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Yorkshire screening of urine trial (YORKSURe)

Submission date 07/06/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 09/06/2022	**Overall study status** Ongoing	
Last Edited 19/03/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Yorkshire has some of the lowest survival rates from bladder cancer in Britain. Survival rates could be improved through the earlier diagnosis of bladder cancer. Blood in the urine is a common symptom of bladder cancer but is not always visible. Testing for non-visible blood in the urine could be a way to detect bladder cancer early. The YORKSURe study aims to detect bladder cancer early through home self-testing of urine, in selected people across Leeds, Sheffield, and areas of South Yorkshire. If the study results are promising e.g., people find it acceptable to self-test and we are able to detect bladder cancers at an earlier stage, there will be a larger study in the future to test this in more people.

Who can participate?
YORKSURe will invite people in three different groups (cohorts):
Cohort 1 will be formed of 2000 men and women aged 55-80 years from the Yorkshire Lung Screening Trial. These participants will have given their consent for contact from other research teams.
Cohort 2 will be formed of 3000 men aged 65-79 years. These men will be identified through a database search at selected GP practices in South Yorkshire. Selected GP practices are those considered to be in areas where bladder cancer survival rates are low.
Cohort 3 will be formed of men and women aged 65-79 years that will be investigated for potential bladder cancer in the 2 Week Wait pathway (suspected cancer pathway).

What does the study involve?
All identified participants will be sent a urine self-testing kit in the post. Participant information will instruct participants to collect and test a urine sample (using the test strips provided in the kit) once a day for up to 6 days in a row. Participants will have the option to use the study mobile App or a freephone system to record their test strip results. Before recording the first day's results, participants will be asked to complete a bladder symptoms questionnaire in the App or by freephone.
Participants in Cohort 2 only will be randomly allocated to one of two groups following self-testing. The group will inform which test result the participant (and their GP) will receive. For example, participants in Group 1 will be informed of their glucose results (whether glucose (sugar) has been found in their urine), and Group 2 will be informed of their blood results (whether blood has been found in their urine). The result of the other test (blood or glucose) will be stored and concealed from the study team until the end of the study. The participant and

their GP will not receive the concealed result.
Self-testing results recorded by participants will be assessed by a research nurse. The research nurse will assess the results for the presence of blood in the urine for Cohort 1, Cohort 2 (Group 2), and Cohort 3. The presence of glucose in the urine will be assessed for Cohort 2 (Group 1) only.
If blood in the urine is found in Cohort 1 and Cohort 2 (Group 2) these participants will be invited to a study clinic for further tests. The tests will include an ultrasound scan (to view the bladder and other surrounding organs) and the collection of a urine sample for more detailed testing. The purpose of these tests is to find out why the blood is present and direct further tests or treatment. The tests may show signs of cancer, in which case the participant will be referred to their local urology department under the 2 Week Wait (suspected cancer) pathway.
If glucose is found in the urine for Cohort 2 (Group 1) these participants will be invited to a study clinic for a blood test. The blood test will check average blood glucose levels over the last 2-3 months (HbA1c test). The result of the blood test may suggest that the participant has diabetes, or that existing diabetes is not well controlled. These participants will be referred to their GP for appropriate management.
Cohort 3 will already be in the 2 Week Wait pathway. Following self-testing, the only additional study procedure will be the collection of a urine sample at the 2 Week Wait appointment for more detailed testing. The outcome of the 2 Week Wait appointment will be collected for the study e.g., whether cancer was found or not.
Finally, follow-up data from a national cancer registry will be collected for all participants that self-test and therefore consent to the trial. This data will be collected for 3 years after the end of the study and will include new diagnoses of cancer in this time period.

What are the possible benefits and risks of participating?
For Cohorts 1 & 2 urine self-testing and subsequent other tests may detect bladder cancer at an early stage. Bladder cancer symptoms are often reported as aligned to ageing-related changes and therefore can go undetected. The benefit of picking up bladder cancer early is that treatment is much more effective.
For those in Cohort 2 randomised to receive their glucose result, urine self-testing may indicate diabetes.
Cohort 3 participation is considered altruistic as these participants will already be in the 2 Week Wait pathway and will have the gold-standard tests for the investigation of potential bladder cancer.
Participants from all three cohorts will be contributing to important research that may benefit other people in the future.
Urine self-testing is widely used and has no safety concerns. There is a small risk of overdiagnosis and overtreatment, without proof that urine screening is beneficial in terms of improved survival. However, many bladder cancers can be managed without radical treatment. Participants who need to have further tests or treatment in the hospital may be exposed to additional risks such as urinary tract infection following one of the hospital tests (cystoscopy).

