Oncimmune Evaluation Project

Final Report

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September 27, 2022

Executive Summary

This report presents a clinical evaluation of the Oncimmune EarlyCDT-Lung Community Screening Feasibility Study, which was a pilot study conducted in two GP practices in the Great Yarmouth and Waveney area of Norfolk in early 2021. These practices were selected because of their high levels of lung cancer and smoking prevalence.

EarlyCDT-Lung, manufactured by the pharmaceutical company Oncimmune, is a simple blood test offered to high-risk patients that can detect possible biomarkers for early-stage lung cancer. As with all cancers, early diagnosis of lung cancer is associated with better patient outcomes. Blood was taken in a primary care setting and then an Elisa test was performed at Norfolk & Norwich University Hospital. Patients who tested positive were offered a CT scan and if this indicated further investigation was necessary, the patient was urgently referred to the main lung cancer diagnostic pathway.

Our evaluation addressed the following questions:

1. What impact has the screening programme had on the stage of lung cancer at diagnosis?
2. What impact has the screening programme had on health service use, particularly emergency attendances, inpatient admissions and diagnostic activity in secondary care (such as CT scans) for suspected lung cancer?
3. What impact has the screening programme had on the Faster Diagnosis Standard?
4. What impact has the screening programme had on staff satisfaction?
5. What are the cost implications of the screening programme?

A staff survey was conducted to address question 4 and a computer simulation model developed to address questions 1, 2, 3 and 5. The model assumes that patients will continue to present via the standard pathway while the screening programme is in operation and that in the short term, these numbers will not change. Further work (not covered by this report) will include modelling the longer-term consequences of screening, which will require data not available to us.

Based on the limited data available, and using 2019 smoking prevalence in adults and 2020 population age distribution as a proxy for eligibility for the test, we extrapolated our findings to estimate the impact of extending the screening programme to all areas within the Great Yarmouth & Waveney area. Note that these results should be treated with caution, as the eligibility criteria specified a minimum number of packs smoked and also included ex-smokers.

1. What impact has the screening programme had on the stage of lung cancer at diagnosis?

Within the pilot study practices, the programme had a significant impact on the stage of lung cancer at diagnosis, identifying seven previously undiagnosed early-stage primary cancers among the 1,919 patients who took part. No late-stage cancers were detected. Using the results from a clinical trial of EarlyCDT-Lung (Sullivan et al, 2021) we can infer that around half of these seven screen-detected cases would otherwise not have been detected until stages 3 or 4.

The model results show that even with 20% take-up, in Great Yarmouth & Waveney around 10 patients a year would be diagnosed at stages 1 or 2 who would otherwise not have been diagnosed until stages 3 or 4, where curative treatment may no longer have been possible. With take-up of 40%, this number rises to 28 or 29.

2. What impact has the screening programme had on health service use, particularly emergency attendances, inpatient admissions and diagnostic activity in secondary care (such as CT scans) for suspected lung cancer?

The pilot study had a significant impact on health service use in terms of diagnostic activity in secondary care (additional CT scans and further investigations) and inpatient admissions for curative surgery. In the absence of secondary care data other than for diagnostics, we were unable to draw any conclusions on emergency attendances or admissions relating to late-stage cancers. The table below shows the predicted annual resource utilisation across the whole of Great Yarmouth & Waveney for the two screening take-up scenarios.

	CT Scans	X-rays	Blood Tests
Standard pathway only	82	45	-
Standard + screening (20% take-up)	990	47	10,951
Standard + screening (40% take-up)	1,892	46	21,087

3. What impact has the screening programme had on the Faster Diagnosis Standard?

The pilot study data did not contain the dates of diagnosis or treatment; the latest date we had was the date of the initial out-patient appointment following a suspicious CT scan. Moreover, all the date data we were given for the pilot study was of the form MM:YY to avoid the risk of identifying individual patients. Hence it was not possible to come up with even a rough estimate of the number of screened patients who met the 62-day target from referral to treatment.

However, assuming that (worst case) a patient had their CT scan in the first week of the month and their out-patient appointment in the last, and also that patients on the screening pathway had their CT scans assessed and reported at the same rate as patients on the standard pathway, six of the seven patients with cancer definitely met the 2-week-wait target. We were unable to draw any conclusions about the remaining patients, including the one with cancer, as their CT scan was in month N and their out-patient appointment in month N+1.

It is important to note that a) the pilot study was partially undertaken during lockdown, which may have affected demand for out-patient appointments from other patients, and b) additional CT scan capacity was purchased as part of the pilot study. It is therefore not possible to draw any firm conclusions about the impact on these targets if screening were to become 'business as usual' with no additional CT resource.

4. What impact has the screening programme had on staff satisfaction?

The study had a largely positive impact on staff satisfaction. Overall, despite the administrative burden, staff were enthusiastic about the programme, because they felt it so clearly had the potential to save lives. Based on the findings from the survey, we make the following four recommendations:

1. Ensure adequate staff availability and time to conduct a programme such as this, taking into account that the practice of administering such a programme may be significantly more demanding than it might seem in theory.
2. Explore means of alleviating patients' fear associated with testing programmes. Such means might include the incorporation of future testing programmes as part of routine health

monitoring, or emphasis in health educational initiatives on the benefits and positive outcomes of early detection of cancer.

3. Patient information leaflets should be revised in the light of experience, and staff need to be informed of questions that are arising, and the responses that are appropriate.
4. The procedure regarding follow-up CT scans for patients who test positive but whose CT scans are negative needs to be fixed and clarified, in particular allocating responsibility for administering this procedure to the appropriate unit, bearing in mind available resources and facilities.

5. What are the cost implications of the screening programme?

The cost implications are considerable. The table below shows the average annual additional costs for take-up rates of 20% and 40%, compared with the standard pathway, and the benefits including the total gain in quality-adjusted life years (QALYs) and the cost per QALY gained. These figures are scaled up for the whole Great Yarmouth & Waveney area.

	20% take-up	**40% take-up**
Cost of additional CT scans performed	£181,677	£367,448
Cost of blood tests performed	£900,270	£1,792,433
Total costs	£1,081,947	£2,154,384
Total additional early-stage cancers detected	10.06	23.74
Total gain in QALYs	32.92	77.68
Cost per QALY gained	£32,870	£27,735

For both take-up rates, the cost per QALY gained is comparable with the £30k used by NICE (the National Institute for Health and Care Excellence) as a cost-effectiveness threshold. However, **the QALY results should be treated with caution** as they are based solely on the findings of the Feasibility Study in which all screen-detected cancers were stage 1 or 2. This was not the case in larger clinical trials of EarlyCDT-Lung, in which some cancers were detected at stage 3 or 4. If screening were to be rolled out more extensively, some later-stage cases might also be detected and this could increase the cost per QALY gained.

The model was also used to explore the impact of changing the eligibility criteria from ages 55-75 to 50-75. We found that there was **little benefit** in this as considerably more blood tests and additional CT scans would be required for a relatively small improvement in early-stage cancers detected.

Contents

1. Introduction and background: Early diagnosis of lung cancer

Based on data from Cancer Research UK, 48,500 new cases of lung cancer are diagnosed each year in the UK with 34,800 deaths per annum. However, if diagnosed early lung cancer is often both treatable and curable. Figure 1 shows that 56% of patients diagnosed with Stage 1 lung cancer are still alive five years after diagnosis; this figure drops to 3% for patients diagnosed at Stage 4 (Cancer Research UK). This improved survival is partly because patients diagnosed at the earliest stage have different treatment options than those diagnosed later. Many patients miss out on potentially curative treatment because they are diagnosed at a late stage of disease. In England 48% of lung cancers are at stage 4 when detected (Cancer Research UK).

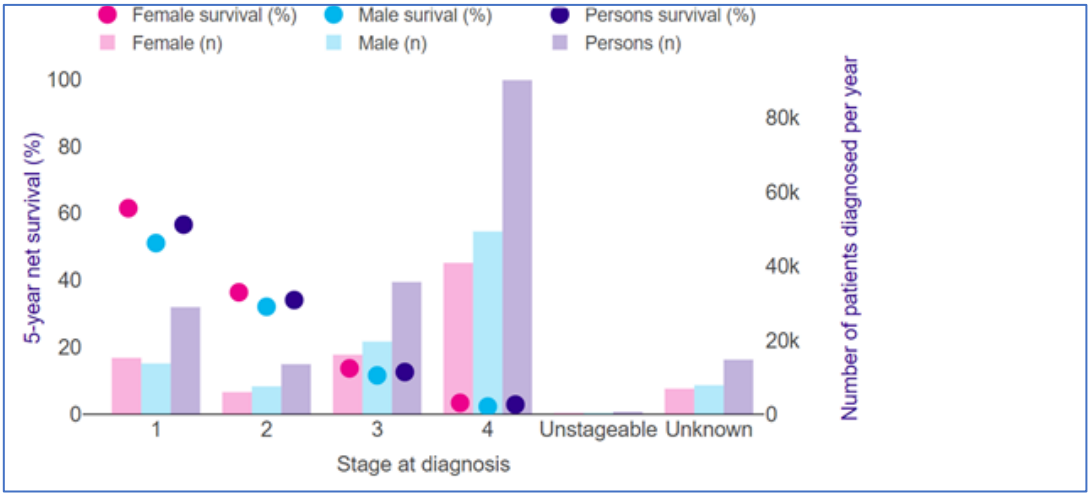

Figure 1. Five-year survival by stage and gender at diagnosis.

