Impact of immediate AI enabled patient triage to chest CT on the lung cancer pathway: LungIMPACT

Short title: LungIMPACT

RESEARCH REFERENCE NUMBERS

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SPONSOR: Nottingham University Hospitals NHS Trust

PROTOCOL VERSION NUMBER AND DATE: v1.3 8th February 2023

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: DocuSigned by: 3B8141695E2049B... Date: ...../...../..... 02-Mar-2023 | 9:09:21 AM GMT

Name (please print):

Dr Maria Koufali

Position:

Managing Director of R&I

Chief Investigator:

Signature: ..... Date: ..8./.Feb./..2023..

Name (please print): Professor David Baldwin

Position: Consultant Respiratory Physician

Nottingham University Hospital

KEY STUDY CONTACTS

Chief Investigator	Professor David Baldwin, Email - David.Baldwin@nottingham.ac.uk
Study Co-ordinator	Nadia Frowd Email – Nadia.Frowd@nuh.nhs.uk
Sponsor	Nottingham University Hospital NHS Trust Address Queens Medical Centre, Derby Road, Nottingham, NG7 2UH
Funder(s)	SBRI Healthcare Programme The Clatterbridge Cancer centre NHS Foundation Trust
Key Protocol Contributors	Dr Nick Woznitza, nicholas.woznitza@nhs.net Prof David Baldwin, David.baldwin@nuh.nhs.uk Dr Richard Lee , Richard.Lee@rmh.nhs.uk Dr Neal Navani, n.navani@ucl.ac.uk Dr Arjun Nair , arjun.nair1@nhs.net Janette Rawlinson, j.rawlinson@justrealsolutions.com Prof Tricia McKeever, Tricia.McKeever@nottingham.ac.uk Dr Leslie Smith L.F.Smith@leeds.ac.uk Dr Elena Pizzo, e.pizzo@ucl.ac.uk Dr Tuba Saygin Avsar, t.avsar@ucl.ac.uk Dr Markella Boudioni markella.boudioni@rmh.nhs.uk
Committees	Trial Management Group Prof David Baldwin Dr Nick Woznitza Dr Richard Lee Dr Thomas Round

	Dr Neal Navani Dr Arjun Nair Mrs Janette Rawlinson Dr Markella Boudioni Trial Manager Data Monitoring Committee/Trial Steering Committee Professor Matthew Callister, Consultant Respiratory Physician (chair) Dr Paul Beckett, Consultant Respiratory Physician Professor Sarah Lewis, Professor of Medical Statistics Dr Helen Powell, Consultant Respiratory Physician Dr Emma O'Dowd, Consultant Respiratory Physician Professor David Baldwin, Consultant Respiratory Physician Dr Nick Woznitza, Consultant Radiographer Mrs Janette Rawlinson (patient co-investigator) Nadia Frowd (Sponsor representative)

STUDY SUMMARY

Study Title	**Impact of immediate AI enabled patient triage to chest CT on the lung cancer pathway: LungIMPACT**
Internal ref. no. (or short title)	LungIMPACT
Study Design	Prospective
Study Participants	Non-recruiting study; CXRs referred from primary care at an institution-level
Planned Size of Sample (if applicable)	150,000 chest X rays (CXR) for clinical evaluation [Part A]
Follow up duration (if applicable)	Not applicable
Planned Study Period	12 Months
Study end definition	The study ends 12 months after the start of first active AI deployment
Research Question/Aim(s)	○ What is the impact of AI support at the time of CXR aquistion on the time to diagnosis of lung cancer? ○ What is the agreement between an AI algorithm and human reporters when interpreting CXRs referred from primary care? ○ Does immediate AI supported reporting of CXRs referred from primary care reduce the number of non-cancer diagnoses referred for an urgent lung cancer appointment? ○ For people referred from primary care, is the use of AI support at the time of CXR aquisition cost effective?

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**DETAILS OF FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
The Clatterbridge Cancer Centre NHS Foundation Trust	£3,221,710 Providing financial support for the study
SBRI Healthcare Programme	SBRI healthcare programme is being funded by NHS England and NHS improvement, SBRI Healthcare Programme will be providing Project management support to the company and act as support between Clatterbridge and awardee
Qure.ai Technologies	Project management support

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor will monitor the study conducted against applicable regulatory standards. The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities including a patient representative, who is very active and a member of the NCRI consumer forum, UCL Lung and wider PPIE group. We plan to recruit an additional patient representative, to have two patient experts. The TMG will be responsible for overseeing the trial. The TMG will review substantial amendments to the protocol prior to submission to the REC and provide input for study findings and data analysis. All investigators will be kept informed of substantial amendments through their nominated responsible individuals.

A single independent committee will perform the functions of Data Monitoring Committee and Trial Steering Committee (TSC/DMC). The committee will involve members who are independent of the investigators, funders, patient representatives and sponsor. The study will be conducted according to Good Clinical Practice guidelines. The TSC/DMC will monitor data accrual and trial progress and conduct and advise on scientific credibility. The TSC/DMC and will meet regularly (for example every 6 months). The TSC/DMC will also provide a monitoring function for certain aspects of safety relating to the patient pathway and software functionality, eg. Impact on patient flow, software issues. Aspects concerning accuracy of the AI will be reported by the independent statistical analysis at the defined time point in the study.

A trial master file will be kept at NUH by the sponsor and an Investigator Site File at all research sites. These will be composed in accordance with our sponsor's regulations and will be kept securely, but will be accessible to regulatory authorities. The maintenance of these files will be assigned to a dedicated researcher at each site.

Roles and responsibility of Technology Provider

Qure.ai has provided project management support to the clinical oversight team and writing support for the protocol but has not contributed or influenced the protocol design, study outcomes or data variables. Qure.ai team has adapted the qTrack tool at the request of and under the guidance of the clinical oversight group for use as the trial management database at each site.
Qure.ai will be the technology provider and will provide all necessary assistance to the investigators in understanding and operating the AI solution including integration at the clinical partner sites. Qure.ai will engage with IT teams at participating hospital sites of the study to lend support in the deployment of qXR. Qure.ai will, where requested, provide support in promoting the published findings of the trial.

Protocol contributors

CONTRIBUTOR(S) (Names and contact details of ALL individuals providing contribution to the protocol)	**DETAILS OF CONTRIBUTION GIVEN**
Dr Nick Woznitza, nicholas.woznitza@nhs.net	Trial design, protocol development and review
Prof David Baldwin, David.baldwin@nuh.nhs.uk	Trial design, protocol development and review
Dr Richard Lee, Richard.Lee@rmh.nhs.uk	Protocol development and review, lung cancer expert
Dr Neal Navani, n.navani@ucl.ac.uk	Protocol development and review, lung cancer expert
Dr Arjun Nair, arjun.nair1@nhs.net	Protocol development and review, thoracic radiology expert
Prof Tricia McKeever, Tricia.McKeever@nottingham.ac.uk Dr Leslie Smith L.F.Smith@leeds.ac.uk	Statistical plan and sample size calculation
Dr Markella Boudioni, markella.boudioni@rmh.nhs.uk	Support with patient and public involvement
Janette Rawlinson, j.rawlinson@justrealsolutions.com	Patient co-investigator; review of protocol, patient involvement and engagement throughout the study
Dr Elena Pizzo, e.pizzo@ucl.ac.uk Dr Tuba Saygin Avsar, t.avsar@ucl.ac.uk	Health Economic Assessment