Where is the study run from?
The Cancer Prevention Trials Unit at King’s College London is coordinating the study. The research nurse team will be based at Sheffield Teaching Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
May 2021 to October 2028

Who is funding the study?
Yorkshire Cancer Research (UK)

Who is the main contact?
Megan Goff (YORKSURE Trial Manager) (UK)
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
302276

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 51635, IRAS 302276

Study information

Scientific Title
Early detection of bladder cancer in Yorkshire: feasibility assessments for implementing a targeted study in populations with high disease-specific mortality risk

Acronym
YORKSURe

Study objectives
1. Invited men and women will undertake urine self-testing to examine the presence of haematuria and glycosuria (Cohort 1, 2, and 3)
2. Men and women with haematuria or glycosuria will attend Early Detection Clinics for full evaluation (Cohort 1 and 2)
3. Embedding bladder cancer testing within lung screening may improve compliance whilst targeting smokers (Cohort 1)
4. Urine cytology and urinary tract ultrasound are acceptable and reliable non-invasive tools to detect bladder cancer (Cohort 1, 2, and 3)

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 25/03/2022, London – Riverside Research Ethics Committee (Chelsea & Westminster Hospital, 369 Fulham Road, London, SW10 9NH, United Kingdom; +44 (0)207 104 8193; riverside.rec@hra.nhs.uk), ref: 22/LO/0018

Study design
Randomized interventional

Primary study design
Interventional

Study type(s)
Screening

Health condition(s) or problem(s) studied
Bladder cancer

Interventions

Current intervention as of 15/07/2022:
This study aims to assess the feasibility of urine self-testing as an early detection method for bladder cancer. The study will also collect data to help design a larger trial in the future.
Three different populations are included in this study:
Cohort 1: 2000 participants of the Yorkshire Lung Screening Trial (YLST)
Cohort 2: 3000 male participants identified to live in a high-risk bladder cancer mortality region
Cohort 3: 1000 NHS patients being investigated for bladder cancer in the 2 week wait (2WW) pathway.

Identification
Cohort 1 identification will integrate with Visit 2 of the YLST to identify participants. The YLST, based in Leeds, is an implementation study, primarily measuring participation rates of a community-based lung cancer screening programme. Patients eligible for YLST are registered with a GP in the Leeds CCG area. YLST participants identified to be at high risk of lung cancer are invited to attend a mobile lung health check which includes a CT scan of the lungs. Most participants are invited for a second scan 2 years after their first (Visit 2). On attending the YLST Visit 2
participants are asked for their consent for contact from other research teams. Personal data from those that give this consent will be securely transferred to KCL in order to invite them to take part in the study. A study invitation will not be sent to these participants for at least 2 months after their YLST visit so as not to overlap with trial or clinical follow-up.
Identification of YORKSURe participants through the YLST will target smokers (who are at increased risk of bladder cancer as well as lung cancer) and test the acceptability of urine self-testing in a population already engaged with a screening programme/study. This may indicate whether embedding lung and bladder cancer screening programmes would be successful in the future national roll-out.
Cohort 2 participants will be identified through a database search of 8-10 selected GP practices located in the Sheffield, Rotherham, Doncaster, and Barnsley CCG areas in South Yorkshire and identified to be in a high-risk bladder cancer mortality region.
Cohort 3 participants will be identified through 2WW referral lists for the investigation of haematuria at participating NHS Trusts.

Urine self-testing (all cohorts):
Urine self-testing was selected as the screening test to optimise participation for those most at risk of bladder cancer. Urine self-testing kits will be directly mailed over a 12-month period to identified participants for all three cohorts. For Cohort 1 and 2, this invitation will be presented as a ‘Bladder Health Check'. Participant details will be securely transferred from King's College London to the mailout company.
Urine self-testing kits will include a trial invitation letter, 6 x urine test strips, instructions for self-testing (including use of App/freephone), and a participant information booklet.
Participant information will instruct participants to collect and test a urine sample using the test strips for 6 consecutive days and to start this as soon as possible after receipt of the kit (detection of haematuria requires testing over several days as it can be intermittent). Test strips can be discarded after use.
The urine test strips contain 5 coloured panels that may change colour with testing. The test strip will test for haematuria (blood in the urine), glycosuria (sugar in the urine), nitrites, protein, and white blood cells. Participants will be blinded to the meaning of each colour change. Only the haematuria result (Cohort 1 & 2) and glycosuria result (Cohort 2) will trigger further study related procedures. Test results for Cohort 3 will not inform any study procedures. Participants and GPs will receive only the haematuria result (Cohort 1, Cohort 2 as per randomisation) or the glycosuria result (Cohort 2 as per randomisation). The other three test strip results (nitrites, protein, white blood cells) will not be available for the research nurse to review and will

therefore not be notified to the participant and GP. A reminder letter will be sent after 3 weeks to non-responders of the initial invitation in Cohort 1 and 2. If the initial kit becomes damaged, is misplaced, or is unusable, replacement kits can be requested by participants in the 4 weeks following their initial study invitation being sent out. We expect a 40% uptake for urine self-testing in Cohort 1 & 2 (~2000 participants) and a 50% uptake in Cohort 3 (~500 participants).