Source: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/survival#heading-Three

The UK Government has set a challenging ambition for 75% of cancers to be diagnosed at stage 1 or 2 by 2028. Early diagnosis is a multifaceted problem that requires a multifaceted solution. Removing barriers to screening and help-seeking, and ensuring provision of enough staff and equipment to conduct timely diagnostic tests, are key. The latency period for lung cancers attributable to smoking is at least 20 years, which accounts for the fact that 85% of cancers are found symptomatically in people aged 60 and over. These cancers are often detected by a chest X-ray when they are usually advanced, and the chances of long-term survival are low.

CT-led lung cancer screening has the potential to help prevent lung cancer deaths, with a 20% mortality benefit demonstrated in recent large scale clinical trials, i.e. ECLS (Sullivan et al, 2021), NLST (National Lung Screening Trial Research Team, 2011) and NELSON (de Koning et al, 2020). Since 2019, NHS England has been piloting its Targeted Lung Health Check (TLHC) scheme (https://www.cancerresearchuk.org/about-cancer/lung-cancer/getting-diagnosed/lung-health-checks) in areas with high rates of lung cancer mortality. Patients aged 55-75 who have ever smoked are offered an appointment with a nurse, either at their GP surgery or by telephone, at which they are asked a number of questions about their current health, lifestyle and medical history, including any personal history of cancer or family history of lung cancer. Patients who are assessed as being at increased risk of lung cancer (based on a statistical risk prediction model) are then offered a low dose CT scan. The initial assessment can take up to 45 minutes and hence is quite labour-intensive; moreover the scheme has not yet been fully evaluated.

Lower treatment costs for healthcare systems and improved patient outcomes associated with early cancer detection need to be balanced against the burden of large-scale screening programmes utilising high cost CT equipment. In many NHS organisations there is a significant deficit in CT scanner access time and radiologist capacity to report on the resulting CT scans. Eligibility for screening programmes is also a key element in designing an effective programme for detecting early stage cancers in a population. At 55 years old or over, and a minimum of 30 pack years smoking history, the clinical criteria for both the NLST and NELSON studies cover only 27% of lung cancers that will occur in the target population.

EarlyCDT-lung, manufactured by the pharmaceutical company Oncimmune, is a blood test that measures a panel of seven autoantibodies to tumour associated antigens related to lung cancer. Autoantibodies are produced in the early stages of solid tumour cancer, but remain present and measurable in all stages. Studies have shown that EarlyCDT-lung can detect lung cancer up to 4 years before clinical diagnosis through standard care pathways (Sullivan et al, 2021). The test can be performed by local pathology providers who possess the relevant equipment. Therefore, EarlyCDT-lung potentially represents an effective method of identifying very high risk patients that may require a subsequent CT scan. EarlyCDT-lung was designed for use in lower risk cohorts, retaining the NLST and NELSON entry criteria age to 55 (age 40 with secondary risk factors) but reducing the smoking history to 20 pack years. This covers approximately 40% of lung cancers in a population, allowing more cancers to be included than NLST and NELSON.

2. The Oncimmune EarlyCDT-Lung Community Screening Feasibility Study

The Feasibility Study took place from 25 January to 14 May 2021 in five GP practices (technically, two practices of which one operated across four sites) in Great Yarmouth. Its aim was to assess the practicality of introducing the Oncimmune EarlyCDT-lung biomarker blood test into primary and secondary care settings within the NHS in England to support the earlier diagnosis of lung cancer. The study was mainly funded by the East of England Cancer Alliance, with additional support from Eastern Academic Health Science Network and Oncimmune. The Great Yarmouth and Waveney area contains one of the most deprived wards in the county. Only 23.8% of patients in the area are diagnosed with lung cancer at stage 1 or 2, with a directly standardised rate (DSR) per 100,000 of 69.6, compared to a neighbouring area, South Norfolk, which has a DSR of 35 (data from 2016). Smoking prevalence rates in adults vary widely across Norfolk & Waveney, from 57.9% in the areas of highest social deprivation down to 13% in the more affluent areas of the county. The histopathology laboratory at the Norfolk & Norwich University Hospital has Elisa DS2 analysers and was chosen to take part in the feasibility study.

The target population was current smokers and ex-smokers aged 55-75 with at least a 20 pack-year smoking history. Ex-smokers had to have been a smoker for at least 15 of the past 25 years.

- A total of 4,890 patients were invited for screening.
  - Of these, 1,919 attended, a response rate of 39.2%.
    - Of these, 298 (15.53%) had a positive blood test and were booked for CT scan. Seven patients did not attend so 291 scans were performed in total.
      - Of these 291, 20 (6.87%) were deemed to require further investigation and were put on the fast-track pathway for MDT and/or further diagnostic tests.
        - Of these 20, nine (45%) were subsequently found to have lung cancer. The remaining 11 patients were flagged for follow-up in either six or 12 months time. None of these patients had had any previous indication of lung cancer.

Of the nine lung cancers detected, seven were primary tumours, one was secondary to kidney cancer, and one was secondary to urothelial cancer. The patient with kidney cancer was referred for surgery and the patient with urothelial cancer, for CT-guided biopsy and chemotherapy. Of the seven patients who were diagnosed with primary lung cancer, five were identified as being stage 1 in the TNM staging system, and two at stage 2. One of the stage 1 patients was referred for radiotherapy but all the other patients were immediately referred for surgery. The outcomes following surgery are not known.

Of the 271 patients who had a positive blood test followed by a negative CT scan, 185 were invited for a follow-up CT scan roughly one year later. We do not have complete information about all 185, but based on the data we do have, only 107 patients attended and many of the patients who did not attend either declined, had changed GP practice, or had died. Of the 107 who attended, only one had a suspicious CT scan which indicated further investigation was required, but we have no information about whether cancer was found to be present.

In summary, of the total 1,919 patients in the trial **15.53%** tested positive on the blood test and **291** additional CT scans were performed. Following CT scan, **1.04%** were found to require further investigation. **0.47%** were subsequently diagnosed with lung cancer; **0.36%** with primary lung cancer (all at stage 1 or 2) and **0.11%** secondary to another cancer. In addition, based on an interview conducted as part of the staff survey, a previously undetected breast cancer was identified following CT scan. This did not show up in the data, presumably because the patient did not have lung cancer. The follow-up CT scan only picked up one potential further cancer.

3. Clinical evaluation of the Feasibility Study

A team from the University of Southampton was commissioned by Eastern Academic Health Science Network to conduct a clinical evaluation of the study. We were asked to address the following five questions:

1. What impact has the screening programme had on the stage of lung cancer at diagnosis?
2. What impact has the screening programme had on health service use, particularly emergency attendances, inpatient admissions and diagnostic activity in secondary care (such as CT scans) for suspected lung cancer?
3. What impact has the screening programme had on the Faster Diagnosis Standard?
4. What impact has the screening programme had on staff satisfaction?
5. What are the cost implications of the screening programme?

To address question 4 we conducted a survey of staff involved in the programme. Participants were identified and then contacted by the CCG. More details are given in section 3.4 below.

With the help of the AHSN, we set up a Clinical Steering Group (CSG) consisting of a number of people who had been involved, directly or indirectly, in the Feasibility Study. Further information about the CSG and other practical aspects can be found in Appendix H.

We note that in other trials of EarlyCDT-Lung, notably ECLS (Sullivan et al, 2021), cases of lung cancer were detected at all stages. Hence while our evaluation is based on the findings of the Feasibility Study, in which all screen-detected cases were stage 1 or 2, it is important to bear in mind that this may not always be the case in future if the screening programme were to be rolled out more extensively.

From a statistical perspective, 1,919 is a fairly small sample compared with other studies such as ECLS. Therefore, to address the remaining questions, we adopted a simulation modelling approach.

In the model, individual patients are created on entry and given characteristics such as age, gender and cancer stage, sampled either from national or local data (for patients on the current diagnostic pathway) or the trial data (for patients on the screening pathway). They are then tracked through the system and various performance metrics and patient outcomes calculated. The model takes account of variability between individual patients in terms of age, cancer stage at presentation, disease progression and response to treatment. It also accounts for variability in the time spent waiting at each stage in the pathway, and captures uncertainty in terms of the sensitivity and specificity of the various diagnostic tests. Probability distributions were fitted for these parameters from observed data where available, and otherwise from the clinical literature. By repeatedly running the model a number of times, statistically valid results can be obtained which consist not only of point estimates, but the whole distribution of values of each performance metrics, including confidence intervals.

A technical description of the simulation model is provided as Appendix A. Appendix B contains a full list of the model parameters and the associated data sources, and Appendix C describes the assumptions behind the model and its main limitations.

As it stands, the model is based on the findings from the Feasibility Study and therefore assumes that in the short term there would be minimal change in the number of diagnoses on the standard pathway. To calculate the longer-term impact of screening on diagnosis rates by stage, especially for areas other than Great Yarmouth & Waveney, the model would need to be extended so that it tracked every individual with lung cancer in the general population (both diagnosed and undiagnosed) and also, included inflows to and outflows from the screen-eligible population over time as people age. This would require an estimate of the true underlying incidence and prevalence of lung cancer by patient age and cancer stage in the local population, the rates of disease progression, and the size of the eligible population. Unfortunately these data were not available to us, and hence this report focuses specifically on the short-term impact of the screening programme on the five practices in the Feasibility Study. Future work is planned to include these factors.

