GP Information Sheet NHS-Galleri Trial

Purpose

This information sheet is designed to answer questions raised by GPs in response to the NHS-Galleri trial in areas where the trial is taking part. The target audiences are health professionals and supporting organisations participating in the trial. This information sheet is not designed for trial participants or for circulation outside of the trial at this time.

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1. What is the NHS-Galleri trial?

The NHS-Galleri trial is a prospective, randomised, controlled trial to assess the performance and clinical utility of a multi-cancer early detection test (Galleri™) for population screening in the United Kingdom (UK) when added to standard of care. The trial is designed to establish if screening with the Galleri test reduces the incidence of late stage cancer when used in an asymptomatic population in combination with existing NHS cancer screening programmes. The trial will be managed by the Cancer Research UK & King's College London (KCL) Cancer Prevention Trials Unit (CPTU) on behalf of GRAIL Bio UK Ltd. (GRAIL) and NHS England (NHSE). The trial aims to enrol 140,000 participants, 15-20,000 people from each participating Cancer Alliance.

2. Who is GRAIL Bio UK Ltd?

GRAIL Bio UK Ltd (GRAIL) is the commercial sponsor of the NHS-Galleri trial. GRAIL is a branch of GRAIL, Inc., a company based in the United States (US) that developed the Galleri test.

3. Who can take part in the NHS Galleri trial?

In order to take part in the NHS-Galleri trial, participants must be:

- age 50-77 years old;
- registered at a postcode within a participating Cancer Alliance; and
- not diagnosed with cancer in the past 3 years or currently under diagnostic follow up/treatment for cancer

4. Which Cancer Alliances are taking part in the NHS-Galleri trial?

The trial will work with eight Cancer Alliances:

- Cheshire and Merseyside
- East Midlands
- East of England – North
- Greater Manchester
- Kent and Medway
- Northern
- South East London
- West Midlands

5. How will the NHS-Galleri trial be rolled out?

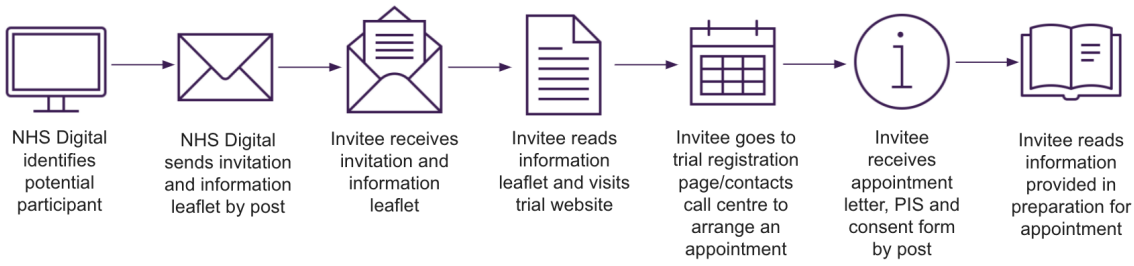
5.1. Receiving an invitation

Eligible participants who have not opted out of research using their NHS data will be invited to take part by a central NHS Digital mailout based on their age, postcode and recent cancer history. Invitation letters will be sent by post with an information leaflet about the trial. A small number of GP practices/Primary Care Networks (PCN) may be asked to send invitations on behalf of the trial.

5.2. Making an appointment

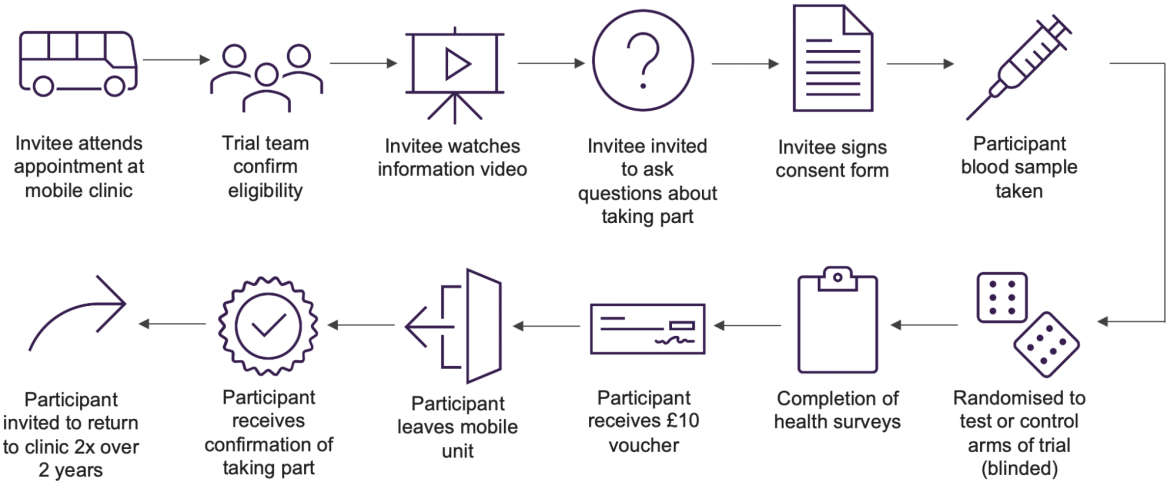
Each invitation will include an invitation code. The code will be needed to make an appointment using the trial registration website/call centre. Appointments will take place at mobile units, which will be based in an area local to invitees for a defined period of time. Invitees are therefore encouraged to make an appointment within two weeks of receipt of invitation. Confirmation of appointment will be sent by post with a Participant

Information Sheet (PIS). PIS are available in English or alternatively Punjabi, Gujarati, Bengali and Urdu if requested.



