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Psychological Impact of the Galleri test (sIG(n)al): protocol for a longitudinal evaluation of the psychological impact of receiving a cancer signal in the NHS-Galleri trial

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ABSTRACT

Introduction Multi-cancer early detection (MCED) blood tests look for cancer signals in cell-free deoxyribonucleic acid. These tests have the potential to detect cancers at an earlier (asymptomatic) stage, improving cancer outcomes. Any screening method needs careful consideration of the psychological harms prior to implementation. The aim of this research is to explore the psychological impact of having a cancer signal detected following an MCED blood test.

Methods and analysis The project is embedded in the NHS-Galleri trial (ISRCTN91431511; NCT05611632), a large clinical trial in eight Cancer Alliances in England. In the trial, over 140 000 members of the general population aged 50–77 have been randomised 1:1 to either the intervention (blood tested with MCED test) or control (blood stored) arm. The proposed project focuses on participants in the intervention arm, who have a cancer signal detected. All participants who have a cancer signal detected (expected to be around 700 assuming a 1% test positive rate) will be sent a questionnaire at three timepoints: soon after receiving their result, 6 months and approximately 12 months later. The primary outcome is anxiety, assessed using the short-form 6-item Spielberger State Trait Anxiety Inventory. We will also assess the psychological consequences of screening (using the Psychological Consequences of Screening Questionnaire), reassurance/concern about the test result, understanding of results and help/health-seeking behaviour. A subsample of 40 participants (20 with a cancer diagnosis and 20 for whom no cancer was found) will be invited to take part in a one-to-one semistructured interview.

Ethics and dissemination Ethical approval for this work has been granted by the Wales Research Ethics Committee as part of the NHS-Galleri trial (Ref 21/WA/0141). Consent to be sent questionnaires is collected as part of the main trial. A separate consent form will be required for interview. Results will be disseminated via peer-reviewed publication and conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multiple aspects of psychological impact will be considered across three timepoints, ensuring our understanding of impact is wide ranging and extends beyond anxiety alone.
⇒ Test results are only communicated to participants if a cancer signal is found (in order to maintain blinding), so it is not possible to collect data from those receiving a negative result following their first blood test; comparative information on psychological impact from previous research in the cancer screening context will be needed.
⇒ Data will be collected within the context of a clinical trial, so our findings will need to be interpreted with appropriate caution.
⇒ Translation and interpreting services will not be used for the questionnaires or interviews, which means those who do not read or speak English may not be able to take part.

INTRODUCTION

Population-based cancer screening aims to identify signs of cancer among asymptomatic individuals at an early stage. The goal is to achieve better outcomes than would be expected if cancer was only identified following symptomatic presentation. The UK National Screening Committee (UKNSC) currently recommends population-based screening for cervical, breast and bowel cancer, and all three programmes are estimated to have saved thousands of lives.[1] In 2022, the UKNSC also recommended that targeted lung cancer screening be rolled out for people at high risk. A 2019 review of screening programmes in England stated that 'Screening programmes are effectively judged on whether the benefits to those who get earlier treatment outweigh the harms to those people who get treated unnecessarily, or who are subject to unnecessary anxiety' (p18).[2] The premise of screening is such that most healthy individuals will not benefit from participation, so participation

in screening involves risk-benefit considerations for all who take part.[3]

Most research evidence exploring psychological harms following screening focuses on anxiety as the primary endpoint.[4] Anxiety is a mental state associated with intense emotion, worry or apprehension.[5] People who receive 'positive' (sometimes called abnormal) cancer screening results can have higher anxiety levels than those who test 'negative' or are not tested, as demonstrated in the context of cervical screening,[6 7] colorectal cancer screening[8 9] and mammography.[10–12] For those receiving a positive screening result that does not ultimately lead to a diagnosis of cancer, or a precancerous condition that requires treatment (sometimes called a 'false positive' result), raised anxiety is most evident in the short term, but can continue for a significant period afterwards, especially if diagnostic tests are invasive.[13] Though anxiety can reduce over the months following the test, there is evidence that outcomes which are more test specific, such as cancer worry and perceived risk of a future diagnosis can persist.[14 15] 'Positive' screening results also have the potential to influence health behaviours more broadly[16 17] acting as a motivating or demotivating factor for future health behaviours and reattendance. Studies in existing screening contexts provide little evidence of false reassurance among those with false-positive results, but future research should continue to explore this as a possibility.[18] Consequently, it is vital that the psychological harms and subsequent behavioural impacts are considered thoroughly before screening is offered at a population level. Evaluations of new screening modalities are therefore encouraged to include assessment of psychological harms.[19]