Participant options for recording self-test results:
Participants will be instructed to record their completed test strips via a trial specific mobile phone App (preferred option) or a freephone system. The freephone service will be an automated system whereby participants use their keypad to enter their responses to programmed questions, and test-strip results. The freephone service requires confirmation of the test strip colour result by the participant (colour chart and full instructions will be provided), whereas App users will simply take a photograph of their completed test strip which will be submitted for interpretation by the research nurse. For this reason, the App will be the preferred method for the study and participant information will encourage use of this. The study objectives include comparison of uptake, sensitivity, and specificity of both methods of reporting results.

Urine symptoms questionnaire:
The App and freephone will prompt participants to complete a questionnaire (this will be a modified and unvalidated version of the Urinary Tract Infection Symptom Assessment (UTISA)) which will collect information on bladder symptoms within the past 4 weeks. All data pertaining to the questionnaire will be kept separate from urine self-testing results until the end of the trial. Access to this data will be restricted during the study. As the trial is assessing the use of the test strips alone for early detection, it is deemed not appropriate for the trial team to have sight of the symptom questionnaire data and not act on this (for example if there were symptoms indicating need for onward referral).
Therefore, all trial clinical decision making will be based on the results of the urine test strips alone and the symptoms questionnaire data will be revealed at the end of the trial.

Randomisation (Cohort 2 only)
Men participating in Cohort 2 will be tested for both haematuria and glycosuria but will be randomised to receive the result of only one of these two tests (reveal/conceal design). Randomisation will occur once self-testing is completed but before the research nurse reviews the self-test results.

Reveal/conceal reciprocal design:
A reveal/conceal reciprocal design will be incorporated into Cohort 2. With a reciprocal design, all participants at each timepoint will get the result of one test and serve as a control for the other test. This is particularly appealing here because the two tests are done on the same sample (test strip). The complication is that the samples cannot be stored for future testing and in practice all strips will test for both haematuria and glycosuria. We will therefore implement the reciprocal design by either concealing or revealing each test result.
A participant randomised to the haematuria group will have their haematuria test result revealed and their glucosuria test result concealed. Similarly, participants randomised to the glucosuria group will have their glucosuria test result revealed and their haematuria test result concealed. This approach has the advantage that at the end of the study we will be able to find out what the concealed result was, and this greatly increases the power of the study. The acceptability of this approach will be compared with Cohort 1 in which everyone using a test strip will receive their (haematuria) test result, tested predominantly through participant compliance/uptake.
Glycosuria has been chosen as the comparator because its detection is robust, and urine based.

It may indicate a disease with significant health impact (diabetes), and there is a simple blood test to determine the presence or absence of diabetes which allows a safe discharge from the trial.
A reveal/conceal design has been used in other screening trials as it maximises design efficiency. This will be important to reduce the sample size required for a future randomised phase 3 controlled trial. Patient and Public Involvement work has indicated that this design will be more acceptable than other designs where the control group would receive no test result. The ethical impact of concealing test results has been carefully considered and discussed with PPI representatives.

Self-testing results - Cohort 1 & 2:
A research nurse will assess and determine results received through the App (photos of completed test strips) or freephone system (participant reported test strip results) after 6 test strips have been tested, or one week after the last test if less than 6 strips are tested.
For all test strip parameters, an overall positive result for that parameter is applied based on the presence of at least 1 positive parameter in the 6 days of testing e.g., haematuria detected on 1 out of 6 test strips will be considered an overall positive result. An overall negative result will only be applied if all 6 test strips (or however many were completed) were negative for that parameter.
Participants will receive a letter within 14 days following completion of self-testing (or last self-test result received) to summarise their results and detail any further actions required:
1. Haematuria/glycosuria result negative - No further tests or actions required. Participants will be thanked for their participation.
2. Haematuria positive (Cohort 1, and Cohort 2 haematuria group) - Participants will be invited to an Early Detection clinic for further tests
3. Glycosuria positive (Cohort 2 glycosuria group) - Participants will be invited to an Early Detection clinic for further tests

Self-testing results - Cohort 3:
A research nurse will assess and determine results received through the App or freephone system after 6 test strips have been tested, or one week after the last test if less than 6 strips are tested. Participants will receive a letter within 14 days following completion of self-testing (or last self-test result received) to summarise their results.