3.1. What impact has the screening programme had on the stage of lung cancer at diagnosis?

Within the pilot study practices, the programme had a significant impact on the stage of lung cancer at diagnosis, identifying seven previously undiagnosed early-stage primary cancers among the 1,919 patients who took part. No late-stage cancers were detected.

The obvious inference is that in subsequent years the rate of presentations at stages 3 and 4 will decrease, but we were not able to calculate an exact number based on the data available. Since under routine care only 23.8% of lung cancer patients in the whole of Great Yarmouth and Waveney are currently diagnosed at stages 1 or 2, it is reasonable to conclude that without screening, several of these seven patients (who had no idea they had cancer) would not have been diagnosed until their cancer had progressed to stage 3 or 4. Based on the study data alone we cannot say precisely how many, since it is possible that some may have presented anyway while their cancer was still at an early stage. However, a clinical trial of EarlyCDT-Lung (Sullivan et al, 2021) found that after two years the proportion of early-stage diagnoses in the intervention arm was double that in the control arm. Therefore we can infer that around half of the seven screen-detected cases would otherwise not have been detected until stages 3 or 4.

To provide a more rigorous answer to this question, we ran the model 100 times for two simulated years, for three scenarios: no screening, screening with a 40% response rate (as in the Feasibility Study) and screening with an arguably more realistic response rate of 20%, since all other reported trials, including the Manchester Lung Health Check study which led to the TLHC pilot, had much

lower response rates. Table 2 presents the mean (average) total number of cancers that would be diagnosed in the pilot study practices over two years, assuming that screening is offered once a year and patients who did not attend in year 1, attend in year 2. The minor differences between scenarios in stage 3 and 4 diagnoses are solely due to sampling variation.

Standard pathway only	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**
Mean	4.02	2.91	7.74	23.11
Standard Deviation	1.97	1.79	2.57	4.59
CI width	0.39	0.35	0.50	0.90
Standard + screening (20% take-up)				
Mean	6.69	3.89	7.48	23.43
Standard Deviation	2.57	1.89	3.13	4.54
CI width	0.50	0.37	0.61	0.89
Standard + screening (40% take-up)				
Mean	10.17	5.39	8.10	22.59
Standard Deviation	3.32	2.16	3.12	5.21
CI width	0.65	0.42	0.61	1.02

Table 2. Number of patients diagnosed in the pilot study practices, by stage (total over 2 years)

The standard deviation is a measure of the variability over the 100 simulation runs, i.e. individual variability between patients and uncertainty about the test accuracy. 'CI width' denotes the width of the 95% confidence interval, i.e. the interval within which it is possible to be 95% confident that the true value will lie.

Table 3 shows the expected (average) number of additional early-stage cancers diagnosed in the two screening scenarios.

	Stage 1	**Stage 2**	**Total**
Screening (20% take-up)	2.67	0.98	3.65
Screening (40% take-up)	8.15	2.30	10.45

Table 3. Expected number of additional early-stage cancers diagnosed in the pilot study practices (total over 2 years)

In Table 4 we have scaled up the results from Table 3 for the whole Great Yarmouth region, assuming (in the absence of any data to the contrary) that the proportion of eligible patients is the same as in the pilot study practices. This is only an estimate, since based on 2019 data from Public Health England (https://fingertips.phe.org.uk/) smoking prevalence in adults varies considerably across the region, with upper and lower 95% confidence intervals of 14.3% and 32.4% respectively.

	Stage 1	**Stage 2**	**Total**
Screening (20% take-up)	14.68	5.39	20.06
Screening (40% take-up)	44.80	12.64	57.44

Table 4. Expected number of additional early-stage cancers diagnosed in the whole Great Yarmouth region (total over 2 years)

Based on the results from Sullivan et al (2021), we can conclude that even with 20% take-up, in Great Yarmouth & Waveney around 10 patients a year would be diagnosed at stages 1 or 2 who would otherwise not have been diagnosed until stages 3 or 4. With take-up of 40%, this number rises to 28 or 29.

3.2. What impact has the screening programme had on health service use, particularly emergency attendances, inpatient admissions and diagnostic activity in secondary care (such as CT scans) for suspected lung cancer?

The pilot study had a significant impact on health service use in terms of diagnostic activity in secondary care (additional CT scans and further investigations) and inpatient admissions for curative surgery. In the absence of secondary care data (other than for diagnostics), we were unable to draw any conclusions on emergency attendances or admissions relating to late-stage cancers.

Table 5 presents the model results for diagnostics (blood tests, X-ray and CT scans) for patients in the pilot study practices. In Table 6, the mean (average) values are scaled up for the whole Great Yarmouth & Waveney region.

Standard pathway only	**CT Scans**	**X-rays**	**Blood Tests**
Mean	29.9	16.3	0
Standard Deviation	5.6	4.00	0
CI width	1.1	0.8	0
Standard + screening (20% take-up)			
Mean	360.4	17.3	3853.9
Standard Deviation	21.4	3.9	84.3
CI width	4.2	0.8	16.5
Standard + screening (40% take-up)			
Mean	688.4	16.9	7673.0
Standard Deviation	27.6	3.8	110.9
CI width	5.4	0.7	21.7

Table 5. The impact of different screening take-up levels in the pilot study practices (total over 2 years)

	CT Scans	**X-rays**	**Blood Tests**
Standard pathway only	164	90	-
Standard + screening (20% take-up)	1,981	95	21,183
Standard + screening (40% take-up)	3,784	93	42,175

Table 6. The impact of different screening take-up levels in the whole Great Yarmouth region; mean values only (total over 2 years)

3.3. What impact has the screening programme had on the Faster Diagnosis Standard?

The pilot study data did not contain the dates of diagnosis or treatment; the latest date we had was the date of the initial out-patient appointment following a suspicious CT scan. Moreover, all the date data we were given for the pilot study was of the form MM:YY to avoid the risk of identifying individual patients. Hence it was not possible to come up with even a rough estimate of the number of patients who met the 62-day target from referral to treatment.

However, assuming that (worst case) a patient had their CT scan in the first week of the month and their out-patient appointment in the last, and also that patients on the screening pathway had their CT scans reported at the same rate as patients on the standard pathway, six of the seven patients with cancer definitely met the 2-week-wait target. It is not possible to draw any conclusions about the remaining patients, including the one with cancer, as their CT scan was in month N and their out-patient appointment in month N+1.

It is important to note that a) the pilot study was partially undertaken during lockdown, which may have affected demand for out-patient appointments from other patients, and b) additional CT scan capacity was purchased as part of the pilot study. It is therefore not possible to draw any definitive conclusions about the impact on these targets if screening were to become 'business as usual' with no additional CT resource. In addition to a reluctance to trouble their GP over what they perceived as minor issues during the pandemic, many people were also less willing to attend ED other than in a real emergency, so it is possible that during the study period diagnosis rates on the standard pathway were lower than normal.

3.4. What impact has the screening programme had on staff satisfaction?

To address this question, we surveyed staff who were involved with the programme using an online questionnaire. A more detailed analysis of the results of the survey can be found in Appendix E; Appendix F1 contains the actual questionnaire.

Links to the online questionnaire were sent by Eastern AHSN to 11 staff members of the East Norfolk Medical Practice (ENMP) and Park Surgery in Great Yarmouth (where the screening programme was carried out). These staff included GPs, administrators, and phlebotomists. They also each received an electronic copy of a Participant Information Document (Appendix F2) outlining the purpose of the survey, so they could decide whether they wished to participate or not. The survey asked questions about relevant personal details such as job role, detailed impressions of the screening programme, and more general overall impressions about its use and value.

Four responses were received from people with a range of duties and job roles. (This is actually quite a good response rate for this kind of survey!) We were able to conduct follow-up interviews with two of the participants. All participants were promised anonymity, so in this report we cannot refer to them by name or job role. Given the low number of respondents (which was anticipated), analysis of the survey is not statistical (nor was it intended to be). Rather, it picks up comments and observations from staff which may be of interest, both in relation to the particular study, and more generally (when running similar studies in future, for example). The analysis that follows makes use of data from both the questionnaire survey and the follow-up interviews. To preserve the anonymity of respondents, as required by ethical governance conditions, neither respondents nor their job roles have been identified in this report.

The findings of the survey, and our recommendations, are as follows. (For more details, see Appendix E.)

1. The programme required more time and effort to administer than was expected.

It was easy to identify candidate patients from the Practice's patient database. This was based on patient's ages and smoking history. However, contacting patients and arranging appointments was more time-consuming than expected.

Patients were contacted by phone rather than by letter, because previous experience suggested this would be more effective. Up to three attempts were made to contact each patient by phone.

Some patients were unwilling to take part. Patients who were undecided about whether they wanted to take part or not were offered the option of being phoned back a week or so later to give them time to think about their choice. In several such cases, they decided they would participate.

The programme required considerably more time and effort to manage than expected. While contacting patients and inviting them to attend an appointment for a blood test might seem very straightforward, in practice it can be quite demanding of time.

We assume that if such a programme were to become a standard part of the activities of a medical practice, adequate time would be factored in for it. As part of the standard routine of the practice, it would probably require less time and effort than in this case anyway.