A novel approach to cancer screening is to use multicancer early detection (MCED) blood testing. MCED blood tests look for cancer 'signals' in cell-free deoxyribonucleic acid and have the potential to identify multiple cancer types. There are currently several blood-based MCEDs in development,[20] but evidence regarding their clinically relevant impact on cancer outcomes is yet to be determined. To be considered acceptable for population-wide screening, these tests should detect multiple cancer types, including cancers associated with lowest survival, accurately identify the tumour site, have low false-positive rates and high positive predictive values and ideally be affordable and cost-effective.[20] Understanding the potential psychological impact of having a cancer signal detected is also a vital part of evidence needed alongside clinical outcomes.[21]

In 2021, a randomised controlled trial began in England (trial name: NHS-Galleri trial, ISRCTN91431511; NCT05611632). This trial is designed to assess whether offering a blood-based MCED test (Galleri® test, GRAIL, LLC) for men and women aged 50–77 years, without personal history of invasive cancer within the last 3 years, can reduce the number of late-stage cancers diagnosed.[22] Within the trial, participants are invited for three blood tests at 12-month intervals. Those with a cancer signal -detected are referred into an National Health Service (NHS) urgent care referral pathway or rapid diagnostic pathway for diagnostic testing. Participants who do not have a cancer found following diagnostic testing are invited for second and third rounds of screening at 12 months and 24 months. Our work on the psychological impact of having a cancer signal detected via MCED testing (acronym: sIG(n)al) is nested within the NHS-Galleri trial. The aim is to assess the psychological impact of having a cancer signal detected at three timepoints; shortly after receiving MCED test results, and then at 6-month and approximately 12-month follow-up. Our primary objectives are (1) to establish levels of anxiety among participants, who have been informed that a cancer signal was detected, shortly after receiving their results; (2) to compare longer-term anxiety between those subsequently diagnosed with cancer and those who have a diagnostic workup but no cancer is found, at 6-month and 12-month follow-up and (3) to explore in depth the experiences of men and women who have a cancer signal detected (using qualitative methods).

METHODS AND ANALYSIS

Design

A longitudinal observational design with a nested qualitative study. Survey data are collected at three timepoints. Semistructured one-to-one interviews will be carried out to explore patient experiences and understanding of results in more depth.

Participants and eligibility

The NHS-Galleri trial has enrolled over 140 000 participants aged 50–77 years (August 2021–July 2022) across eight participating Cancer Alliances in England (Cancer Alliances represent large geographic areas, see Neal *et al*[22] for more information about the Cancer Alliances in the NHS-Galleri trial), randomising to control or intervention arms (1:1). Participants in the intervention arm who have a cancer signal detected after their first MCED test are sent paper questionnaires at three timepoints unless they opt out (figure 1). A subsample of 40 participants (20 with a cancer diagnosis and 20 with a cancer signal detected but no cancer found following diagnostic workup) are invited to take part in an interview to explore their experience in depth. In line with the trial protocol design,[22] participants who do not have a cancer signal detected remain blinded to their allocation arm and are not given an explicit test result; we are thus unable to recruit a comparison group receiving a negative result. Completion of the sIG(n)al study is expected by March 2024. Final analysis for the NHS-Galleri trial is expected in 2026.

Procedures

Paper questionnaire packs are sent to participants' homes. These include a participant information sheet explaining the purpose of the survey, a paper survey and