Cohort 1 & 2 Early Detection clinics:
Cohort 1 and 2 participants who have a positive result for haematuria (Cohort 1 & 2) or glycosuria (Cohort 2 only) will be invited to an Early Detection Clinic usually within 4-6 weeks (at this point non-visible haematuria is not a trigger for anything more urgent) at a local GP practice for further investigations as part of the trial. Written informed consent will be obtained for this part of the trial.

The Early Detection Clinic for investigation of haematuria will triage participants. This triage will be based on the results of the 2 clinic procedures which are a urinary tract ultrasound (to examine for masses which may indicate cancer), and a urine sample for cytology (laboratory analysis to check for cancerous cells). Those with abnormal results suggestive of cancer will be referred (following standard 2WW criteria) to their local urology service and the outcome of this 2WW appointment e.g. bladder cancer diagnosis, will be collected for the study. This pathway will reserve the 2WW appointments (which includes invasive procedures such as cystoscopy) to those that need it, and may impact the future 2WW pathway if early detection assessments can be done prior to the 2WW appointment.

Those with normal results will receive a letter to confirm this, and their GP will be asked to review them in 6 weeks.

Urine samples collected for cytology will also undergo inclusion in development of a platform for AI analysis (computer automated analysis) which will be of benefit for the future larger study.

As part of the reciprocal design, glycosuria investigations will include a HbA1c blood test (to test for diabetes). Those found to have an elevated HbA1c result (as defined by local reference ranges) will be referred to their GP for diabetic management. Those with a normal HbA1c will receive a letter to confirm this.

Cohort 3 2WW appointment:
The 2WW appointment is scheduled as part of usual care with additional study procedures and data collection. All procedures will usually take place on the same day. At the 2WW appointment, participants will undergo the following as part of usual care:
1. Urine sample and test strip to check for the presence of infection
2. Ultrasound scan of the urinary tract
3. Cystoscopy
The additional study procedures will include:
1. Taking written informed consent
2. Urine sample for cytology and AI study.
3. Collection of data including outcome of 2WW appointment

Collection of cystoscopy related urinary tract infections (UTIs) - all cohorts (post 2WW appointment):
One of the procedures carried out at the 2WW appointment as part of standard care is a flexible cystoscopy. This is an invasive procedure which can commonly cause urinary tract infections which may require antibiotic treatment. Those referred for a 2WW appointment from Cohort 1 and 2 will undergo this procedure earlier than they would normally
(prior to symptoms), and there is a risk that the procedure may be undertaken unnecessarily and cause adverse effects for the patient. Although cystoscopy is undertaken outside of the study, the study will affect the pathway to the 2WW appointment. For this reason incidences of urinary tract infections will be collected after the 2WW for all cohorts.
Data on cystoscopy related UTIs will be collected through either of the following methods;
1. Telephone call: A research nurse will call the participant between 14 days and 30 days following their 2WW appointment. The purpose of the phone call is to collect information on any treated incidences of UTI following cystoscopy.
2. Primary care prescribing records

Long term follow-up:
Passive follow-up data (identification of cancer diagnosis and stage) will be collected through the National Cancer Registration & Analysis Service (NCRAS) for all participants that self-test (all cohorts) at 1, 2, and 3 years after the end of the trial.

Previous intervention:
This study aims to assess the feasibility of urine self-testing as an early detection method for bladder cancer. The study will also collect data to help design a larger trial in the future.
Three different populations are included in this study:
Cohort 1: 2000 participants of the Yorkshire Lung Screening Trial (YLST)
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Urine self-testing kits will include a trial invitation letter, 6 x urine test strips, instructions for self-testing (including use of App/freephone), and a participant information booklet.
Participant information will instruct participants to collect and test a urine sample using the test strips for 6 consecutive days and to start this as soon as possible after receipt of the kit (detection of haematuria requires testing over several days as it can be intermittent). As only those who wish to take part will complete and record their test strips, consent is implicit. This will be made clear in the participant information. Test strips can be discarded after use.
The urine test strips contain 5 coloured panels that may change colour with testing. The test strip will test for haematuria (blood in the urine), glycosuria (sugar in the urine), nitrites, protein, and white blood cells. Participants will be blinded to the meaning of each colour change. Only the haematuria result (Cohort 1 & 2) and glycosuria result (Cohort 2) will trigger further study related procedures. Test results for Cohort 3 will not inform any study procedures. Participants and GPs will receive only the haematuria result (Cohort 1, Cohort 2 as per randomisation) or the glycosuria result (Cohort 2 as per randomisation). The other three test strip results (nitrites, protein, white blood cells) will not be available for the research nurse to review and will therefore not be notified to the participant and GP. A reminder letter will be sent after 3 weeks to non-responders of the initial invitation in Cohort 1 and 2. If the initial kit becomes damaged, is misplaced, or is unusable, replacement kits can be requested by participants in the 4 weeks following their initial study invitation being sent out. We expect a 40% uptake for urine self-testing in Cohort 1 & 2 (~2000 participants) and a 50% uptake in Cohort 3 (~500 participants).