Our general recommendation applies to both adopting the screening as standard, but also to running pilot programmes such as this one:

Recommendation 1: *ensure adequate staff availability and time to conduct a programme such as this, taking into account that the practice of administering such a programme may be significantly more demanding than it might seem in theory.*

2. Patients' attitudes towards the programme were mixed.

Patient attitudes to the study seemed to be mixed. Some patients were positive towards it. Others were less enthusiastic, and generally chose not to take part.

Some patients who were unwilling to take part may have been fearful of what the test might show, rather than just lacking interest.

A very small number of patients (one or two) for whom the blood test was positive (indicating a possibility of cancer) decided not to go on to be CT scanned (which would have given a more conclusive result).

These findings suggest that there are patients who appear inclined to avoid confronting the risks of lung cancer.

Our recommendation here suggests that a good way of reducing the fear associated with lung cancer is to make testing programmes part of routine healthcare, and improve public understanding of the benefits of screening. (Publishing the results of programmes such as this one could be part of this improvement; as one of the people we surveyed commented, "it is a great programme that could save many lives".)

Recommendation 2: *explore means of alleviating the fear associated with testing programmes. Such means might include the incorporation of future testing programmes as part of routine health monitoring, or emphasis in health educational initiatives on the benefits and positive outcomes of early detection of cancer.*

3. Patients were reasonably well-informed about the test.

An information leaflet was supplied to all those patients who participated in the programme. Our survey respondents commented that patients seemed well-informed. This was presumably as a result of the leaflet and their phone conversations with the Practice. Some patients has questions

which weren't answered by the leaflet, and in some cases staff weren't immediately able to answer either.

Some of these questions involve the individual circumstances of patients, so it would be difficult to prepare fully for them.

Our recommendation here is that the leaflets should be revised, and staff better prepared to answer questions, in the light of experience.

Recommendation 3: *patient information leaflets should be revised in the light if experience and staff need to be informed of questions that are arising, and the responses that are appropriate.*

4. Generally, staff were firmly positive about the benefits of the programme to patients.

Staff were firmly positive about the study. They said it was straightforward and unambiguous in terms of what it offered, and that several cases where it was likely to have been very beneficial to patients' lives had been picked up – cases where a lung cancer might successfully be treated because of its early detection. One staff member said: "it is a great programme that could save many lives" All the staff who responded to the survey felt that the programme was a "good use" or "very good use" of the resources of the practice (staff, facilities, equipment, staff time and money)

Other unexpected benefits of the programme were that one or two cases of other serious conditions were picked up.

One member of staff suggested that patients who were smokers might be reminded by the programme of the health risks of smoking and so be encouraged them to give up.

Our recommendation here concerns the issue of where in the healthcare system responsibility for follow-up CT scanning one year on from a negative CT scan following a positive test might lie. This needs to be settled and clarified.

Recommendation 4: *the procedure regarding follow-up CT scans for patients who test positive but whose CT scan are negative needs to be fixed and clarified, in particular allocating responsibility for administering this procedure to the appropriate unit (presumably either GP Practice or Radiology) bearing in mind available resources and facilities.*

3.5. What are the cost implications of the screening programme?

To calculate the additional NHS costs, we used a estimated total cost of £85 for the blood test (£60 for the test kit and £25 for laboratory processing) and £200 for a CT scan (which includes the reporting cost). These costs are taken from Appendix A of the Operational Report from the study. The study costs also include primary care support and publicity costs, but we omit these from the following analysis as they are shown as an overall total rather than per patient. Table 7 shows the average annual additional costs and early-stage cancers detected for the (probably more realistic) 20% and 40% take-up scenarios, compared with the baseline no-screening scenario. These figures are scaled up for the whole Great Yarmouth area in Table 8.

	20% take-up	40% take-up
Cost of additional CT scans performed	£33,053	£66,851
Cost of blood tests performed	£163,789	£326,103
Total costs	£196,842	£391,954
Additional stage 1 cancers detected (mean)	1.34	3.08
Additional stage 2 cancers detected (mean)	0.49	1.24
Total additional early-stage cancers detected	1.83	4.32
Cost per additional early-stage cancer detected	£107,859	£90,835

Table 7. Average annual costs and benefits for varying take-up rates in the five practices

	20% take-up	40% take-up
Cost of additional CT scans performed	£181,677	£367,448
Cost of blood tests performed	£900,270	£1,792,433
Total costs	£1,081,947	£2,154,384
Additional stage 1 cancers detected (mean)	7.37	16.93
Additional stage 2 cancers detected (mean)	2.69	6.82
Total additional early-stage cancers detected	10.06	23.74
Cost per additional early-stage cancer detected	£592,850	£499,277

Table 8. Average annual costs and benefits for varying take-up rates for the whole of Great Yarmouth & Waveney

Clearly, the higher the take-up the greater the total costs, but more early-stage cancers are detected and the cost per case detected reduces. It is clear that the blood test contributes most of the cost, even if £200 is a slight underestimate of the cost of a CT scan.

Finally, we used the simulation model to estimate the total gain in quality-adjusted life years (QALYs) for the whole of Great Yarmouth & Waveney, and the approximate cost per QALY gained. For each patient treated for cancer, the remaining life expectancy based on age and cancer stage was sampled by the model using survival data from Cancer Research UK (Figure B1 in Appendix B). To estimate quality of life, we used utility values of 0.823 for a year lived after a diagnosis of stage 1 or 2 lung cancer, and 0.573 for a year lived after a diagnosis of stage 3 or 4 lung cancer (Sturza et al, 2010). A utility value of 1 corresponds to a year lived in perfect health. Based on ten simulation runs, the average remaining QALYs after diagnosis for a person detected on the routine pathway was 1.55. For a person detected by screening, this increased to 3.27.

The results are presented in Table 11. It is interesting to note that for both take-up rates, the cost per QALY is roughly in the same ballpark as the £30k used by the National Institute for Health and Care Excellence (NICE) as a cost-effectiveness threshold.

	20% take-up	40% take-up
Total additional early-stage cancers detected	10.06	23.74
Total gain in QALYs	32.92	77.68
Cost per QALY gained	£32,870	£27,735

Table 11. Average QALYs gained and cost per QALY for varying take-up rates, for the whole of Great Yarmouth & Waveney

Important caveat. **The results in Tables 7-11 are based on the findings of the Feasibility Study, in which all screen-detected cases were stage 1 or 2. This may not always be the case in future if the screening programme were to be rolled out more extensively. Detecting additional later-stage cancers by screening would reduce the QALYs gained and hence increase the cost per QALY.**

In order to undertake a full cost-benefit analysis, more data are required on treatment costs and patient outcomes on both the standard pathway and the screening pathway. These would then need to be compared with the status quo where the majority of patients are not diagnosed until stages 3 and 4. This is beyond the scope of this report but is something that the planned extended simulation model could potentially estimate.

4. Additional results from the model

Many other scenarios could potentially be simulated; for example, doing repeat blood tests (either for all eligible patients, or for newly eligible patients, or targeting those patients who did not attend the first time) at differing intervals; or changing the interval for follow-up CT scans for patients whose blood test is positive; or combining the blood test with other screening tools, e.g. the Targeted Lung Health Check. We plan to produce an article for a scientific journal that explores some of these scenarios.

For the purposes of this report, we present the potential impact of changing the age criteria to include patients aged 50-54, and also of uncertainty about the test sensitivity (the true test sensitivity is 39%). The following results are for the pilot study practices and are for one year only. Table 10 shows that there is little benefit in including these younger patients, as considerably more blood tests and CT scans are required to detect a relatively small number of additional cancers.

39% Sensitivity	**CT Scans**	**X-rays**	**Blood Tests**	**Cancer Stage 1**	**Cancer Stage 2**	**Cancer Stage 3**	**Cancer Stage 4**
Mean	298.20	8.51	2989.36	4.65	2.30	3.67	10.91
Standard Deviation	18.77	3.16	54.63	2.18	1.43	1.94	3.56
CI width	3.68	0.62	10.71	0.43	0.28	0.38	0.70
49% Sensitivity							
Mean	302.72	8.36	2997.30	5.08	2.40	3.80	11.68
Standard Deviation	18.80	2.48	60.63	2.29	1.36	2.04	3.27
CI width	3.69	0.49	11.88	0.45	0.27	0.40	0.64
59% Sensitivity							
Mean	300.71	8.87	2989.00	5.80	2.96	4.01	11.50
Standard Deviation	19.09	3.19	56.15	2.25	1.61	1.91	3.40
CI width	3.74	0.62	11.00	0.44	0.32	0.38	0.67

Table 9. The impact of different blood test sensitivities (total over 1 year)

Age 55-75	CT Scans	X-rays	Blood Tests	Cancer Stage 1	Cancer Stage 2	Cancer Stage 3	Cancer Stage 4
Mean	298.20	8.51	2989.36	4.65	2.30	3.67	10.91
Std Dev	18.77	3.16	54.63	2.18	1.43	1.94	3.56
CI width	3.68	0.62	10.71	0.43	0.28	0.38	0.70
Age 50-75							
Mean	369.45	8.57	3743.64	4.98	2.75	3.65	11.09
Std Dev	19.22	2.57	60.87	2.38	1.63	1.93	3.75
CI width	3.77	0.50	11.93	0.47	0.32	0.38	0.73

Table 10. The impact of changing the age eligibility criteria (total over 1 year)

5. Conclusion

As noted at the outset, the model assumes that patients will continue to present via the standard pathway while the screening programme is in operation. In the short term these numbers will not change, but in the longer term they should hopefully reduce if screening were to continue and no significant changes occurred in demographics or smoking patterns. Modelling this longer-term impact required data not available to us at the time, but in future we plan to develop the model further so it can estimate the longer-term impact of screening if it were to be rolled out on an ongoing basis, rather than as a one-off as in the pilot study.