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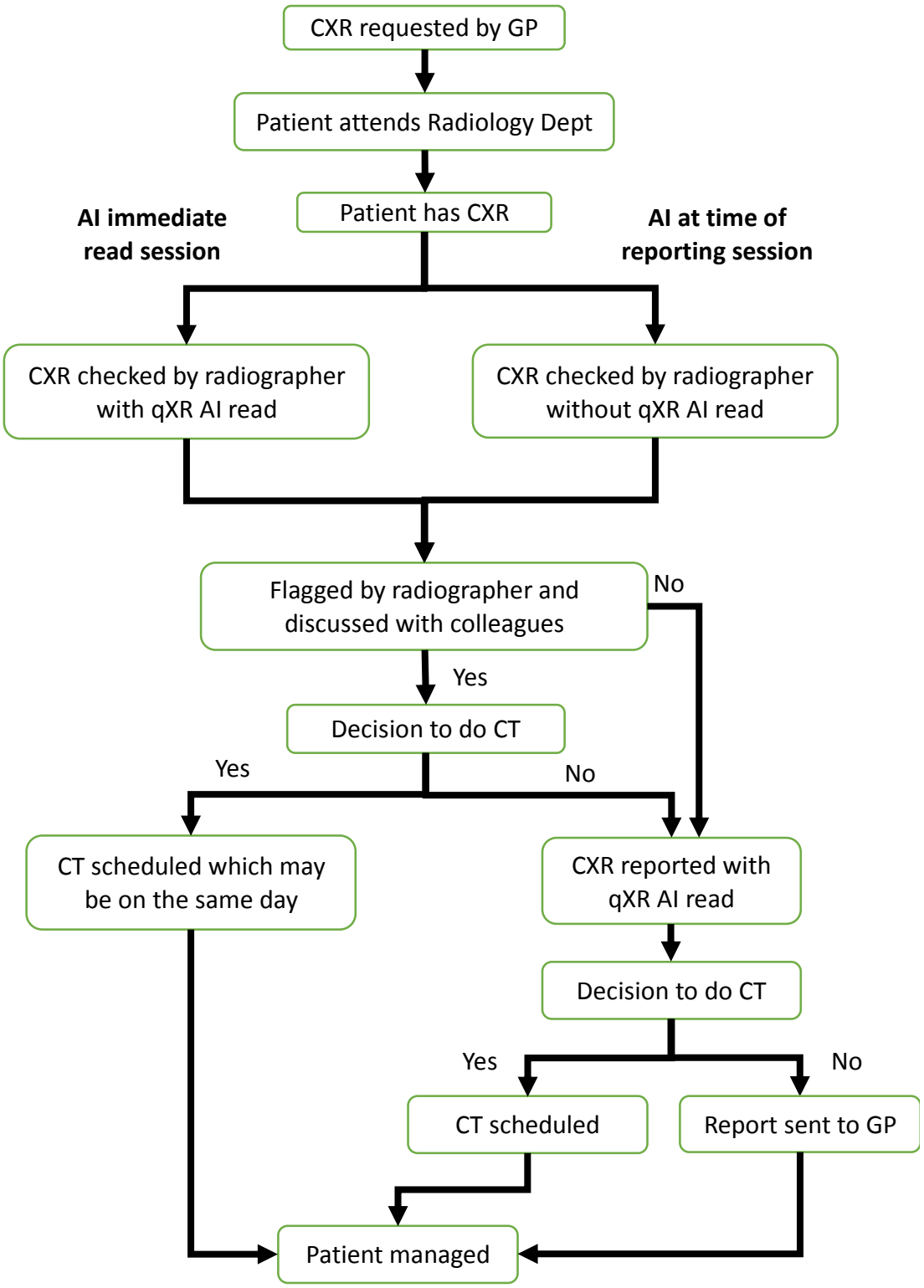
STUDY FLOW CHART



STUDY PROTOCOL

Impact of **im**mediate AI enabled **pa**tient triage to chest **CT** on the lung cancer pathway: LungIMPACT

1. BACKGROUND

Lung cancer is the biggest cause of cancer deaths in the UK. While there has been a recent modest increase in survival, with 12.7% of patients with lung cancer surviving five years[1], 30% of patients die within 90 days of diagnosis[2]. Consequently, recent guidance by the National Institute for Health and Care Excellence (NICE) has lowered the threshold for investigation and referral to specialist care for cases of possible malignancy, including lung cancer (NICE NG12)[3]. Furthermore, the National Optimal Lung Cancer Pathway (NOLCP), designed to accelerate the lung cancer pathway recommends rapid progression from chest X-ray (CXR) to CT and then specialist clinic. Resource is often allocated to fast track reports for patients referred via an urgent cancer pathway, because the NOLCP mandates a progression from suspicious CXR to CT within 72 hours and preferably the same day. This reduces delays experienced by patients including those referred via other routes[4]. Diagnostic pathway delay can worsen outcomes in both early and late stage disease and increase patient anxiety[5-7]. In the National Cancer Experience Survey, a quarter of patients reported deterioration in their condition during diagnostic workup. This is a conservative estimate since respondents for this survey are not representative of the registry patients and this imbalance is more in lung cancer[8]. Conforming to maximum suggested timings for each radiology process is not well aligned with the NOLCP's recommended maximum of six days from CXR to first respiratory appointment. If best case implementation of the NOLCP is achieved, all imaging investigations would be performed in a single diagnostic episode, with suspicious CXR triggering direct referral for a CT chest. A single attendance reduces delays for appointments and should eliminate the chance of communication not being received or understood.

2. RATIONALE

Recently published work performed by members of the study team (Woznitza *et al radioX*) found that immediate radiographer CXR reporting and triage straight to CT significantly reduced time to diagnosis of lung cancer by almost half from a median of 63 days from CXR, to 32 days, (p = 0.03) compared to routine CXR reporting once the patient has left the department[9]. This demonstrated that immediate CXR reporting pathway is feasible and beneficial. A trend for fewer urgent referrals being made to respiratory medicine was also found, with a higher proportion of cancer diagnoses made in those with immediate CXR reporting (18% vs 12%; p = 0.12). What is unclear is if the findings of this single site study with a small number of lung cancers (n=49) is replicable in other settings or scalable at a system level. Benefits of other interventions successful in single clinical sites are not always transferrable when evaluated in multi-site trials for many reasons, including implementation barriers. Since immediate reporting has resource and workforce implications, it is crucial that if immediate reporting is to be rolled out nationally, it is done so based on robust evidence.

Nearly two million CXRs referred from primary care are performed annually in England and CXR is one of the most frequently performed investigations[10]. Not all CXRs will have findings suspicious for cancer, and this may be an incidental finding (CXR requested for a reason other than suspected cancer). One way to optimise the limited imaging workforce could be to use an artificial intelligence (AI) tool as assistance in decisions to triage CXRs referred from primary care that have findings suspicious for lung cancer. This would enable immediate flagging and reporting to be prioritised for patients most likely to benefit from a same-day CT scan. AI clinical decision support was identified as one way to reduce observer variability in CXR interpretation by NICE[11] as well as supporting current NICE care pathways for suspected cancer, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis and tuberculosis.