Participant options for recording self-test results:
Participants will be instructed to record their completed test strips via a trial specific mobile phone App (preferred option) or a freephone system. The freephone service will be an automated system whereby participants use their keypad to enter their responses to programmed questions, and test-strip results. The freephone service requires confirmation of the test strip colour result by the participant (colour chart and full instructions will be provided), whereas App users will simply take a photograph of their completed test strip which will be submitted for interpretation by the research nurse. For this reason, the App will be the preferred method for the study and participant information will encourage use of this. The study objectives include comparison of uptake, sensitivity, and specificity of both methods of reporting results.

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The App and freephone will prompt participants to complete a questionnaire (this will be a modified and invalidated version of the Urinary Tract Infection Symptom Assessment (UTISA)) which will collect information on bladder symptoms within the past 4 weeks. All data pertaining to the questionnaire will be kept separate from urine self-testing results until the end of the trial. Access to this data will be restricted during the study. As the trial is assessing the use of the test strips alone for early detection, it is deemed not appropriate for the trial team to have sight of the symptom questionnaire data and not act on this (for example if there were symptoms indicating need for onward referral).
Therefore, all trial clinical decision making will be based on the results of the urine test strips alone and the symptoms questionnaire data will be revealed at the end of the trial.

Randomisation (Cohort 2 only)
Men participating in Cohort 2 will be tested for both haematuria and glycosuria but will be randomised to receive the result of only one of these two tests (reveal/conceal design). The result of the other test will be notified at the end of the trial (and actioned if necessary). Randomisation will occur once self-testing is completed but before the research nurse reviews the self-test results.

Reveal/conceal reciprocal design:
A reveal/conceal reciprocal design will be incorporated into Cohort 2. With a reciprocal design, all participants at each timepoint will get the result of one test and serve as a control for the other test. This is particularly appealing here because the two tests are done on the same sample (test strip). The complication is that the samples cannot be stored for future testing and in practice all strips will test for both haematuria and glycosuria. We will therefore implement the reciprocal design by either concealing or revealing each test result.
A participant randomised to the haematuria group will have their haematuria test result revealed and their glucosuria test result concealed until the end of the study. Similarly, participants randomised to the glucosuria group will have their glucosuria test result revealed and their haematuria test result concealed until the end of the study. This approach has the advantage that at the end of the study we will be able to find out what the concealed result was, and this greatly increases the power of the study. The acceptability of this approach will be compared with Cohort 1 in which everyone using a test strip will receive their (haematuria) test result, tested predominantly through participant compliance/uptake.
Glycosuria has been chosen as the comparator because its detection is robust, and urine based. It may indicate a disease with significant health impact (diabetes), and there is a simple blood test to determine the presence or absence of diabetes which allows a safe discharge from the trial.
A reveal/conceal design has been used in other screening trials as it maximises design efficiency. This will be important to reduce the sample size required for a future randomised phase 3

controlled trial. Patient and Public Involvement work has indicated that this design will be more acceptable than other designs where the control group would receive no test result. The ethical impact of concealing test results has been carefully considered and discussed with PPI representatives.

Self-testing results - cohort 1 & 2:
A research nurse will assess and determine results received through the App (photos of completed test strips) or IVRS (participant reported test strip results) after 6 test strips have been tested, or one week after the last test if less than 6 strips are tested.
For all test strip parameters, an overall positive result for that parameter is applied based on the presence of at least 1 positive parameter in the 6 days of testing e.g., haematuria detected on 1 out of 6 test strips will be considered an overall positive result. An overall negative result will only be applied if all 6 test strips (or however many were completed) were negative for that parameter.
Participants will receive a letter within 14 days following completion of self-testing (or last self-test result received) to summarise their results and detail any further actions required:
1. Haematuria/glycosuria result negative - No further tests or actions required. Participants will be thanked for their participation.
2. Haematuria positive (Cohort 1, and Cohort 2 haematuria group) - Participants will be invited to an Early Detection clinic for further tests
3. Glycosuria positive (Cohort 2 glycosuria group) - Participants will be invited to an Early Detection clinic for further tests
The letter will remind Cohort 2 participants that one of their results will be hidden until the end of the study, and that they will be informed of this result and any clinical follow-up required, at the end of the study.