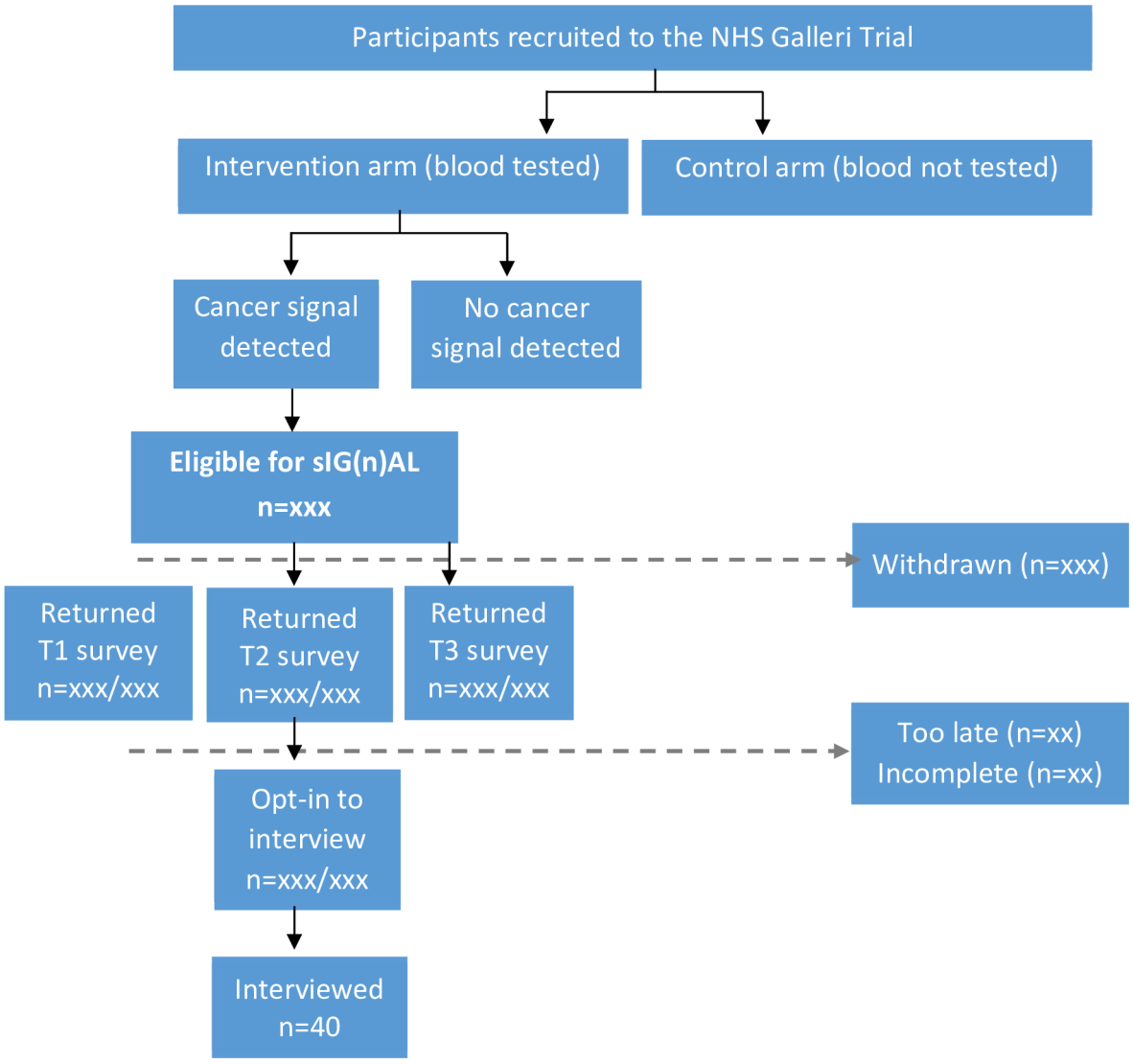

Figure 1 Study flow

Table 1 Description of the surveys	
Time 1 (T1)	Sent to all participants with a cancer signal found along with their written results letters, approximately 7 days after they have been given their results by a research nurse over the phone.
Time 2 (T2)	Sent to participants with a cancer signal found 6 months after their written results letter was dispatched, with a reminder for those who have not returned the survey within 2 weeks. A single survey is sent, but sections of the survey are designed for 'If you were told you have cancer' AND 'If no cancer was found following tests'.
Time 3 (T3)	Sent approximately 12–14 months after the initial result, with a reminder for those who have not returned the survey within 2 weeks. Three slightly different versions of T3 are used as follows: A. Participants who attend a second blood test B. Participants identified as having received a cancer diagnosis and undergoing treatment (and so not offered a second blood test within the trial) C. Participants who do not attend their second blood test appointment Differences in the content of these versions are outlined in table 2.
Note: All surveys are available online https://osf.io/uj86p	

a freepost envelope for returning completed questionnaires to the research team at King's College London (KCL). An option to complete the questionnaire online is also available, by visiting a website printed on the information sheet and the front of the questionnaire. Participants need to enter a unique code (also printed on the questionnaire) to access the survey. Questionnaires are sent at three timepoints with reminders sent 2 weeks later for the follow-up surveys (see table 1 for details). All surveys are available on Open Science Framework (OSF: https://osf.io/uj86p). Our follow-up timepoints were selected to be consistent with existing research exploring the longer-term impact of screening results,[4] but also take into account when participants are expected to have less intensive contact with other aspects of the trial or medical intervention (ie, diagnostic testing or cancer treatment).