5.3. At the appointment

At the mobile unit, trial staff will confirm the participant's eligibility to take part and provide more information about the NHS-Galleri trial, including an information video. Attendees will be given an opportunity to ask questions about the trial, and if they choose to take part, they will be asked to sign a consent form.
Consented participants will give a blood sample and complete health questionnaires. After the appointment, participants will receive confirmation by post that their blood sample has been received. Participants will be invited to return to a mobile clinic to give further blood samples and complete health questionnaires approximately 12 and 24 months after their first visit. Participants will be given a £10 voucher to compensate for their time and inconvenience at each visit. The trial aims to enrol 140,000 participants, 15-20,000 people from each Cancer Alliance.



5.4. Study design

This is a randomised control trial. Each participant will be randomly assigned to the intervention or control arm of the trial. To enable study blinding, participants will not be told which arm of the trial they have been assigned to. In the intervention arm, all samples will be tested. In the control arm, samples will be stored for future analysis. For those who consent to future research, blood samples will be used to improve the Galleri test and/or develop new tests. Blood samples for analysis will be shipped to the US. Participants will not be given their results with the exception of those in the intervention arm that receive a 'Cancer Signal Detected' result.

- Participants in the intervention arm with a 'Cancer Signal Detected' result will be referred directly to the two-week wait cancer referral pathway for follow up diagnostic testing as agreed by NHSE. GPs will be informed if their patient receives a 'Cancer Signal Detected' result (see section: *What happens when a participant receives a 'Cancer Signal Detected' result?*)
- All other participants will remain blinded
- All participants are encouraged to continue with routine cancer screening and remain vigilant for symptoms that might indicate cancer

6. What is the role of GPs and primary care staff?

GP practices in participating Cancer Alliances will be notified that eligible patients in their area will be invited to join the trial. To minimise the burden on primary care, NHS Digital will identify and invite eligible participants. GRAIL will contract an independent company to provide and manage mobile health units. These health units will be set up as centres for participants to consent to join the trial, give blood samples and complete study questionnaires. If a patient contacts you to discuss whether or not they should take part, you can advise them that it is their decision to make on the basis of the information provided to them by the trial team. Patients can find more information on the NHS-Galleri trial website (www.nhs-galleri.org).

- If the patient has received an invitation and if they would like to discuss their questions or receive further information, they can email the trial team at participant_help@nhs-galleri.org or telephone 0800 030 9245.
- If the patient has not received an invitation and would like to discuss their questions or receive further information, they can email the trial team at info@nhs-galleri.org.

7. What information will GPs receive about a patient's participation in the trial?

GPs will be informed if any of their patients decide to take part. If a participant's Galleri test returns a 'Cancer Signal Detected' result (see section: '*What is the Galleri test and how does it work?*') a trial research nurse will inform the participant and their GP. The research nurse will refer the participant for diagnostic follow up (see section: *What happens when a participant receives a 'Cancer Signal Detected' result?*). The participant's GP does not need to make a referral as this is part of the trial.

8. What is the Galleri test and how does it work?

The Galleri test is a new biomarker technology for early cancer detection that has been developed by GRAIL, Inc in the US as a cancer screening test to complement existing screening programmes. The Galleri test recognises methylation patterns in cell-free DNA (cfDNA) isolated from peripheral whole blood. The detection of a methylation pattern associated with cancer is returned as a 'Cancer Signal Detected' result. If no cancer is detected, the test will return a 'Cancer Signal Not Detected' result. When a cancer signal is detected, the report will include one or two predicted 'Cancer Signal Origin' (CSO). 21 possible CSOs are reported based on 24 cancer classes, representing more than 50 different cancers. The CSO cannot be used to confirm a cancer diagnosis but can be used to inform the diagnostic pathway. The Galleri test does not determine an individual's genetic risk for cancer.

9. What happens when a participant receives a 'Cancer Signal Detected' result?

A 'Cancer Signal Detected' result is not a diagnosis of cancer and diagnostic follow up is needed to confirm whether a participant has cancer. In clinical studies, the test was found to be highly specific, with a low false positive rate of 0.5% (Beer *et al*., 2021; Klein *et al.*, 2021). In more than 40% of participants with a 'Cancer Signal Detected' result, a cancer diagnosis was confirmed (Beer *et al*., 2021).