In principle, such a model could be used to answer much wider questions about the future impact of the screening programme. For example: should patients be screened more than once, and if so how frequently? What are the associated trade-offs in terms of costs and benefits for different screening intervals? Is it worth offering the screening test in areas with low smoking prevalence? However, this would require data that were not available to us, and hence this report focuses on the impact of the screening programme as offered in the Feasibility Study. This follow-up work will be additional to this report.

Appendix A: The simulation model

The model was developed in the simulation software AnyLogic (https://www.anylogic.com/). The initial step was to develop a baseline model representing patient flow through the current lung cancer diagnostic pathway, which we refer to as the standard pathway. The screening intervention was then added as a new pathway that can be turned on or off for selected subsets of the population, and the results compared.

Figure 2 presents a diagrammatic representation ('conceptual model') of the two pathways, with the screening pathway shown in red. We are very grateful for the help of the CSG, and in particular Emma Schofield, for helping us understand all the complexity. Developing the conceptual model was an iterative process that involved a number of online meetings and email exchanges to sense-check the pathway diagram.

Like any model, it is a simplification of the real-world system, although it does reflect the pathway followed by the vast majority of patients in the area and the National Optimal Lung Cancer Pathway[1]. Although the model does not distinguish between different types of lung cancer, in reality there are many different types and the diagnostic pathway is extremely complex. Patients may undergo a series of different diagnostic tests (biopsy, PET/MRI scans, bronchoscopy, spirometry, etc), not always in the same order, before a diagnosis is made and a treatment plan developed. Patients may be discussed at several multi-disciplinary team (MDT) meetings before getting a definitive diagnosis and treatment plan. We did not have any patient-level secondary care data for patients on the standard pathway, so for simplicity the model assumes that the decision to treat (DTT) is made at the first MDT meeting. However, since the main focus of the evaluation was on the initial part of the diagnostic pathway, the model treats the post-MDT part as a 'black box' which does not contain any detail or consider resource use but simply calculates patient survival time post DTT, based on cancer stage at diagnosis.

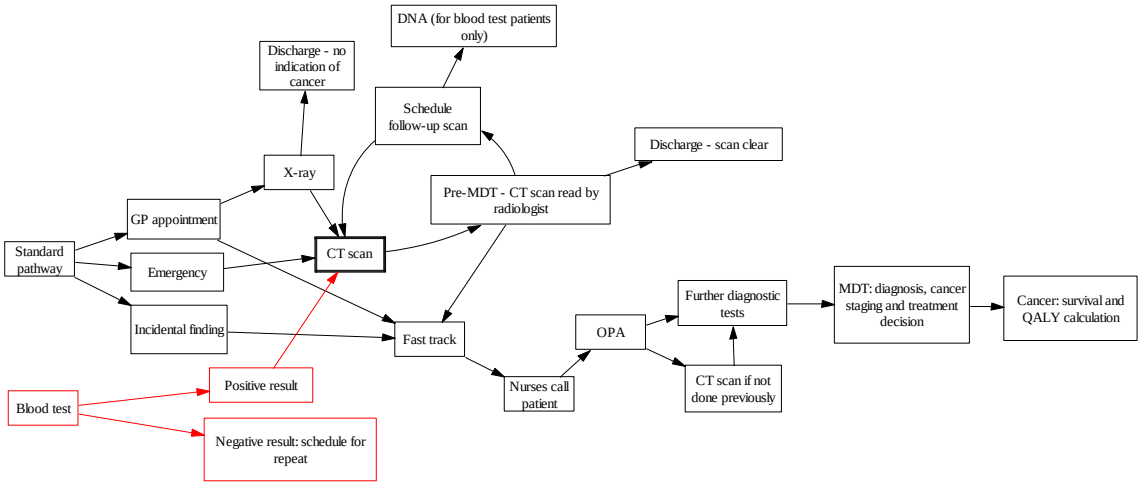

Figure 2. Schematic of the model showing the standard and screening pathways to diagnosis

In Figure 2, 'Fast track' denotes the point in time at which patients are referred (or 'upgraded') onto the main lung cancer pathway. Patients are then called by a cancer nurse, who informs them they have suspected cancer and books an urgent outpatient appointment (OPA) with a lung physician. There is a national target of 49 days between this point and the time when the patient starts treatment, but our model is not able to calculate this metric due to data limitations. However the

[1] https://www.cancerresearchuk.org/sites/default/files/national_optimal_lung_pathway_aug_2017.pdf.

model does estimate performance against a second target, the 'two week wait', which relates to patients on the GP appointment route and denotes the time between GP referral for chest X-ray and the date of the OPA.

On the standard diagnostic pathway, patients present in three possible ways:

a) At a routine GP appointment, with 'red flag' symptoms such as haemoptysis, persistent cough, smoking history, etc. The vast majority of patients are referred to the 2-week wait lung cancer pathway for a chest X-ray, and if the X-ray is suspicious the radiologist will arrange an urgent CT scan. However a small number are immediately fast-tracked.
b) As an emergency (normally via ED); patients then have an urgent CT scan.
c) As an incidental finding, typically following a CT scan while being investigated for something else (either as an inpatient or an outpatient). These patients are always fast-tracked.

Following CT scan, the results are reviewed by a radiologist and potentially other staff at a pre-MDT meeting. If the scan is suspicious, the patient will be fast-tracked. If the scan is clear, the patient will be discharged and given a follow-up CT scan in 3 or 6 months time; if this second scan is also clear the patient is discharged. In reality the follow-up process after a negative CT scan is more complicated than this, and will depend on the size and nature of any lesion. The patient may also be referred onto a lung nodule pathway, but the model does not consider this.

Following the first OPA further diagnostic investigations, including a CT scan if not previously performed, may be carried out before a final diagnosis is made at a full MDT meeting and a decision made on further treatment/management. The model essentially ends at this point and simply calculates expected patient survival time post 'treatment' based on cancer stage at diagnosis.

On the screening pathway, eligible patients are invited to attend their GP surgery for the blood test. If the test is negative (low level of autoantibodies) they are discharged. If it is positive (medium or high level) they are referred for a CT scan and they then follow the standard pathway, with the exception that if the CT scan is clear they get a follow up scan after one year, rather than 3/6 months. In the trial, a fairly large fraction (c.20%) of patients did not attend this follow-up.

Appendix B: Model data

Node	Description	Value	Source	Notes
Standard Pathway entry point	Inter-arrival time for patients (all three routes)	15.8 days (exponential distribution)	Norfolk & Waveney CCG	Average number of patients presenting with lung cancer per year in study area is 23.1. Inter-arrival time is 365/23.1 = 15.8 days. This is scaled for the three entry points in the model.
	Distribution used to sample individual patient age on arrival	See table B1 below	Norfolk & Waveney CCG https://cruk.org/cancerstats	Practice data on age at diagnosis provided by Maggie Tween. Distribution assumed to be independent of entry route
	Cancer stage on presentation, by route	See table B2 below	https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/	Assumption: cancers do not progress between presentation and diagnosis
	Routing out percentage	41% GP 39% emergency 20% incidental finding	CRUK data (England) Elliss Brookes et al (2012) Also discussed with CAG	Separates patients into the three routes
GP Appointment Route	Routing out percentage	98% to X Ray 2% to Fast track	Estimate based on "small number miss an x ray" comment in CAG meeting	On the basis of Emma Schofield's email, it looks like this is a VERY small number
X Ray	Duration of appointment plus pre-appointment wait	5.8 days (fixed distribution)	England et al (2021a,b)	
	Routing out percentage	Stages 1&2: 80% to CT scan, 20% discharge. Stages 3&4: 100% to CT scan	Estimate, based on two references: Gavelli et al (2000) Toyoda et al (2008)	In this context the 'sensitivity' of X-ray actually means its ability to determine whether further investigation is required. The first (admittedly fairly old) reference suggests it might sometimes miss early stage cancers but overall is good at identifying stages 3 and 4. Confirmed by second slightly more recent reference

Node	Description	Value	Source	Notes
CT Scan	Duration of appointment plus pre-appointment wait	Uniform[5.9,13.9] for GP route; 1 day (fixed) for emergency route; Beta(3.99, 5.44) for screening route	England et al (2021a,b) Assumption Trial data (fitted)	Reference gives mean of 9.9 days for the 2ww pathway Assume patients on the emergency route will have an urgent CT scan within 24 hours Caveat about dates in data
	Sensitivity	100% for stages 3 & 4 85% for stages 1 & 2	Toyoda et al (2008)	References available are for low dose CT scans
Pre-MDT (review of CT scan by radiologist)	Duration	Uniform[4.4,6.4]	England et al (2021a,b)	Reference gives mean of 5.4 days
	Routing out	If positive: to fast track. If negative (first scan): to schedule follow-up. If negative (2nd scan): to discharge	Discussion with CAG and email from Emma Schofield	Time taken to review CT scan and report. If scan is suspicious, patient is immediately fast-tracked (referred to lung cancer pathway)
Schedule for CT Follow Up	Time until follow up CT scan	3 or 6 months (standard pathway); 1 year (screening pathway)	Discussion with CAG	
	Routing out	Standard pathway: 100% to CT scan Screening pathway: 80% to CT scan, 20% to DNA	Assumption Trial data	Caveat – several patients were lost to follow-up in the trial data (deceased or changed GP practice)
Fast Track	Duration	0 (fixed)		Point in time: start of the lung cancer pathway
Nurses Call	Duration	1-3 days (uniform distribution)	Discussion with Emma Schofield	This happens very quickly after the patient has been referred