Self-testing results - cohort 3:
A research nurse will verify results received through the App or IVRS after 6 test strips have been tested, or 1 week after the last test if less than 6 strips are tested. Participants will receive a letter within 14 days following completion of self-testing (or last self-test result received) to summarise their results and invite them to an early detection clinic appointment if required.

Cohort 1 & 2 early detection clinics:
Cohort 1 and 2 participants who have a positive result for haematuria (Cohort 1 & 2) or glycosuria (Cohort 2 only) will be invited to an Early Detection Clinic usually within 4-6 weeks (at this point non-visible haematuria is not a trigger for anything more urgent) at a local GP practice for further investigations as part of the trial. Written informed consent will be obtained for this part of the trial.

The Early Detection Clinic for investigation of haematuria will triage participants. This triage will be based on the results of the 2 clinic procedures which are a urinary tract ultrasound (to examine for masses which may indicate cancer), and a urine sample for cytology (laboratory analysis to check for cancerous cells). Those with abnormal results suggestive of cancer will be referred (following standard 2WW criteria) to their local urology service and the outcome of this 2WW appointment e.g. bladder cancer diagnosis, will be collected for the study. This pathway will reserve the 2WW appointments (which includes invasive procedures such as cystoscopy) to those that need it, and may impact the future 2WW pathway if early detection assessments can be done prior to the 2WW appointment.

Those with normal results will receive a letter to confirm this, and their GP will be asked to review them in 6 weeks.

Urine samples collected for cytology will also undergo inclusion in development of a platform for AI analysis (computer automated analysis) which will be of benefit for the future larger study.

As part of the reciprocal design, glycosuria investigations will include a HbA1c blood test (to test for diabetes). Those found to have an elevated HbA1c result (as defined by local reference ranges) will be referred to their GP for diabetic management. Those with a normal HbA1c will receive a letter to confirm this.

Cohort 3 2WW appointment:
The 2WW appointment is scheduled as part of usual care with additional study procedures and data collection. All procedures will usually take place on the same day. At the 2WW appointment, participants will undergo the following as part of usual care:
1. Urine sample and test strip to check for the presence of infection
2. Ultrasound scan of the urinary tract
3. Cystoscopy
The additional study procedures will include:
1. Taking written informed consent
2. Urine sample for cytology and AI study.
3. Collection of data including outcome of 2WW appointment

Collection of cystoscopy related UTIs - all cohorts (post 2WW appointment):
One of the procedures carried out at the 2WW appointment as part of standard care is a flexible cystoscopy. This is an invasive procedure which can commonly cause urinary tract infections which may require antibiotic treatment. Those referred for a 2WW appointment from Cohort 1 and 2 will undergo this procedure earlier than they would normally
(prior to symptoms), and there is a risk that the procedure may be undertaken unnecessarily and cause adverse effects for the patient. Although cystoscopy is undertaken outside of the study, the study will affect the pathway to the 2WW appointment. For this reason incidences of urinary tract infections will be collected after the 2WW for all cohorts.
Data on cystoscopy related UTIs will be collected through either of the following methods;
1. Telephone call: A research nurse will call the participant between 14 days and 30 days following their 2WW appointment. The purpose of the phone call is to collect information on any treated incidences of UTI following cystoscopy.
2. Primary care prescribing records

Long term follow-up:
Passive follow-up data (identification of cancer diagnosis and stage) will be collected through the National Cancer & Registration Service (NCRAS) for all participants that self-test (all cohorts) and from non-responders in Cohort 2, at 1, 2, and 3 years after the end of the trial.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measures as of 15/07/2022:
As this is a feasibility study there are multiple primary outcomes which will all be assessed at the end of the trial:
1. Acceptability of urine self-testing and Early Detection Clinic procedures will be measured via:
1.1. The proportion of invitees who report results for at least 1 test strip
1.2. The proportion of participants who attend and consent for cytology and urinary tract ultrasound following detection of haematuria on self-testing