Patient feedback also supports the need for timely reporting. Patients who undergo investigations are often anxious about the results, with research suggesting that the time between having a test and receiving the results is particularly worrying for the patient[12-15]. This waiting period is typically characterised by the uncertainty of all possible scenarios. Indeed, reduced anxiety from immediate results was emphasised as a benefit of patients receiving the results at the time of their CXR by the patient panel [PP] that supported the initial review of the study design and grant application. The patient group emphasised the importance of being told results with compassion; this may require additional communication skills training for imaging staff as currently results are not routinely given to the patients by imaging professionals, but rather by the GP if referred via primary care. Patients anticipated that having immediate results would turn a passive period of waiting into something seemingly more proactive and less uncertain; feeling reassured by the knowledge that their X-ray had been read and next steps were in motion:

> '*As a patient, the worst thing is the waiting. Once I knew, I felt relieved that there was a diagnosis and that I was doing something about it*.' [Patient Representative]

Patients who require additional investigations based on an abnormal test are likely to be more anxious than those that do not require further imaging. Most patients are happy to have all tests performed quickly, even on the same day as a 'one-stop shop' and was a consistent theme to emerge from the PP.

> '*Prefer results/observations on the day if possible – this could be the next test/scan/appointment….*' [Patient Representative]

Imaging capacity is an important barrier to implementation of the NOLCP, with a chronic shortage of consultant radiologists and increasing workload. Current (December 2021) median reporting times for CXRs referred from primary care (1 day) and waiting time for CT chest (16 days) do not meet the NOLCP standards (72 hours from abnormal CXR to CT). In addition, approximately 15% of Trusts (21/122) either require referral to respiratory medicine prior to CT request authorisation or perform less than five GP CT chest scans per month which may indicate an immature or ineffective referral pathway[16].

qXR is class IIa CE approved device for normal/abnormal classification, worklist prioritisation and for the detection of 11 (12 including normal abnormal classification) abnormalities on a CXR (Table 4). qXR is a post-processing application and does not require additional radiation dose to the patient. qXR is a clinical decision support tool intended to support healthcare practitioners when interpreting CXRs, qXR is not intended for autonomous reporting. qXR was trained with 2.3 million images collected from 45 centres across the world. This software has been validated on a large dataset (Putha 2019, Table 1). It has also been validated in UK population (Table 2). The false positive rate of qXR depends on the prevalence of an abnormality and the operating point set for that abnormality. qXR threshold (operating point) is adjustable and calibration is part of the pre-deployment procedure (last paragraph of section 2 of protocol). The performance of qXR on default high specificity and high sensitivity operating points are shown in Table 1 of the protocol. qXR threshold can be calibrated based on the odds of an abnormality being suspicious for lung cancer (high sensitivity operating point for abnormality having higher odds- odds can be derived from Table 3) or on investigators opinion on the relative cost of false positives and true positives. In a recent study conducted with a high sensitivity operating point, qXR had a specificity of 83% on normal versus abnormal triage. The FPR would be around 17%. See *Diagnostics* 2022, *12*(11), 2724; https://doi.org/10.3390/diagnostics12112724

Two separate external clinical evaluation studies have been performed; one included 100,000 CXRs with a single radiologist report, the other included 2,000 CXRs with a robust ground truth of consensus interpretation of three independent radiologists reported sensitivity of 86.30 – 94.94 for each of the abnormalities. (unpublished).

Table 1: Performance of qXR in validation set taken from Putha *et al*.

Findings	**AUC (95% CI)**	**High sensitivity operating point**		**High specificity operating point**	
		Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Normal	0.922 (0.910-0.934)	0.90 (0.88-0.91)	0.81 (0.78-0.84)	0.79 (0.77-0.82)	0.90 (0.87-0.92)
Blunted costophrenic angle	0.956 (0.933-0.978)	0.89 (0.83-0.94)	0.88 (0.86-0.90)	0.87 (0.80-0.91)	0.90 (0.87-0.92)
Cardiomegaly	0.957 (0.936-0.978)	0.88 (0.83-0.92)	0.89 (0.86-0.91)	0.88 (0.81-0.92)	0.90 (0.87-0.92)
Cavity	0.947 (0.870-1.00)	0.93 (0.61-0.98)	0.97 (0.95-0.98)	0.87 (0.61-0.98)	0.97 (0.95-0.98)
Consolidation	0.950 (0.920-0.979)	0.88 (0.80-0.93)	0.84 (0.81-0.87)	0.84 (0.75-0.90)	0.90 (0.87-0.92)
Fibrosis	0.930 (0.896-0.963)	0.90 (0.82-0.94)	0.75 (0.72-0.78)	0.84 (0.75-0.90)	0.90 (0.87-0.92)
Hilar enlargement	0.885 (0.831-0.939)	0.89 (0.78-0.95)	0.72 (0.69-0.75)	0.60 (0.46-0.71)	0.90 (0.88-0.92)
Nodule	0.913 (0.868-0.958)	0.86 (0.74-0.92)	0.90 (0.88-0.92)	0.86 (0.74-0.92)	0.90 (0.88-0.92)
Opacity	0.941 (0.925-0.957)	0.89 (0.86-0.92)	0.80 (0.77-0.83)	0.84 (0.80-0.87)	0.90 (0.87-0.92)
Pleural effusion	0.980 (0.965-0.995)	0.94 (0.89-0.97)	0.90 (0.88-0.92)	0.89 (0.84-0.94)	0.96 (0.94-0.97)

qXR performance has been investigated in the UK population. A service evaluation was conducted at East Kent Hospitals University Foundation Trust (EKHUFT). In a consecutively selected sample from all referral sources (emergency department, primary care, inpatient, and outpatient), the performance of qXR was tested against ground truth established by two radiologists. Of the 1,040 cases, both radiologists agreed on the presence or absence of an abnormality in 633 cases (456 diseased and 177 non-diseased). The sensitivity and specificity (95% confidence intervals) of qXR were 99.3% (97.8 – 99.7) and 75.7% (68.9 – 81.4) respectively. Among those CXRs referred from primary care qXR sensitivity and specificity were 96% and 80% respectively (UNPUBLISHED).

Table 2: Performance of qXR in UK population (East Kent) for CE IIa findings

Abnormality	Number diseased	Number non-diseased	Sensitivity (%)	Specificity (%)
Blunted Costophrenic Angle	104	529	95.2	97.9
Cardiomegaly	26	607	96.1	82.2
Cavity	11	622	81.8	98.7
Consolidation	194	439	82.5	84.5
Hilar Enlargement	30	605	70.0	99.3
Fibrosis	29	604	75.8	88.6
Nodule	72	561	84.7	88.2
Opacity	248	395	97.9	48.6
Pleural effusion	158	475	90.5	91.8
Pneumothorax	15	618	86.7	98.5
Radiological signs of Tuberculosis	NA	NA	NA	NA

The performance of qXR was investigated in a case control study with 108 biopsy confirmed cancer cases and 104 CT confirmed non-cancer cases from the University Hospital of Leicester NHS Trust. 103 (95.4%) of the cancer cases were flagged as having at least one abnormality by qXR and 36 (34.6%) of the non-cancer cases were flagged as having abnormalities (manuscript in preparation). Table 2 summarises the number and percentage of different abnormalities in cancer and non-cancer cases.