Node	Description	Value	Source	Notes
OPA	Duration	1 – 7 days (uniform distribution)	Assumption, based on discussions with Clinical Advisory Group.	Includes waiting time between cancer nurse call and the actual appointment
	Routing out	90% to Other tests; 10% to CT scan if not done previously	Estimate	Assumes all patients who have not had a scan will be sent along the "CT scan if not done previously" route. Not critical to aims of the evaluation.
Other Tests	Total elapsed time	Average of 14 days (exponential distribution)	Estimate	Literature suggests this is highly variable. Also not critical to aims of the evaluation.
CT scan if not done previously	Duration of appointment plus pre-appointment wait	5 days	Estimate	Assumes this would be done quite quickly, but not critical to aims of the evaluation.
MDT	Duration	1 – 7 days (uniform distribution)	Estimate based on CAG discussion	Not critical to aims of the evaluation.
Cancer survival	Survival probability up to 10 years, by stage at diagnosis	See graph (Figure B1) below	https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed	ONS Cancer Survival in England: adults diagnosed between 2013 and 2017 and followed up to 2018. 1-year and 5-year age-standardised survival data.

Node	Description	Value	Source	Notes
Screening route entry point	Inter-arrival time, based on pilot study.	(0.282, 0.141, 0.094) days (exponential distribution) Three values based on take-up: 20% (low); 40% (mid); 60% (high)	Pilot study data	Scenarios used in experiments. Pilot study had 39% response rate
	Percentage of entrants in each cancer stage	0.26% stage 1; 0.1% stage 2; 0% stages 3 and 4; 99.54% no cancer	Pilot study	ECLS found some stage 3 & 4 cancers but none were detected in the pilot study.
Blood Test	Test accuracy	Sensitivity 37-41% Specificity 91%	Sullivan et al (2020)	
	Routing Out	Cancer: 39% to CT scan, 61% to schedule repeat test. No cancer: 9% to CT scan, 91% to schedule repeat test.	Sullivan et al (2020)	Depends on true cancer status of patient. Use average value for sensitivity
Schedule repeat blood test	Time until follow up	2 years	Assumption, based on discussions with Clinical Advisory Group.	Not used – model only run for 2 years. Could potentially be used in future experiments

	Cases		Rates per 100,000	
Age Range	**Female**	**Male**	**Female**	**Male**
0 to 04	1	1	0	0
05 to 09	0	0	0	0
10 to 14	2	1	0.1	0.1
15 to 19	4	2	0.2	0.1
20 to 24	7	3	0.3	0.1
25 to 29	14	14	0.6	0.6
30 to 34	20	25	0.9	1.1
35 to 39	49	51	2.3	2.4
40 to 44	119	121	5.8	6
45 to 49	339	367	14.7	16.3
50 to 54	746	766	31.5	33.4
55 to 59	1,423	1,473	67.1	71.4
60 to 64	2,294	2,417	124.9	137
65 to 69	3,571	3,895	197.8	229.5
70 to 74	4,460	4,918	278.1	335
75 to 79	4,024	4,656	340.5	462.2
80 to 84	3,133	3,563	338.2	500.4
85 to 89	2,026	2,110	327.6	538.8
90+	1,032	899	257.7	505.2
All Ages	**23,265**	**25,284**	**70.1**	**90.6**

Table B1: Age distribution of lung cancer cases at diagnosis (England)

Source: https://cruk.org/cancerstats

	% via this route	Stage at diagnosis (%)			
		1	**2**	**3**	**4**
GP	41	23	10	26	41
Emergency	39	3	7	17	73
Incidental finding	20	14	8	22	56

Table B2: Cancer stage at presentation and diagnosis, by route (England)

Source: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/

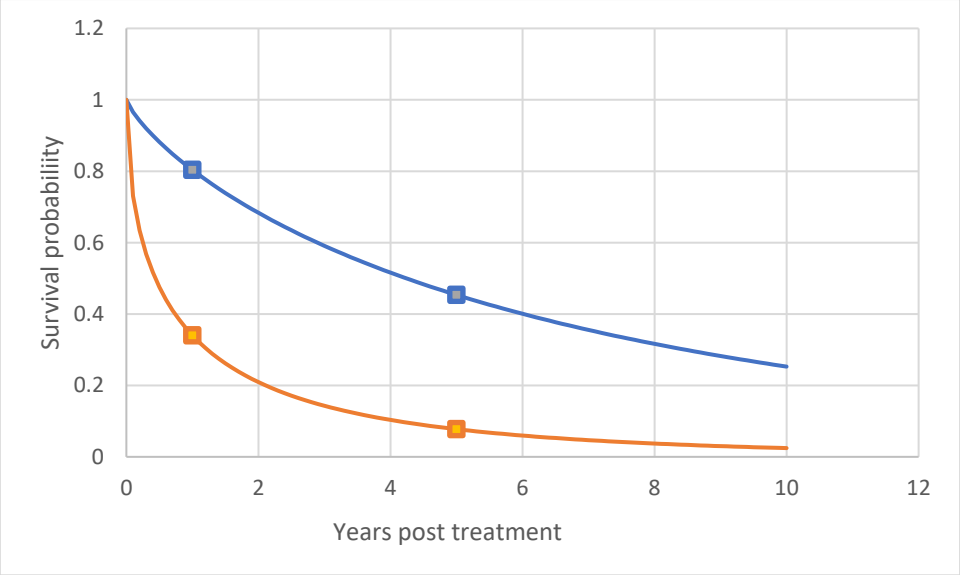

Figure B1. Survival probability following lung cancer diagnosis in England, by stage at diagnosis. Blue = stages 1 & 2; orange = stages 3 & 4. Fitted to ONS age-standardised data for 1-year and 5-year survival. Source: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed

The data provided by the primary care practices involved in the trial contained the following items. Note that all the dates were of the form MM:YY to avoid the risk of patients being identified, which meant that wait times could only be estimated approximately.

- Patient's age
- Patient's gender
- Smoker or ex-smoker
- Blood test appointment date
- Attended (Y/N)
- Blood test result - POSITIVE / NEGATIVE
- Patient referred for CT scan (Y/N)
- Date of CT scan
- Patient attended CT scan (Y/N)
- CT scan indicates possibility of lung cancer (Y/N)
- Date of outpatient appointment in secondary care
- Lung cancer detected (Y/N)
- Stage and grade of lung cancer present
- Next stage of treatment

Appendix C: Model assumptions and limitations

It is clear from the description above that the model is a simplification of a highly complex system. In reality, after treatment patients typically receive regular follow-up CT scans, but these are not modelled; neither is demand for CT scanning for all other patients. Since the aim of the evaluation was to understand the impact of the screening programme on resource use (Question 2), the model only considers those CT scans that are performed as part of the lung cancer diagnostic process.

On the standard pathway, the model only considers patients with lung cancer. Around 60% of patients who present to their GP with symptoms that might indicate lung cancer actually turn out to have some other condition, and since the overwhelming majority of these are identified by X-ray they are not included in the model. On the screening pathway, of course, the model considers patients both with and without lung cancer.

Perhaps the most limiting assumption concerns the 'arrival rate' of patients on the screening pathway. This was based on the total number of number of patients who attended for screening during the study period, converted into a weekly average; in other words, attendances are spread out over a whole year rather than being concentrated into 3.5 months. This is a more realistic reflection of how such a screening programme would operate in reality, but in order to capture the 12-month follow-up CT scans for people who screen-tested positive but then had a negative CT scan, the model was run for two years under the assumption that screening would be offered again the following year and patients would continue to attend at the same rate. This is almost certainly an overestimate: if screening were to be offered again in year 2, either to everyone or just to those people who did not attend in year 1, it is likely that attendance would be less than that observed in the study. For all regular screening programmes, the take-up rate depends on a number of factors, including a) the size of the eligible population; b) patient-related factors such as ease of access, health behaviours and attitudes (perceived benefits and disbenefits of screening); and c) system-related factors such as capacity limits and the effort put into encouraging patients to attend. In principle these factors can all be modelled, but in this case we had no data on many of them. Therefore, to provide a more realistic comparison, we varied the attendance rate and found that a rate of 20% (half the 39% take-up observed in the trial) would still show benefits.

The arrival rate on the standard pathway is calculated using the annual number of patients diagnosed with lung cancer in the five GP practices in the pilot study. The model assumes that in the short term, these will not change. The data used to calculate eligibility for screening reflects the demographic profile of the population of Great Yarmouth and Waveney, which contains areas of very high deprivation, but this could easily be modified to represent other populations at local authority, ICB, regional or even national level.

For patients on the standard pathway, the model assumes that the cancer stage at diagnosis is the same as cancer stage at presentation. We are aware that for a very small number of cases, cancer may progress extremely rapidly, but in general the elapsed time between presentation and diagnosis will be sufficiently small for this assumption to be valid. Of course, in reality patients who have a negative CT scan (on both standard and screening pathways) may have very early stage cancer that will have progressed by the time they get the follow-up scan.