1.3. Proportions of participants who attend and consent for HbA1c blood testing following the detection of glycosuria on self-testing.
2. Compliance with urine self-testing will be measured via:
2.1. The proportion of participants who report results for i) all 6 test strips, and ii) 3 or more test strips
2.2. The number of test strips returned on average in those who return at least one test strip
3. Haematuria in the population will be measured via the proportions of haematuria in participants (≥1 test strip positive for haematuria)
4. Glycosuria in the population will be measured via the proportions of glycosuria in participants (≥1 test strip positive for glycosuria)
5. Haematuria clinic outcomes will be measured via:
5.1. The proportion of positive or abnormal cytology in those where a urine sample is collected
5.2. The proportion of participants scanned who have an abnormal ultrasound scan
6. Glycosuria clinic outcomes will be measured via the proportions of those with an elevated HbA1c following collection of a blood sample
7. Urinary symptoms will be measured via symptom scores from the urine symptoms questionnaire (as completed prior to self-testing)
8. Bladder cancer in the tested population will be measured via the proportions of bladder cancer and corresponding stage in identified participants (excluding non-responders and withdrawals)
9. The accuracy of self-testing, cytology, and ultrasound scan will be measured via:
9.1. The sensitivity, specificity, positive predictive value, and negative predictive value of the following in men and women with cancer as identified by cystoscopy results at the 2 Week Wait appointment
9.1.1. Self-testing (App vs. freephone)
9.1.2. Cytology and ultrasound (separately and in combination) as a triage test in those with positive haematuria
9.2. The predictive value of symptoms in combination with self-testing:
9.2.1. Haematuria positive/ symptoms positive
9.2.2. Haematuria negative /symptoms positive
9.2.3. Haematuria positive / symptoms negative
9.2.4. Haematuria negative / symptoms negative
10. Recruitment rates will be measured via the number of invitations sent out versus uptake

Previous primary outcome measures:
As this is a feasibility study there are multiple primary outcomes which will all be assessed at the end of the trial:
1. Acceptability of urine self-testing and Early Detection Clinic procedures will be measured via:
1.1. The proportion of invitees who report results for at least 1 test strip
1.2. The proportion of participants who attend and consent to Early Detection Clinic procedures.
1.3. Proportions of participants who attend and consent for HbA1c blood testing following the detection of glycosuria on self-testing.
2. Compliance with urine self-testing will be measured via:
2.1. The proportion of participants who report results for i) all 6 test strips, and ii) 3 or more test strips
2.2. The proportion of test strips returned on average in those who return at least one test strip
3. Haematuria in the population will be measured via the proportions of haematuria in participants (≥1 test strip positive for haematuria)
4. Glycosuria in the population will be measured via the proportions of glycosuria in participants (≥1 test strip positive for glycosuria)
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5.1. The proportion of positive or abnormal cytology in those where a urine sample is collected

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9.2.1. Haematuria positive/ symptoms positive
9.2.2. Haematuria negative /symptoms positive
9.2.3. Haematuria positive / symptoms negative
9.2.4. Haematuria negative / symptoms negative
10. Recruitment rates will be measured via the number of invitations sent out versus uptake

Key secondary outcome(s))

Current secondary outcome measures as of 15/07/2022:
1. Reporting of self-test results via mobile app or freephone will be measured by the proportions of app or phone line use, and the impact on sensitivity and specificity to detection of cancer at the end of the trial
2. The acceptability of the reciprocal design will be measured by the proportions of compliance /attendance/surveys at the end of the trial

Exploratory outcome measures:
1. Comparison of populations, demographics and cancer incidence of those who complete self-testing and those who do not will be measured by comparing the characteristics of participants who are invited to take part to those not invited to take part (to compare characteristics where available including sex, age group, quintile of deprivation, smoking history). All participants that self-test will be flagged in NCRAS for cancer diagnoses at 1, 2 and 3 years following the end of the trial.
2. The development of an artificial intelligence (AI) platform for the assessment of urine samples for cytology analysis for the future study will be measured by the accuracy of the AI read versus the manual read at the end of the trial.
3. The potential harm of cystoscopy adverse effects, specifically urinary tract infections requiring medical treatment, will be measured by the proportions of participants that have a UTI requiring medical treatment following cystoscopy at the end of the trial.
4. The development of a health economics model using the information from this feasibility study that could be used to develop a future community-based screening programme for bladder cancer will be measured at the end of the study by:
4.1. Resource usage in each arm (number of clinics used, blood tests, ultrasound tests, extra NHS tests)
4.2. Rate of cancers and other illnesses per arm

5. The addition of other urinary contents (leukocytes, nitrate, protein) in relation to the risk prediction of bladder cancer will be measured by other positive test strip panels in addition to haematuria at the end of the trial

Previous secondary outcome measures:
1. Reporting of self-test results via mobile app or freephone will be measured by the proportions of app or phone line use, and the impact on sensitivity and specificity to detection of cancer at the end of the trial
2. The acceptability of the reciprocal design will be measured by the proportions of compliance /attendance/surveys at the end of the trial