Trial nurses will refer the participant to the most appropriate urgent/two-week wait referral pathway in accordance with the predicted CSO via a centrally agreed process using the e-Referral Service. However, referral to secondary care must be within the boundaries of the eight participating Cancer Alliances (see section: *Which Cancer Alliances are taking part in the NHS-Galleri trial?*).

When a cancer signal is detected, one or two CSOs are reported. If pathway specific diagnostic investigations have been carried out for the first indicated CSO and no cancer is found, then the second CSO site should be investigated. Responsibility of ensuring the second CSO is further investigated will be managed by secondary care. Interim results from the PATHFINDER study (prospective cohort, n = 6629) (NCT04241796) indicate that the proportion of correctly predicted first or second CSO among true positive cases is high, at 96.3% (95% CI: 81.7-99.8) (Beer *et al.*, 2021).

It could take up to 30 days for a 'Cancer Signal Detected' result to be returned to trial participants. This is largely dependent on sample transit to the US.

10. How will secondary care communicate with GPs regarding follow-up diagnosis /discharge?

Once a participant has been referred to an urgent/two-week wait pathway their care is managed by the NHS. Secondary care will communicate the patient outcome to primary care as per standard clinical practice.

11. What happens when the Galleri test returns a 'Cancer Signal Detected' result and diagnostic follow up does not confirm the presence of cancer?

Failure to confirm cancer could mean that:

- the result of the Galleri test is a false positive and the participant does not have cancer
- the participant has a cancer, but it is not identified by the follow up diagnostic procedures used
- the participant has cancer that is located in a different part of the body than predicted by the Galleri test

All participants with a 'Cancer Signal Detected' result who do not have cancer confirmed on follow up testing will be offered a Galleri test at 12 and 24 months post first appointment.

All participants should be reminded to attend national screening appointments and report changes or any unusual symptoms that might indicate cancer.

12. What should patients do if they haven't received a result from the trial?

If a participant has not received any results from the trial, no action needs to be taken. This is because participants will not be told if they have been assigned to the control or intervention arm of the study and should not expect to receive a Galleri test result. Participants in the intervention arm of the trial will only be informed of a Galleri test result if their test returns a 'Cancer Signal Detected' result. No other results will be returned.

13. What do I do if I need more information about a specific patient's Galleri result?
As a participant's GP, you will be informed if your patient receives a 'Cancer Signal Detected' result. If you need further information about your patient, please contact the NHS-Galleri trial team at KCL-CPTU by email (clinical_help@nhs-galleri.org) or call 0800 030 9245. Additional information can be found on the NHS-Galleri trial website (www.nhs-galleri.org).

14. Should participants continue to attend national screening appointments?
It is very important that participants continue to attend their screening appointments and inform their GP if they have any new or unusual symptoms. Participants cannot assume that participation in the trial will tell them if they have cancer or not. A Galleri test is unlikely to detect all cancers and participants have a 50% chance of being assigned to the control arm and to not receive a Galleri test (see section: *study design*). The trial also aims to understand if screening using the Galleri test can improve early cancer detection alongside *existing* NHS cancer screening programmes. It is therefore very important patients continue to attend their screening appointments and look out for any new or unusual symptoms.

15. What happens if my patient is diagnosed with cancer outside of the trial whilst participating?
If a patient is diagnosed with cancer outside of the trial (i.e., they receive a cancer diagnosis between study visits), they remain in the trial and will continue to be followed via the National Cancer Registration and Analysis Service (NCRAS) and their data monitored in Hospital Episode Statistics (HES). However, the participant is not required to return to the mobile clinic to give any further blood samples. GPs are not required to inform the trial if their patient has received a cancer diagnosis or has been referred for further testing under suspicion of cancer.

References

- Beer TM, McDonnell CH, Nadauld L, Liu MC, Klein EA, Reid R, Marinac CR, Chung K, Lopatin M, Fung ET and Schrag D, 2021, *Interim Results of PATHFINDER, a Clinical Use Study Using a Methylation-Based Multi-Cancer Early Detection Test*. American Society of Clinical Oncology (ASCO), 4-8 June, virtual conference (https://grail.com/wp-content/uploads/2021/06/ASCO-2021-Pathfinder-Beer_FINAL-for-upload.pdf)
- Klein EA, Donald R, Cohn A, Tummala M, Lapham R, Cosgrove D, Chung G, Clement J, Gao J, Hunkapiller N, Jamshidi A, Kurtzman KN, Seiden MV, Swanton C and Liu MC, 2021, *Clinical Validation of a Targeted Methylation Based Multi-Cancer Early Detection Test.* American Association for Cancer Research (AACR) Annual Meeting, 10-15 April and 17-21 May, virtual conference (https://grail.com/wp-content/uploads/2021/04/CCGA3_Klein_AACR_2021_oral_FINAL.pdf)