Table 3: qXR CE IIa Abnormalities among cancer and non-cancer cases from Leicester data

Abnormality	**Cancer cases (n = 108)**	**Non-cancer cases (n = 104)**
Blunted Costophrenic Angle	37 (34.6)	6 (5.8)
Cardiomegaly	7 (6.5)	18 (17.3)
Cavity	7 (6.5)	0 (0)
Consolidation	54 (50.0)	1 (0.9)
Hilar Enlargement	17 (15.7)	3 (2.8)
Fibrosis	41 (37.9)	5 (4.8)
Nodule	64 (59.3)	19 (18.3)
Opacity	96 (88.9)	16 (15.4)
Pleural effusion	54 (50.0)	7 (6.7)
Pneumothorax	41 (37.9)	7 (6.7)
Radiological signs of Tuberculosis	43 (39.8)	0 (0)

qXR is CE class I certified for an additional 18 findings including mediastinal widening, and tracheal shift (Table 4). qXR will read eligible CXRs (primary care referral, over 18 years) and identify those that are possibly abnormal for all 29 findings (11 CE Class II approved findings excluding normal abnormal classification and 18 CE Class I findings) and prioritise for immediate review on intervention days. This will ensure patient safety is maintained by providing the reporting practitioner with all available information.

Table 4: qXR CE Class IIa & I findings

Finding	CE Class IIa findings	CE Class I findings
1	Blunted Costophrenic Angle	Atelectasis
2	Cardiomegaly	Calcification
3	Cavity	COVID-19 risk
4	Consolidation	Degenerative spine changes
5	Hilar Enlargement	Elevated hemidiaphragm
6	Fibrosis	Hyperinflation
7	Nodule	Linear opacity
8	Opacity	Lung nodule malignancy
9	Pleural effusion	Mediastinal widening
10	Pneumothorax	Placement of gastric tube
11	Radiological signs of Tuberculosis	Placement of tracheal tube
12	Normal abnormal classification	Presence of gastric tube
13		Presence of tracheal tube
14		Pneumoperitoneum
15		Reticulonodular pattern
16		Rib fractures
17		Scoliosis
18		Tracheal shift

Quality assurance and calibration are part of the standard operating protocol of qXR deployment, and this will be performed at each site prior to the commencement of the study. This site-specific threshold adjustment is a part of the routine pre-deployment.

The primary objective of LungIMPACT study is to evaluate the effectiveness of AI flagged triage of abnormal CXR on faster diagnosis of lung cancer. qXR validation is not an objective of this study, only agreement between reporting practitioners and the software will be evaluated in this study.

3. THEORETICAL FRAMEWORK

If AI solutions are to be introduced into the NHS, it is important that they are evaluated in a clinically relevant way[17]. In this trial the impact of a CXR reporting solution on the lung cancer pathway is being tested because even relatively small increases in time to diagnosis are associated with adverse outcomes in lung cancer. The main outcomes measure how AI assistance at the point of CXR acquisition impacts the time to CT and the diagnosis of lung cancer. The pathway is not being altered in any way other than more information being available at the time of the CXR. The hypothesis is that this will lead to a change in the timing of the CT scan for people with suspicious CXRs. The study will also test the accuracy against human radiologists and the cost effectiveness.

4. RESEARCH QUESTION / AIM(S)

- What is the impact of AI support at the time of CXR acquisition for primary care referrals on the time to CT and the diagnosis of lung cancer?

- What is the agreement between an AI algorithm and human reporters when interpreting CXRs referred from primary care?

- Does immediate AI supported reporting of CXRs referred from primary care reduce the number of non-cancer diagnoses referred for an urgent lung cancer appointment?

- For people referred from primary care, is the use of AI support at the time CXR acquisition cost effective?

4.1 Objectives

This study is one part of a larger programme of work.
Part A is a health service evaluation with the primary objective to examine the impact of AI support at the time of CXR acquisition and prioritisation for immediate review of CXRs referred from primary care on the time to CT chest and the time to diagnosis of lung cancer.

Secondary objectives include:

- The agreement between qXR (AI algorithm) and CXR reports for normal/abnormal decisions
- The impact of AI support at the time of CXR acquisition and prioritising for immediate review on the number of non-cancer diagnoses referred for an urgent lung cancer appointment

Part B includes a health economic analysis on the use of AI immediate CXR read and prioritisation for review.

- To estimate the cost-effectiveness of artificial intelligence (AI) immediate CXR read and prioritisation for review for lung cancer diagnosis from the NHS perspective.

4.2 Outcome

The outcomes can be classified as those related to the effectiveness of the AI support at the time of CXR acquisition for immediate review (immediate report and straight to CT where appropriate; Part A) and those related to the health economic assessment [Part B]. A discrete choice experiment will be conducted to inform the health economic analysis, led by University College London (UCL) health economists [Part C] and will be reviewed by UCL ethics. Patient experience and communication preferences [Part D] and staff engagement [Part E] are components of the larger programme of work and independent evaluation, performed in partnership with UCLPartners and City University. City University ethical approval is already in place for the staff engagement [Part E reference ETH2223-0030 and will be applied for [Part D]. Workstreams C-E are part of the larger programme and are outside the scope of this protocol.

Outcomes related to clinical evaluation [Part A]

The primary outcomes related to clinical evaluation (Part A) are:

A1. The difference in time (in days) to the diagnosis of lung cancer for patients who have CXRs with an AI support at the time of CXR acquisition and prioritisation for immediate review and those that have no immediate read but the AI read is available at the time of reporting.

A2. The difference in time (in days) to CT for patients with suspected lung cancer who have CXRs with an AI support at the time of CXR acquisition and prioritisation for immediate review and those that have no immediate read but the AI read is available at the time of reporting.

Rationale for choice of two primary outcomes:

A strength of the trial is the multisite, pragmatic design of the clinical evaluation. Pre-trial review has demonstrated heterogeneity in radiology workflows (CT scanner capacity, community sites without CT on-site, CT reporting times), referral routes and lung cancer pathway design (respiratory review prior to CT, virtual triage) at the clinical sites. Time to lung cancer diagnosis is clinically meaningful and time to CT will be the least affected by the heterogeneity inherent in this study. Both outcomes will be considered primary and there are no hierarchy among these two. A sub-group analysis will be undertaken for these endpoints by sites and time periods (quarterly interval).

Other steps in the patient pathway for the diagnosis of lung cancer are included as secondary outcomes. The secondary outcomes are:

- Time to first appointment for urgent lung cancer referrals as defined by time between CXR acquisition, time to urgent lung cancer referral (2WW) and time of first consultation (first appointment)
- Time to treatment start for lung cancer patients
- Agreement between qXR and human readers for normal/abnormal diagnosis of CXRs referred from primary care
- Number of urgent lung cancer (2WW) referrals
- Incidence of lung cancer

- Stage of lung cancer at diagnosis

Secondary outcomes related to the health economic assessment (Part B) are:

- Cost-effectiveness of AI support at the time of CXR acquisition and prioritisation for immediate review of CXRs; to be measured by difference in costs per patient diagnosed, per percentage increase in early-stage diagnosis and potentially per QALY subject to the availability of health utilities in the published studies

5. STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

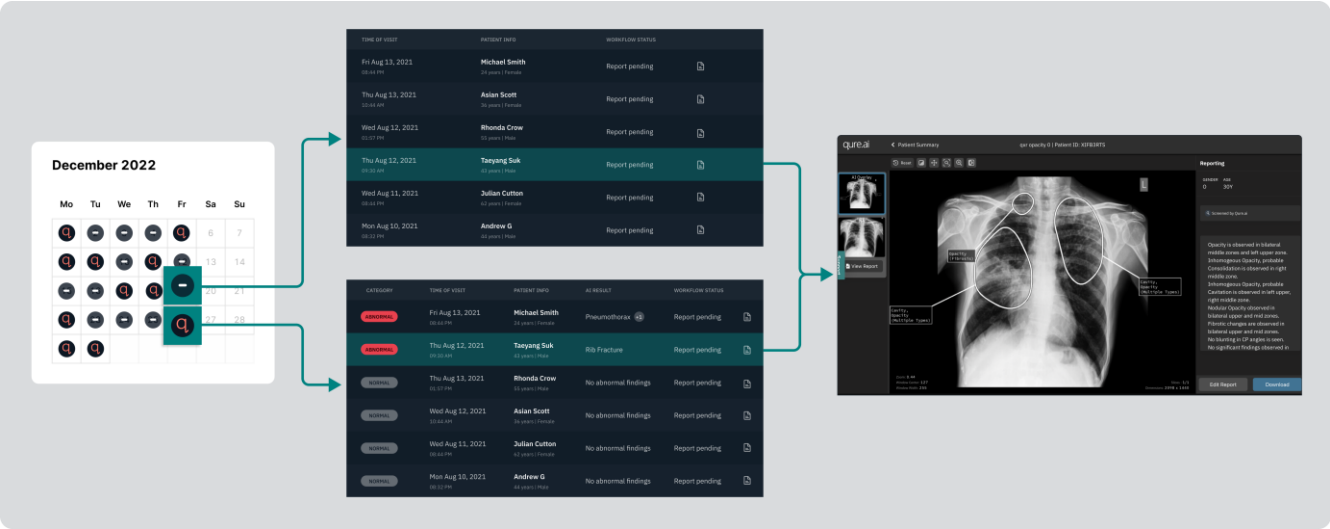
Part A: Clinical Evaluation

This is a prospective, multi-centre healthcare service delivery study with the primary objective of assessing the effectiveness of AI immediate read and worklist prioritisation for immediate review on the time to diagnosis of lung cancer and the time to CT chest following abnormal CXR. The study will be conducted over a 12-month period at eight NHS Trusts in England. qXR, a class IIa CE certified deep learning algorithm already in routine clinical use in some NHS Trusts, will be used in this study. All patients in the study will have their CXRs read by qXR. The only difference is the timing of the information from the AI. The process adopted in radiology departments is that the patient attends for a CXR and it is performed by a radiographer. The radiographer may, at their discretion flag abnormalities that may require further action and this may result in a CT scan being done, sometimes on the same day as is a preferred option in the NOLCP. The radiographer flag can also happen for any other (non-cancer) findings where they consider that action is potentially needed. The usual clinical pathway will be followed where action is confirmed to be necessary or optimal. Where there is no flag, the CXR is later reported by a radiologist or reporting radiographer. This study is testing whether having an AI immediate tag influences that process and shortens time to diagnosis. The pathway is shown on the study flowchart (page 10).

AI clinical decision support will be available to the reporting practitioner (consultant radiologist, specialist registrar or reporting radiographer) for all CXRs. The intervention is the timing of the CXR alert from the AI, on intervention (worklist prioritisation for immediate report) and non-intervention (routine reporting time) days. On intervention days, an active notification will be sent to the worklist for any ‘qXR-suspected-abnormal cases, so these can be prioritised for immediate reporting. Pre-allocation to intervention (qXR AI support at the time of CXR acquisition and worklist prioritisation for immediate CXR review) and routine care (normal reporting with

qXR read available) will occur using random sampling (Monday – Friday when routine imaging is performed). All patients over 18 years will have qXR decision support available. Patients will receive routine care, no additional diagnostic tests will be performed. Data will be collected from existing routine clinical data sources. All imaging (CXR or CT) will be performed as part of routine care, and no additional radiation exposure will be required. The reporting practitioner will have the AI decision support information for all cases and all days, the intervention is only the timing of the AI information (immediate reporting or with usual reporting). The reporting practitioner can choose to accept the alert and refer the patient for CT chest and/or referral onto the lung cancer pathway where appropriate. Patients who are referred for CT will follow the current CT and post-CT pathways of the participating clinical sites, which may include placing them on a cancer pathway. On non-notification days, the AI tool information will be available at the time the CXRs are reporting by the reporting practitioner (Figure 1). The PACS will have both the original image and qXR secondary capture showing the AI attention point.

Figure 1: Intervention and non-intervention days in RIS



Where AI flagging of abnormalities are rejected by the reporting practitioner they will be reviewed by an expert panel of thoracic radiologists at a weekly interval at each study site according to pre-defined thresholds depending on patient risk/safety (Table 5).

Radiographers will follow their normal duty of care on both notification and non-notification days. Although it is unlikely, undue reliance on AI on notification days and extra vigilance on non-notification days will be measured through numbers actioned by radiographers and the discrepancy check.

Table 5. Proportion of discordant cases to undergo thoracic radiologist review

Abnormality	Proportion
Blunted CP	1,000 CXRs
Cardiomegaly	1,000 CXRs
Cavity	All
Consolidation	All
Fibrosis	20%
Hilar enlargement	All
Nodule	All
Opacity	All
Pleural effusion	20%
Pneumothorax	All

Cases that are flagged (in either arm) as positive but not taken up for further testing will be reviewed and patients with CXRs suspicious for cancer will be called back for further testing. This is done in both arms of the study and is an additional safety check; this is routine clinical practice. The proposed review/recall methodology is a form of radiology peer review, advocated as an effective method of quality assurance[18-22]. Double reading and recall where appropriate is not novel, for example it is used as standard as part of the breast cancer screening programme[23-26].

Variables collected:

Only data collected for routine care will be used and no additional data will be collected. No patient identifiable data will be available outside of the clinical care team; all data will be pseudonymised prior to analysis by the independent statistician. qTrack will be used as the trial management database; it cannot be accessed by the Qure Team. Variables are presented in Table 6.

Table 6. Routine data used for analysis

Variables	**Source**
AI support at the time of CXR acquisition and prioritisation for review	Auto-filled from the sequence generated
Age	DICOM metadata
Sex	DICOM metadata
AI CXR finding	Qure backend - qTrack
CXR report finding/diagnosis	Automated NLP feeding into qTrack
Time of CXR referral	DICOM metadata
CXR taken time	DICOM metadata
CXR report generation time	QTrack
Referral to CT- Yes/No	Cancer nurse/imaging staff from PACS/RIS
Date of CT report	Cancer nurse/imaging staff from PACS/RIS
Diagnosis	Cancer nurse/imaging staff from PACS/RIS
Date of diagnosis of lung cancer	Cancer Waiting Time database
Stage of lung cancer	Cancer Waiting Time database
Date of 2WW referral	Cancer Waiting Time database, automated (.csv if possible)
date of decision to treat	Cancer Waiting Time database
Treatment start date	Cancer Waiting Time database
discharge date	Cancer Waiting Time database
qXR-CXR report agreement	qCheck
Outcome of discordant expert review	Template circulated with outcomes based on CT template
Reporting Practitioner Study ID	DICOM metadata
Reporting practitioner profession	Radiology department staff record

Part B: Health Economic Analysis

Health Economic Analysis

An economic evaluation will be conducted to estimate the cost-effectiveness of artificial intelligence (AI)-based triaging of CXRs for lung cancer diagnosis from the NHS perspective. We shall analyse the cost-effectiveness of AI-based triaging compared to routine reporting. We shall develop a decision-analytic model using available evidence on lung cancer diagnosis and healthcare professionals' expert opinion. The probabilities used in the model will be identified from the clinical study and the literature (e.g., meta-analyses), and national datasets.