Exploratory outcome measures:
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3. The potential harm of cystoscopy adverse effects, specifically urinary tract infections requiring medical treatment, will be measured by the proportions of participants that have a UTI requiring medical treatment following cystoscopy at the end of the trial.
4. The development of a health economics model using the information from this feasibility study that could be used to develop a future community-based screening programme for bladder cancer will be measured at the end of the study by:
4.1. Resource usage in each arm (number of clinics used, blood tests, USS tests, extra NHS tests)
4.2. Rate of cancers and other illnesses per arm
5. The addition of other urinary contents (leukocytes, nitrate, protein) in relation to the risk prediction of bladder cancer will be measured by other positive test strip panels in addition to haematuria at the end of the trial

Completion date
31/10/2028

Eligibility

Key inclusion criteria
Cohort 1:
1. Men and women
2. Aged 55 – 80 years
3. Participants already enrolled within the YLST
4. Registered with a GP within the Leeds CCG area
5. Consented to contact from other research teams at the second YLST Lung Health Check visit

Cohort 2:
1. Men aged 65-79 years
2. Registered with a GP Practice identified as being in a region with a high bladder cancer mortality risk

Cohort 3:
1. Men and women aged 65-79 years referred to a recruiting urological department under the 2WW pathway for the investigation of haematuria (to include cystoscopy and urinary tract ultrasound, ± CT urogram)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
55 years

Upper age limit
80 years

Sex
All

Total final enrolment
1311

Key exclusion criteria
Current exclusion criteria as of 15/07/2022:
Cohort 1:
1. Unable to/did not consent to contact from other research teams
2. Insufficient capacity to give consent to take part in the research as determined by the investigator/person taking consent for those that attend an Early Detection Clinic appointment.

Cohort 2:
1. National Data Opt-outs
2. Ever diagnosis of bladder or kidney cancer
3. Diagnosis with any other cancer within the past 5 years (except non-malignant skin cancer)
4. Insufficient capacity to give consent to take part in the research, defined as the presence of the following conditions coded in GP records:
4.1. Dementia
4.2. Alzheimer's disease
4.3. Parkinson's disease
or as determined by the investigator/person taking consent for those that attend an Early Detection Clinic appointment

Cohort 3:
1. Unable to provide written informed consent
2. Insufficient capacity to give consent to take part in the research, defined as the presence of the following conditions in medical notes:
2.1. Dementia
2.2. Alzheimer's disease

2.3. Parkinson’s disease
or as determined by the investigator/person taking consent at the 2WW appointment
3. Evidence in patient medical record of historic dissent to use of data in research
4. Participant has opted out of data use via the National Data Opt Out

Previous exclusion criteria:
Cohort 1:
1. Unable to/did not consent to contact from other research teams
2. Insufficient capacity to give consent to take part in the research as determined by the investigator/person taking consent for those that attend an Early Detection Clinic appointment.

Cohort 2:
1. National Data Opt-outs
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Cohort 3:
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2. Insufficient capacity to give consent to take part in the research, defined as the presence of the following conditions in medical notes:
2.1. Dementia
2.2. Alzheimer’s disease
2.3. Parkinson’s disease
or as determined by the investigator/person taking consent at the 2WW appointment

Date of first enrolment
03/10/2022

Date of final enrolment
30/09/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Hallamshire Hospital (Lead site)
Sheffield Teaching Hospitals NHS Foundation Trust
Glossop Road

Sheffield
United Kingdom
S10 2JF

Study participating centre
St James' University Hospital
Leeds Teaching Hospitals NHS Foundation Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Doncaster Royal Infirmary
Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Sponsor information

Organisation
University of Sheffield

ROR
https://ror.org/05krs5044

Funder(s)

Funder type
Charity

Funder Name
Yorkshire Cancer Research; Grant Codes: S421

Alternative Name(s)
YCR

Funding Body Type

Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All information related to participants will be kept confidential and managed in accordance with the UK General Data Protection Regulation (GDPR), Data Protection Act (2018), NHS Caldicott Principles, the UK Policy Framework for Health and Social Care Research (2017), and the conditions of Research Ethics Committee Approval. Upon reasonable requests to the study team, only deidentified participant data will be available after the publication of the study outcomes. Use and projects need approval by the Trial Steering Committee. Data will be shared via secure NHS email or a secure data-sharing platform. Robust data-sharing agreements will be put in place with all collaborating organisations as necessary to ensure confidentiality and appropriate data handling. No identifiable personal data will be shared with organisations or individuals outside of these collaborating organisations.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		07/09/2023	08/09/2023	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes