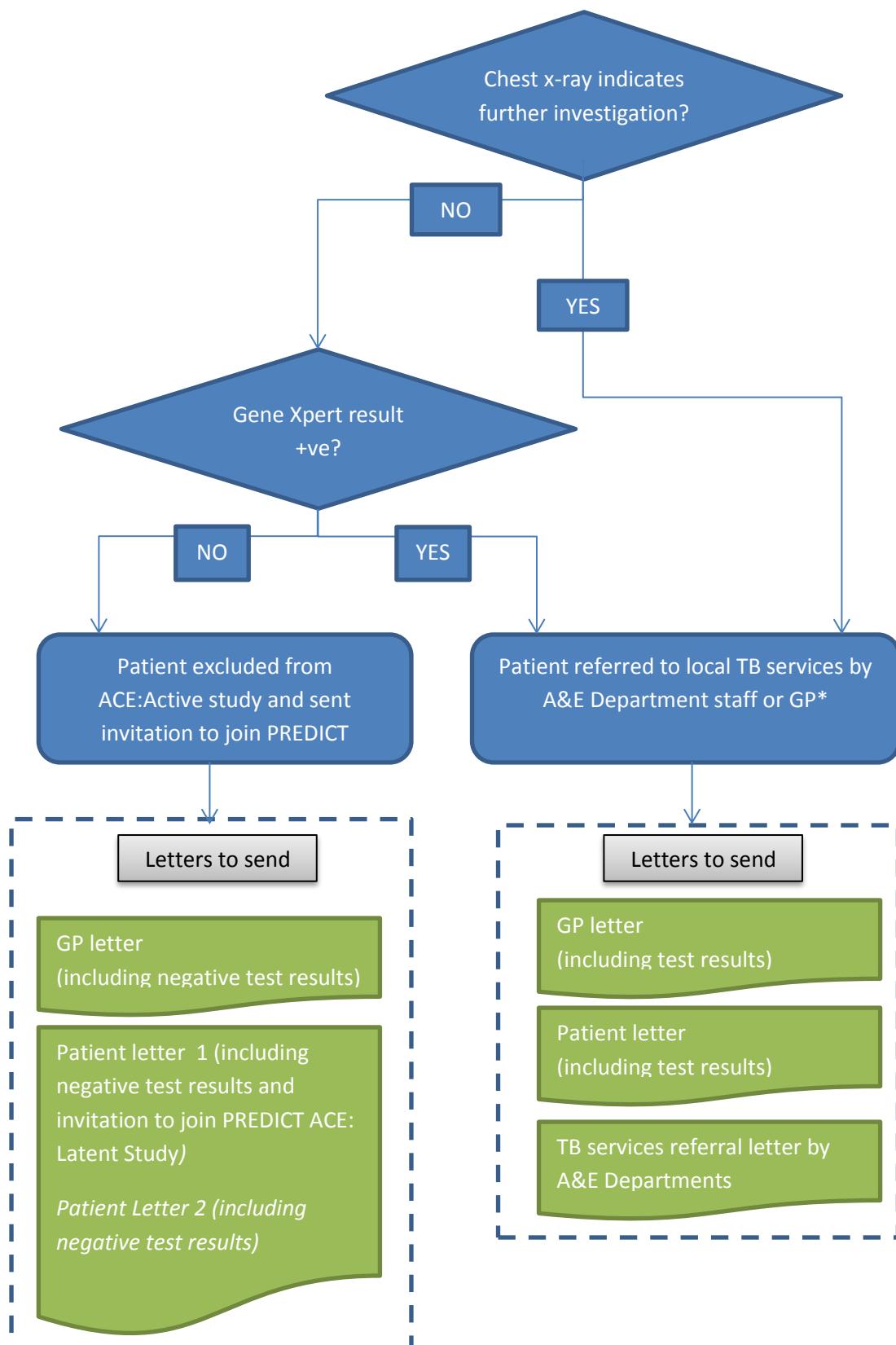
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Appendix 1 – Recruitment flow diagram (the exact order may vary depending on established site procedures in A&E by Trust.)





Appendix 2- Communication flow diagram



*TB services referral may be via established A&E pathway depending on logistics at each site.