Health outcomes for the economic assessment shall be measured in terms of difference in days to diagnosis (time to full work up and decision to refer for treatment / best supportive care at the multidisciplinary meeting) and the stage of diagnosis. Additionally, the impact of early-stage diagnosis on quality of life shall also be incorporated if relevant data to the UK setting will become available from the narrative literature review. The cost parameters required to populate the model will be identified from national datasets, such as the NHS reference costs. Healthcare resource use will be identified as part of staff experience interviews and based on the discussion with the clinical experts in the research team.

We shall assess costs primarily from the perspective of the NHS and personal social services. Thus, we shall estimate the cost to implement the AI support at the time of CXR acquisition and prioritisation for immediate review of CXRs, the training costs, and the maintenance costs, as well as the cost of the usual practice. We shall derive unit costs from standard sources. The time horizon of the main analysis will be 60 days since the clinical study will measure the short-term impacts of the intervention. An additional analysis adopting a lifetime horizon could be potentially conducted if there is sufficient evidence and data (e.g. QALYs). If a lifetime horizon will be adopted costs and outcomes after the first year shall be discounted at a 3.5% discount rate as recommended by NICE. All costs will be reported in 2022 GBP.

Cost-effectiveness of AI support at the time of CXR acquisition and prioritisation for immediate review of CXRs shall be assessed comparing the costs and outcomes of the new intervention and the usual practice. We shall estimate the difference in costs per patient screened, cost per patient diagnosed, and costs per percentage increase in early diagnosis. This will be compared with the difference in effectiveness (e.g. less time to decisions, increase in early-stage diagnosis). Contingent on appropriate data availability in the literature on the impact of early diagnosis on quality of life, we might be able to estimate the difference in costs per additional QALY gained.

If the intervention arm is more effective (less time to decisions, increase in early-stage diagnosis) and less costly, then the intervention would be considered dominant over the comparator. If the intervention provides the same level of effectiveness at a lower cost, it would be considered cost-effective compared to the comparator. If the intervention is more costly and more effective, then the decision-makers need to consider some other factors, such as the availability of radiologists.

A Return-on-investment (ROI) analysis, shall be undertaken, identifying net benefits relative to net costs. We shall estimate payback in different time periods (e. g. one year, five years). ROI demonstrates whether a new technology or service offers value for money, and it is used by local decision-makers. The ROI analysis would help NHS to identify net benefits relative to costs demonstrating value for use by decision-makers.

Deterministic and probabilistic sensitivity analyses will be conducted to explore parameter uncertainty and the uncertainties caused by methodological assumptions. Deterministic sensitivity analysis will identify the key parameters that have a significant impact on the findings, varying one parameter at a time. The probabilistic sensitivity analysis will estimate the confidence intervals for the cost-saving and return on investment estimates, using Monte Carlo simulation.

6. STUDY SETTING

The clinical evaluation study [Part A] will be performed in secondary care at eight acute Trusts in England.

Clinical sites include:

- Nottingham University Hospital NHS Trust
- University College London Hospitals NHS Trust
- Mid Yorkshire Hospitals NHS Trust
- University Hospitals Birmingham NHS Trust
- East Suffolk and North Essex NHS Trust
- University Hospitals of Leicester NHS Trust
- St. Georges University Hospitals NHS Trust
- United Lincolnshire Hospitals NHS Trust

Part B

No separate recruitment will be required for the health economic analysis

SAMPLE AND RECRUITMENT

Part A

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

- CXR referred from primary care
- Age ≥ 18 years
- Anteroposterior (AP) or Posteroanterior (PA) view

7.1.2 Exclusion criteria

- Age <18 years
- CXR referral not from primary care
- Lateral X-ray view of the chest

Part B

7.2 Eligibility Criteria

No separate recruitment will be required for the health economic analysis

7.3 Sampling

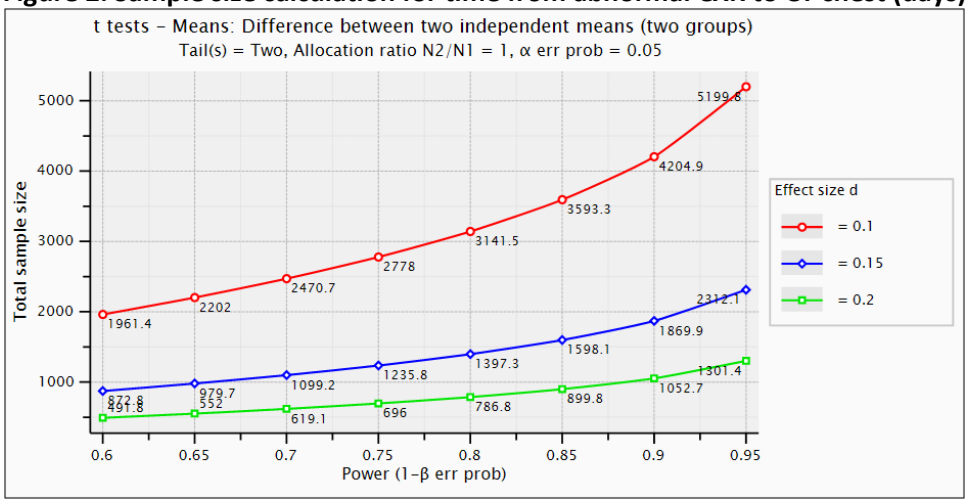
7.3.1 Size of sample

Part A

The primary endpoints of this study are the difference in median time between CXRs suspicious for lung cancer and CT chest and the difference in median time to lung cancer diagnosis between routine reporting with AI available and AI support at the time of CXR acquisition and prioritisation for immediate review of CXRs reporting arms. The expected prevalence of lung cancer in this cohort (primary care referrals for CXR) is 0.6%[9]. Thus for 150,000 CXRs this will lead to the detection of about 900 cancer cases. Using data from previous work,[9] the median time to lung cancer diagnosis was 63 days in the standard reporting group and if we use a conservative reduction of 10 days, with 95% power we would need 265 cases per group (Table 6). Most likely, the time to diagnosis is going to be greater than 10 days such that the sample size will give us plenty of power to detect a difference between the groups on time to diagnosis. Considering that 30% of lung cancer patients die within 90 days of diagnosis, a 10 or more-day difference is clinically significant (Table 7).

The co-primary endpoint of this study is time between an abnormal CXR that is suspicious for lung cancer to CT chest. Based on the NHS Diagnostic Imaging Dataset between 4,000-4,500 CT chest scans referred from primary care are expected during the study period at the clinical sites, median time for England (CT chest request to test) is 14 days, but this data is not segregated between urgent scans and those that are routine or for follow up. The mean and standard deviation of time between abnormal CXR and CT chest are not known for either the intervention (AI support at the time of CXR acquisition and prioritisation for immediate review of CXRs) or routine CXR reporting with AI available. Cohen's d (effect size) was used to estimate sample size with power 0.1, 0.3 and 0.5 are considered small, moderate and large effect size[27]. Assuming approximately equal distribution (Nnotification:Nstandard as 0.8 to 1.2) of the number of scans taken, the estimated 4,000 CT chest scans will give adequate power to detect even the smallest effect size (Cohen's d = 0.1; Figure 2). We have defined a clinically meaningful difference in time from abnormal to CT chest as 3 days, using the maximum time recommended in the NOLCP.

Figure 2. Sample size calculation for time from abnormal CXR to CT chest (days)



We would also like to have enough numbers to examine the secondary outcome if the strength of the agreement between qXR and CXR reporter in normal/abnormal classification. Based on an anticipated abnormal prevalence 40% of primary care CXRs[28] and as measured by kappa (hypothesized as 0.82) an absolute precision of 2%, we would need 3,601 patients included. Not only is the time to diagnosis is important but also the accuracy of diagnosis. The study will also have enough number to report on agreement of individual abnormality with the above precision.

Table 7. Sample size calculation for time (in days) to diagnosis of lung cancer

	Median Days to diagnosis	Hazard	Sample Size	Total sample size	POWER
Routine	38	0.018	201	402	90
qXR immediate	28	0.025			
Routine	32	0.022	156	312	90
qXR immediate	22	0.032			
Routine	63	0.011	759	1518	90
qXR immediate	53	0.013			
Routine	63	0.011	567	1134	80
qXR immediate	53	0.013			
Routine	20	0.035	51	102	90
qXR immediate	10	0.0693			

Part B

No separate recruitment will be required for the health economic analysis

7.3.2 Sampling technique

Part A

A consecutive series of patients referred for CXR by primary care will be included.

Individual patients will not be randomised. Days will be randomised to intervention or standard care, using a randomisation list provided by the study statistician. This is in line with previous studies that have examined the timing or order of X-ray reading but where all examinations are requested as part of routine clinical care and receive reports from the same practitioners[26,29,30]. No patient identifiable data will be available outside of the direct clinical care team. All data is routinely collected (mandatory reporting – cancer waiting times, service

evaluation – reporting times, radiology department activity, peer review) and will be anonymised prior to analysis.

Methodology of pseudo-anonymisation:

In accordance with data sharing and data processing practice, the transfer of DICOM files using Qure's API will be encrypted to prevent data breach. These DICOM files sent from each NHS site will be pseudo-anonymised before it leaves the hospital premise. This means all the patient identifiable data will be removed except for 'Patient ID' and 'Accession number'. These two IDs will be used as unique identifiers to map the AI outputs that would be sent back to the PACS/RIS after de-identification. It is also required to map with the corresponding cancer registry data that needs to be collected for realising the study objectives. Using these IDs would also help during discordance analysis, in case the expert radiologists wanted to check data history of the particular patient to help in decision making.

Part B

No separate recruitment will be required for the health economic analysis

7.4 Recruitment

Part A

The clinical evaluation study [Part A] will not directly recruit patients; it is an evaluation of health service delivery. Patients will have their pseudonymised data collected to provide the outcomes. No additional or different tests will be performed, and all the reporting practitioners currently report CXRs in clinical practice. The comparative aspect of the study is the timing of the AI flagging of a possible CXR abnormality. The intervention can be considered as an additional prompt to consider a further test by the person providing the CXR report (CT scan) but it is not known if this improves the clinical pathway. All patients referred for a CXR by primary care will receive the usual standard of care and referral pathways for each of the eight clinical sites, including the AI decision support, the only difference is the timing of CXR reporting. The intervention is the same at each institution with block randomisation to the intervention or no intervention by day.

Part B

No separate recruitment will be required for the health economic analysis

7.4.1 Sample identification

Part A

A consecutive series of CXRs over a 12 month period referred from primary care will be included. All CXRs will be performed as part of routine care, no additional radiation exposure will be required.

Part B

Not applicable.

7.5 Consent

Part A

Individual patients will not be approached for consent to the study or randomised. Consent is not necessary because there is no change to the standard of care. This is also a necessary part of the study because a consent process would severely disrupt the clinical flow (CXRs are done quickly and in high volume) and likely bias the sample. The intervention is the same at each institution with block randomisation to the intervention or no intervention by day.

Patient details will not be available outside of the direct clinical care team.

All data collected in the study is routinely collected for statutory reporting (cancer waiting times) and service evaluation (radiology activity, reporting times, peer review). No patient details will be accessed outside of the direct clinical care team.

Patients will be provided with information on the role of a CXR and the possible need for additional tests at the time of referral for CXR in primary care, this is already in place at several of the study sites. Information will be displayed via posters and leaflets in radiology waiting rooms for patients, modelled on best practice guidance from the confidentiality advisory group, with links to further information and contact details for the local research team. Most patients have x-rays booked by their GP, and may not see the GP. The service is a walk in so we will provide the leaflets on arrival in the department in addition to asking GPs to provide them at the point they refer. Where appointment letters are sent, all will include the patient leaflet.

Primary care will be notified of the study in writing prior to commencement with the patient leaflets for distribution.

The national data-opt out is limited to research requiring Section 251/Confidential Advisor Group approval so does not apply to this project. Therefore, a local data opt-out is appropriate. Patient will be able to decline for their routine data to be used as part of the research study by either: informing the radiographer performing the CXR, by contacting the local PI by email or by post. Patients will able to opt-out up to two weeks after their chest X-ray, prior to data transfer (occurs every six weeks). Prior to any data transfer to the research team a

member of the clinical team will check for local opt-out requests. Any patients who have opted out will have their data removed prior to transfer.

Part B

No separate recruitment will be required for the health economic analysis

8. ETHICAL AND REGULATORY CONSIDERATIONS

The study will be undertaken with strict adherence to recommended CONSORT guidelines and good clinical practice. The data will be held securely and information governance rules followed rigorously by all persons involved in the management of trial protocol or data at a site level, as well as the investigators

The clinical study [Part A] will not directly recruit patients; it is an evaluation of health service delivery. Individual patients will not be randomised. The intervention is the same at each institution with block randomisation to the intervention or no intervention by day. This is in line with previous studies that have examined the timing or order of CXR reading but where all examinations are requested as part of routine clinical care and receive reports from the same practitioners[9,23,28-31]. No additional test will be performed; any additional tests are part of routine clinical care.

No patient identifiable data will be available outside of the direct clinical care team. All data is routinely collected (mandatory reporting – cancer waiting times; mandatory reporting to NHS Diagnostic Imaging Dataset – reporting times, radiology department activity; service evaluation – peer review) and will be anonymised prior to analysis.

No elements of standard practice are to be changed as part of the trial except reading timing, to test whether the intervention would be effective in normal practice. The intervention can be considered an alternative and at least equivalently good form of standard practice, as nothing about how the CXRs are reviewed and evaluated changes, just the timing in which they are assessed.

The CXR reports will be provided by qualified and registered healthcare practitioners, currently reporting CXRs in clinical practice. The peer review structure in the study follows best practice guidance outlined by the Royal College of Radiologists[18-21,26,27,32].

The national data-opt out is limited to research requiring Section 251/Confidential Advisor Group approval so does not apply to the project. Therefore, a local data opt-out is appropriate. Patient will be able to decline for their routine data to be used as part of the research study by either: informing the radiographer performing the CXR, by contacting the local PI by email or by post. Patients will able to opt-out up to two weeks after their chest X-ray, prior to data transfer (occurs every six weeks). Prior to any data transfer to the research team a member of the clinical team will check for local opt-out requests. Any patients who have opted out will have their data removed prior to transfer.

Part B

No separate recruitment will be required for the health economic analysis

8.1. Assessment and management of risk

The intervention in this study is notification and worklist prioritisation of CXR. The rest of the data collected are those collected in standard of care. Given this nature of the study, we do not envisage any elevation to the harms or to the risk of harms for patients.