As none of the screen-detected patients in the trial were aware they had cancer, the model assumes that in the short term the presentation rates on the standard pathway do not change, although as noted above it is very likely that in the longer term they would, since a larger proportion of cancers would be picked up earlier. Finally, the model assumes that screening patients who have a

suspicious CT scan will wait the same time for further treatment as patients on the standard pathway.

Appendix E: Survey

Introduction

The Oncimmune survey was intended to address the fourth question in the Feasibility Study proposal: what impact has the screening programme had on staff satisfaction? We undertook to design, pilot and implement an online survey to explore this question.

The survey used the University of Southampton's online survey tool iSurvey. A pilot version was made available to members of the CAG in February 2022, and comments and suggestions were received. On the basis of these comments and suggestions, a modified version of the survey – in particular, incorporating more opportunity for multiple-choice tick-box responses – was prepared. This became available in late March. The survey closed in mid-June. The link to the survey was passed to the Eastern AHSN, who in turn distributed it to 11 potential respondents who were involved with the screening programme as personnel of the East Norfolk Medical Practice (ENMP) and Park Surgery in Great Yarmouth (where the screening programme was carried out). Potential respondents included GPs, administrators, and phlebotomists. All potential respondents received a Participant Information Document outlining the purpose of the survey. The survey was approved by the University of Southampton's Ethics and Research Governance Online system (reference number ERGO II 69480).

The survey consisted of three sections: the first (six questions) elicited personal details; the second (26 questions) elicited detailed impressions of the screening programme; and the final section (nine questions) elicited overall impressions of the screening programme. The survey and the Participant Information Document are reproduced in Appendices F1 and F2 respectively.

There were four respondents from the East Norfolk Medical Practice (ENMP) covering a range of duties and job roles. (This would generally be regarded as a good response rate for this type of survey.) Short follow-up interviews with two of these respondents were conducted.

Given the low number of respondents (which was anticipated), analysis of the survey is not statistical (nor was it intended to be). Rather, it picks up comments and observations from staff which may be of interest, both in relation to the particular study, and more generally (when running similar studies in future, for example). The analysis that follows makes use of data from both the questionnaire survey and the follow-up interviews. To preserve the anonymity of respondents, as required by ethical governance conditions, neither respondents nor their job roles have been identified in this report.

Findings 1: effort and resources required for the pilot study

The criteria the Practice used to identify candidate participants in the pilot study were well-defined (essentially based on age and on smoking history) and thus easily identifiable from the Practice patient database. Candidate participants were identified by search of the Practice's SystmOne clinical system, and then those who were deemed inappropriate (perhaps because they had already been identified as cancer patients, or were receiving palliative care) were removed from the list.

Candidate participants were contacted by phone rather than by letter. Experience in the Practice suggested that this approach was more likely to result in participation than written communication: it was explained that "we historically get poor uptake when [we] send letters". Up to three attempts

were made to contact potential participants by phone, after which attempts were discontinued. This approach was generally regarded as being fairly demanding in terms of time and effort. One participant observed that "getting patients to participate was harder [than anticipated]".

Some patients who were contacted were unwilling to take part. One respondent commented that, in their opinion, this was due to a fear of what the Oncimmune test might reveal rather than a lack of interest. Patients who indicated uncertainty about participation were offered the option of being phoned back a week or so later to give them time to think about their choice. In several cases, such patients ultimately decided to participate.

In terms of administration, the programme was more consumptive of time and effort than initially expected. Tasks which might not have been fully factored in initially included answering patients' questions, sending letters to patients (informing them of results), completing referral forms, chasing up referrals, and following up DNAs. One respondent reported that "contacting patients and explaining study … took more time than expected", and that "the study target of completing a set amount of patients within a tight timeframe made the administration difficult". Another explained that the "effort to ensure … adequate patient numbers [by phone contact rather than letter] … was more time consuming".

The programme requirements – to cover a particular number of patients within a particular time frame – were demanding in terms of time and staff. Opinions on the adequacy of time provided for the programme varied from "quite poorly" to quite well". Clearly, a longer time period, greater capacity throughout the study, and more people to assist with approaching patients and booking appointments, would have alleviated these difficulties. Equipment and facilities provided by the Practice seemed entirely adequate.

Presumably the loading on time and resources is a function of the nature of the pilot, and if such a test were to become a normal part of a Practice routine, the load would make itself manifest in a less demanding way. Nevertheless, the general observation – that pilot schemes such as this may be more demanding than anticipated on those involved with delivering them – is worth noting. A respondent commented that administration problems might be alleviated by "a longer deadline, or greater capacity throughout the study, or more people assisting with appointment bookings".

Recommendation: ensure adequate staff availability and time to conduct a programme such as this, taking into account that the practice of administering such a programme may be significantly more demanding than it might seem in theory.

Findings 2: patients' attitudes towards the programme

Patient attitudes to the study seemed to be mixed, with some patients positive towards it, while others – who generally declined to take part – were less enthusiastic.

A number of patients who were contacted were unwilling to take part. One respondent commented that, in their opinion, this was due to a fear of what the test might reveal rather than a lack of interest. Unwilling patients were offered the option of being phoned back a week later to give them time to think about their choice. In several cases, such patients decided to participate.

Alarmingly, perhaps, one or two patients declined further participation despite testing positive.

These findings suggest that there are patients who appear inclined to avoid confronting the risks of lung cancer.

Recommendation: explore means of alleviating the fear associated with testing programmes. Such means might include the incorporation of future testing programmes as part of routine health monitoring, or emphasis in health educational initiatives on the benefits and positive outcomes of early detection of cancer.

Findings 3: patients' level of information about the project

An information leaflet was supplied to participants, and respondents who felt able to comment reported that patients seemed well-informed, presumably as a result of the leaflet and phone conversations during their recruitment. While the leaflet was informative, it is possible that it could have contained more information about the practical implications of particular test results, which staff were not immediately able to provide. For example, patients wanted to know why a CT scan rather than an X-ray was required in the case of a positive test, and, what would happen after a positive or a negative CT scan result.

Clearly there is a limit to what can be covered in a leaflet, as each individual case is likely to develop in a different way.

Recommendation: patient information leaflets should be revised in the light if experience and staff need to be informed of questions that are arising, and the responses that are appropriate.

Findings 4: general comments on the programme

Other conditions of concern (which in some instances were already known about) were picked up in some of the CT scans – mostly cases of atherosclerosis. One case of a breast cancer was unexpectedly found. Such cases were dealt with as appropriate. While these cases were clearly of benefit to the patients concerned, this rather haphazard side-effect of the programme should probably not be regarded as a systematic benefit.

Staff seemed firmly positive about the study, noting that it was straightforward and unambiguous in terms of what it offered, and that several cases where it was likely to have had a high positive impact on patients' lives had been picked up – detection of early lung cancers. One participant commented: "it is a great programme that could save many lives", while another noted that "we were fortunate enough to be able to help a few people". In terms of whether or not the programme constituted good use of resources (personnel, facilities, equipment, time and money), two of the four respondents felt it was "very good use" of all five resources, while the other two described it as "good use".

By actively engaging with Practice patients who were smokers, it was observed that the scheme might serve to remind patients of the health risks of smoking and encourage them to give up. (On the other hand, it might serve to suggest to some patients that lung cancer is treatable, and the programme reduces the risks associated with smoking, so the way it is presented might need to be carefully considered.)

The issue of where responsibility for follow-up CT scanning one year on from a negative CT scan following a positive test might lie was raised. In practice, this needs to be settled and clarified.

Recommendation: the procedure regarding follow-up CT scans for patients who test positive but whose CT scan are negative needs to be fixed and clarified, in particular allocating responsibility for

administering this procedure to the appropriate unit (presumably either GP Practice or Radiology) bearing in mind available resources and facilities.

Appendix F: Questionnaire

F1: Questionnaire

Section 1. Personal details

This section asks you questions which identify yourself and your job role. We should like this information in order to be able to contact you to follow up any responses to questions which may lead to new insights concerning the screening programme. We reiterate that all responses will be treated confidentially. However, as with all questions in this questionnaire, these questions are optional - please do not respond to any about which you feel uncomfortable. Your responses in this survey will still be useful even if they areprovided anonymously.

Question 1.1 Your name
Question 1.2 Your email address
Question 1.3 Your job title
Question 1.4 Your work location
Question 1.5 What is your job role in relation to the programme?

- Practice Manager
- Administrator with responsibility for administration of screening programme
- Phlebotomist
- GP with responsibility for CT referral decisions
- Pathology laboratory administrator
- Pathologist
- CT scan administrator
- CT scan radiologist
- Lung cancer team surgeon
- Lung cancer team specialist nurse
- Lung cancer team respiratory consultant
- Other

Question 1.6 Please add any information regarding your role in the screening programme, if not clear from your job role as identified in the previous question.

Section 2. Your detailed impressions of the screening programme

The questions in this section explore various aspects of your views of the screening programme. Some of the questions may not apply to your particular experiences. Please enter "NA" (not applicable) for any such questions.

Question 2.1. How much effort was required in identifying patients for inclusion in the screening programme? [*options: a great deal; a reasonable amount; very little; not applicable*]

Question 2.2. If appropriate, please comment on the previous answer. (For example, if your response was "a great deal", it would be helpful to explain what specifically required the effort.)