To minimise missed cancer in both arms, this study has weekly peer review for cases where the radiologists rejected the AI findings.

8.2.Research Ethics Committee (REC) review & reports

Research ethics committee reports will be included once considered and a favourable opinion obtained.

8.3. Peer review

Comprehensive peer review of the project and study design has been performed by the funders prior to awarding the grant.

Expert independent peer review of the final protocol has been performed by Dr. Sonyia McFadden, University of Ulster

8.4. Patient & Public Involvement

Janette Rawlinson, an experienced Lung Cancer (LC) partner in research has contributed to the study protocol, discussions with various study team members including Patient & Public Involvement (PPI) contacts and taken part in a patient panel discussion with Royal Marsden patient and carer panel to explore issues of interest to patients having a CXR in these situations. With lived experience of LC and involvement in improving outcomes at local, national and international level, she has contributed perspectives of those not routinely seen at specialist cancer centres, issues around travel costs/time and potential worry/concern by the patient/family if a return visit was necessary and potential relief if patients learn their CXR does not contain anything to worry about. We aim to recruit a second PPIE person to support Janette.

She has provided examples of references, patient information, contributed to design of patient facing materials, suggested and considered information for clinical settings (GP practices and imaging suites/waiting areas in hospitals), and explored the best way to assess how patients view their experiences of imaging, whether called to further investigations or discharged alongside more generic aspects of patient acceptability of AI in a routine healthcare setting and exploring what matters to patients in this situation. Thus, Janette has contributed enormously to the study design.

The study was presented at the Royal Marsden Patient and Carer Research Review Panel meeting on 29th June 2022. The Panel is facilitated by Dr Markella Boudioni, head of PPIE at Royal Marsden NHS Foundation Trust; Dr Charatini Stavroupoulou, City University, presented the study, supported by Janette. The aim was to explore issues of patient acceptability, queries about AI in healthcare more generally and feelings experienced when in an investigational pathway. The Panel consisted of 16 cancer patients and carers having been affected by various cancers and with diverse socio-demographics. Comments and suggestions from that event have been incorporated within the protocol and have informed the team's discussions about the optimum way of exploring patient benefit and acceptability within a study not changing standard care, only potentially accelerating if a CT is required is suspicious for lung cancer. There have been regular clinical team calls about the project (PPI attended) and separate PPI calls with clinical/PPI input to ensure full attention given and clarity of roles/scope between work outside this study's scope but relevant to it in other aspects. Patients and carers also describe the relief if reassured and discharged from the pathway - in other words, they describe time saved doesn't only have to have an economic impact or workload impact but impacts quality of life for anyone formerly fearing they were to progress for a potentially life limiting condition

Janette (patient co-I) will be part of the TMG, involved during the study taken part in regular clinical and PPI team meetings and contribute to results analysis and dissemination of findings to various audiences including relevant charities and patient groups. She has suggested some potential outlets for findings when available in settings that may be accessed by primary care, commissioners and NHS more generally including using technology and innovation in healthcare.

Patient involvement and feedback has resulted in alteration to the initial study design; a decision was taken not to enrol directly impacted by the study due to inappropriateness, and taking views from the Royal Marsden patient group forward to consider important issues like timing, communication style and practitioner training and the impact of same day referrals for other scans/tests. The larger programme of work will examine patient experience and communication preferences [Part C, Part D].

As the study is one of hospital imaging system use and will not recruit patients directly, the issues discussed with the patient group and study team have been to ensure that patients are aware that AI might be used in their imaging in addition to standard care at the Trust and the intention/context behind that, including the known resources shortage impacting the NHS in general and thoracic imaging in particular.

8.5. Regulatory Compliance

No patient identifiable data will be accessed by any person outside of the direct clinical care team.

Access to trial data will be limited to appropriate research personnel for the sole purpose of research and analysis. Data Protection Act (2018) and Information Governance (IG) legislation will be adhered to at all times. Audit trails will be in place to ensure data entry, edit and access is traceable.

Personnel acting on behalf of the trial sponsors and regulatory authorities may access the anonymised trial data.

To minimise the risk of data breach, all data will be stored securely, with keys to participant information stored separately from trial data within each clinical site.

Information governance legislation will be followed when inputting data. To prevent against unintentional or unauthorised data modification audit trails will be kept to enable monitoring by the research team and external regulatory bodies. Non-disclosure contracts will be in place where appropriate.

In line with funder's policy on data sharing, we intend to make our data available to others in a timely and transparent manner for the benefit of the research community. As our research involves human participants, we will initiate appropriate precautions to ensure the privacy of participants, including anonymising data.

On completion of the study, data will be preserved for a minimum of 5 years or as required by the study sponsor.

We will follow guidance outlined under the UK General Data Protection Regulation (Jan 2021) to ensure confidentiality and adhere to ethical principles at all times.

8.6. Protocol compliance

This is a pragmatic health care service delivery evaluation study and there are no safety issues in case of protocol deviation or violation. All cases will be included in the primary and secondary endpoints analysis.

8.7. Amendments

No amendments have been made to this protocol. Standard procedures will be followed if an amendment should be made.

The Sponsor in consultation with the CI and the rest of the TMG will decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the Sponsor will submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment as per their standard response time, informing the HRA of the amendment. Site R&D departments will be provided with the information on the amendment in order to assess their continued capacity and capability. Their level of review will be dictated by the group as assessed by the REC or HRA. Guidance on the categorisation of amendments for studies involving the NHS will be followed as per the HRA website (http://www.hra.nhs.uk/resources/after-you-apply/amendments/).

In the case of non-substantial amendments HRA as well as the relevant R&D departments of participating sites will be notified.

8.8. Adverse Events

The intervention in this study is an active notification so that abnormal CXR can be prioritised. qXR is a post-processing device and patients are not exposed to additional radiation. All patients CXRs will be reviewed by the radiologists as per the standard of care. Adverse events due to qXR are not expected. The recent Healthcare Safety Investigation Branch report recommended evaluation of AI for lung cancer detection on CXRs as a way to improve patient safety[33].

8.9. Data protection and patient confidentiality

No patient identifiable data will be accessed by any person outside of the direct clinical care team.

Access to trial data will be limited to appropriate research personnel for the sole purpose of research and analysis. We will follow guidance outlined under the UK General Data Protection Regulation (Jan 2021) and Information Governance (IG) legislation will be adhered to at all times. Audit trails will be in place to ensure data entry, edit and access is traceable.

Personnel acting on behalf of the trial sponsors and regulatory authorities may access the data.

To minimise the risk of data breach, all data will be stored securely, with keys to participant information stored separately from trial data within each clinical site.

Information governance legislation will be followed when inputting data. To prevent against unintentional or unauthorised data modification audit trails will be kept to enable monitoring by the research team and external regulatory bodies. Non-disclosure contracts will be in place where appropriate.

8.10. Indemnity

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered

8.11. Access to the final study dataset

The chief investigator, trial management group and study statistician will have access to the final pseudonymised dataset. PIs at each clinical site will ensure data integrity and access as well as safe storage of the pseudonymisation keys.

9. DISSEMINATION POLICY

9.1. Dissemination policy

Findings of the study will be disseminated in peer reviewed journals and professional conferences. An evaluation report for the programme will be prepared and submitted to the funders.

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