Question 2.3. If you were involved with the administration of the part of the programme with which you were concerned, how demanding was this administration in terms of a) time and b) effort? [*options: very demanding, reasonably demanding, minimally demanding, not applicable*]

Question 2.4 If appropriate, please comment on your answer(s) to the previous question.

Question 2.5 If there were particular problems with the administration of the programme, what were they?

Question 2.6. If there were particular problems with the administration of the programme, have you any

suggestions as to how they might be alleviated?

Question 2.7. How adequately was the screening programme resourced in terms of a) time, b) equipment, c) facilities? [*options: very poorly, quite poorly, neutral, quite well, very well, not applicable*]

Question 2.8. If you felt resources were inadequate, it would be helpful if you were to comment further.

Question 2.9. To the extent that you are able to judge, were the feelings of patients about the screening programme:

- Strongly positive
- Positive
- Neutral
- Negative
- Strongly negative
- I am unable to judge

Question 2.10. How well informed did patients appear to be about the nature and purpose of the programme?

- Very well informed
- Well informed
- Adequately informed
- Poorly informed
- Very poorly informed
- I am unable to judge

Question 2.11. Were you able to provide appropriate information when asked for it by patients?

Question 2.12 To what extent did your activities relating to the screening programme interfere with your other duties and responsibilities? If there was such interference, on which specific duties and responsibilities did the programme impact?

Question 2.13. To what extent did the screening programme impact negatively on the needs and care of other patients (i.e. those not included in the screening programme)?

- Extreme impact
- Considerable impact
- Significant impact
- Marginal impact
- Negligible impact
- Not applicable

Question 2.14. If you were involved in the collection of blood samples from patients, to what extent was this activity adequately resourced? [options: fully, reasonably, poorly, not applicable]

Question 2.15. If you were involved with the decision to refer patients for CT scanning on the basis of the results of their screening, to what extent was a) the decision well-supported, b) its criteria well-defined? [*options: high, adequate, poor, not applicable*]

Question 2.16. If appropriate, please comment further on your responses to the previous question.

Question 2.17. If you were involved with the pathology lab activities relating to the analysis of blood samples from patients in the screening programme, to what extent were these activities a) well-defined, b) well resourced? [*options: high, adequate, poor, not applicable*]

Question 2.18. If appropriate, please comment further on your responses to the previous question.

Question 2.19. If you were involved with the CT scanning of patients who had been referred for scans as a result of their involvement with screening programme, to what extent were these scanning activities a) well-supported; b) well-resourced? [*options: high, adequate, poor, not applicable*]

Question 2.20. If appropriate, please comment further on your responses to the previous question.

Section 3. Your overall impressions of the screening programme

Question 3.1. Did you feel that you had adequate information to contribute fully to the part of the screening programme with which you were involved? If not, what additional information might have been useful or helpful?

Question 3.2. Do you feel that the screening programme is a good use of the following resources: a) personnel, b) facilities, c) equipment, d) time, e) money? [*Options: very good use, good use, reasonable use, poor use, very poor use, not applicable]*

Question 3.3. If appropriate, please comment further on your response to the previous question (particular if you felt that the programme was a poor or very poor use of one or more resources).

Question 3.4. Are there changes to the programme that might be made to improve its effectiveness and value?

Question 3.5. Would you be willing for us to contact you to follow up any issues of interest that have arisen as a result of this survey?

Thank you for taking this questionnaire.

F2: Participant information sheet

Study Title: Evaluation of the Oncimmune EarlyCDT-Lung Community Screening Feasibility Study

Researcher: Professor Sally Brailsford (evaluation leader)

ERGO number: 69480

You are being invited to take part in the above research study. To help you decide whether you would like to take part or not, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully and ask questions if anything is not clear or you would like more information before you decide to take part in this research. You may like to discuss it with others but it is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

The aim of this study is to evaluate the Oncimmune EarlyCDT-Lung Community Screening Feasibility Study. The evaluation is being carried out by a team from Southampton Business School (University of Southampton), on behalf of the Eastern Academic Health Science Network. The questions to be addressed in the evaluation are:

1. What impact has the screening programme had on the stage of lung cancer at diagnosis?
2. What impact has the screening programme had on health service use, particularly emergency attendances, inpatient admissions and diagnostic activity in secondary care (such as CT scans) for suspected lung cancer?
3. What impact has the screening programme had on the Faster Diagnosis Standard?
4. What impact has the screening programme had on staff satisfaction?
5. What are the cost implications of the screening programme?

The bulk of the evaluation will be carried out by simulation modelling. However, one of the above questions (Q4) concerns the impact of the screening programme on staff satisfaction. This question is to be addressed by the survey in which you are being invited to participate.

Why have I been asked to participate?

You are being invited to participate because you have been identified by the Eastern Academic Health Science Network as someone who was professionally involved in the feasibility study.

What will happen to me if I take part?

If you agree to take part, you will be invited to complete an online survey form detailing your experiences and impressions of the feasibility study. All questions on the form are optional. We anticipate that a full response to the survey form would take about 30 minutes. With your consent, we might follow up your response with an online interview at a time convenient to you (of no longer than 60 minutes). This interview would (assuming you consent) be audio-recorded. For this reason the survey asks for your contact details. If you would prefer not to be contacted, then there is no need to supply these details. The evaluation is due to be completed at the end of March 2022.

Are there any benefits in my taking part?

There are no direct benefits to you. The evaluation is intended to inform decisions concerning healthcare delivery.

Are there any risks involved?

We do not consider that there are any risks involved in participation.

What data will be collected?

Data on your experiences and impressions of the screening programme will be collected. A limited amount of personal data (indicating your relationship with the programme and your contact details for follow-up interview purposes) will be optionally included. Responses will be securely handled and stored on password-protected computers.

Will my participation be confidential?

Your participation and the information we collect about you during the course of the research will be kept strictly confidential. In the case of audio recordings of interviews, the recordings will be destroyed and transcripts retained securely.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check

that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form to show you have agreed to take part. This consent will be part of the online survey.

What happens if I change my mind?

You have the right to change your mind and withdraw at any time without giving a reason and without your participant rights being affected. If you have provided data anonymously, then you will not be able to withdraw your data after you have submitted your survey return. If you have identified yourself in the survey, then it can be withdrawn at any time prior to its inclusion in the data analysis.

If you withdraw from the study, we will keep the information about you that we have already obtained for the purposes of achieving the objectives of the study only.

What will happen to the results of the research?

Your personal details will remain strictly confidential. Research findings made available in any reports or publications will not include information that can directly identify you without your specific consent.

The results of the research will be summarised in a report written by the evaluation team. The results may be made more widely available, for example by publication.

Where can I get more information?

Please contact the following for further information: Mr Mike Hepburn (Evaluation Manager) mike.hepburn@soton.ac.uk

What happens if there is a problem?

If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions.

If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Thank you.

We are grateful to you for taking the time to read the information sheet and considering taking part in the research.

Appendix G: Practicalities

Originally, the evaluation project was due to run from October 2021 to March 2022. We had hoped to be provided with the data from the Feasibility Study by November 2021, together with follow-up secondary care data collected after the end of the pilot (May 2021). However, due to data protection and legal delays beyond our control, we did not receive the data until February 2022, at which time the project deadline was extended to 30 June 2022. Challenges with obtaining follow-up data led to a further extension.

Data Sharing and Non-Disclosure Agreements were set up with East Norfolk Medical Practice and Park Surgery in Great Yarmouth, the owners of the Minimum Data Set collected as part of the pilot study. In order to ensure that it was impossible for individuals to be identified in the data, the day of the month was omitted from all the dates, which to some extent affected our ability to address Question 3. Ethical approval to use these data and conduct the staff survey was obtained from the University of Southampton Research Ethics Committee (ERGO no 69480). As the study was a service evaluation, NHS REC approval was not required.

The original brief also included a question about patient experience, but given the practical challenges in terms of the time needed to obtain ethical approval, and the difficulty of accessing patients at a distance, it was not feasible for us to address this. Moreover, given that the Feasibility Study was largely undertaken at a time when the UK was in lockdown, it is not clear that the views expressed would be representative of the patient experience in normal circumstances: for example, people may have had COVID-related concerns about visiting their GP surgery for the screening test and this may have affected their overall experience. However, we did include a question about patient experience in the staff survey used to address Question 4.

With the help of the AHSN, we set up a Clinical Steering Group (CSG) consisting of a number of people who had been involved, directly or indirectly, in the Feasibility Study. The CSG met online on three occasions throughout the duration of the project, and members also answered questions by email. The CSG was extremely helpful and we are very grateful for their time and input into this study. The members were:

- Dr Linda Hunter, Associate Medical Director Primary Care Liaison and System Integration, Clinical Director East of England Cancer Alliance (North);
- Dr Suzanne Phillips, Clinical Lead, Norfolk and Waveney Cancer Transformation Programme;
- Maggie Tween, Norfolk and Waveney Cancer Programme Manager, NHS Norfolk and Waveney CCG & North EoE Cancer Alliance;
- Dr Ian Hume, Macmillan GP at Macmillan Cancer Support;
- Emma Schofield, Cancer Nurse, James Paget Hospital.

We are also very grateful to Maxine Burton, Management Assistant at East Norfolk Medical Practice, for her hard work in extracting much of the data.

Appendix H: References

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