Within the 6-month questionnaire, participants are asked to indicate if they are happy to be contacted about an interview. Interviewees who consent to be contacted are selected purposefully to represent a range of characteristics (age, gender, index of multiple deprivation (IMD; an area-level measure of relative deprivation based on Lower-layer Super Output Areas or neighbourhood),[23] ethnicity and self-reported cancer diagnosis) based on their questionnaire data. Since recruitment for the interviews is over 10 months (mirroring the 10-month trial recruitment period), we will not have all participants opting into being interviewed at the same time, and purposeful recruitment is thus an iterative process with ongoing review. Interviews are semistructured and follow a topic guide (available on OSF: https://osf.io/cau6p). They are carried out by LAVM or NS-B and are face-to-face or on the telephone, depending on the preference of the interviewee. Interviews last up to 1 hour, and participants are given a £40 voucher to compensate them for their time. All interviews are audiorecorded and transcribed verbatim for analysis. The researchers also keep reflexive journals throughout the process of data collection and during analysis of the data.

Primary outcomes

Our main primary outcome measure is anxiety assessed using the short-form, 6-item version of the Spielberger State-Trait Anxiety Inventory (STAI-6).[24 25] The STAI is a measure of state anxiety that has been validated and used in many studies and is the most commonly used measure of anxiety in the context of cancer screening.[4] We will therefore be able to compare our findings to those from other relevant studies in the UK (eg, in HPV primary screening[26]) and worldwide (eg, in lung screening[27]). We may also be able to compare the results of our study with those that have used the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) using suggested equivalence scores.[28] The STAI also has cut-offs indicative of 'high anxiety' that might be expected to lead to a clinical diagnosis, though the exact cut-offs used do vary across studies.[4] The STAI-6 was selected over the full form (STAI FORM-Y), which has 20 items, due to its shorter length. In addition, validation of the STAI-6 was carried out in England and included a sample of those receiving an abnormal screening result.[25] Validation of the STAI-6 showed that it produced similar scores to those obtained using the full form and is sensitive to fluctuations in state anxiety.[25]

Despite the benefits of using the STAI to assess anxiety, some researchers have suggested that this measure is not sensitive enough or sufficient for identifying changes in psychological outcomes following positive screening results.[29] To address this, we will include additional measures of psychological impact (see table 2). The first is the Psychological Consequences of Screening Questionnaire (PCQ) which measures the impact of screening on an individual's emotional, social and physical functioning.[30] The PCQ also offers the opportunity to assess positive longer-term psychological impact following screening. We will also assess result-specific concern and reassurance, as studies have shown that result-specific outcomes (eg, concern about the test result or future risk of cancer) are more likely to persist longer term.[31 32] In addition to the measures of psychological impact, two types of behavioural impact will be considered as primary outcome measures. These apply exclusively to participants who have a cancer signal detected at the first blood test but no cancer is found. The first is self-reported behaviour change in relation to routine cancer screening attendance and symptomatic help-seeking (reported in the T3 survey). The second is reattendance for a second trial blood test (at 12 months).

Secondary outcomes

Secondary outcomes assess additional constructs relevant to psychological impact (see table 2) including understanding of the test result, perceived cancer risk and satisfaction with different aspects of the trial, future intention to have the Galleri test and decisional regret (using the Decision Regret Scale[33]). We will also measure fear of cancer recurrence among those diagnosed with cancer (using the Fear of Cancer Recurrence-4.[34]).

Participant characteristics and explanatory variables

Sociodemographic variables including age, Indices of Multiple Deprivation (IMD), biological sex, ethnicity, country of birth, marital status and education are collected at the first clinic visit following consent. Additional variables assessing cognitions, emotions and behaviours (assessed in the three surveys) will be treated as explanatory variables. These constructs are expected to facilitate understanding of differences in psychological outcomes and include coping and appraisal, cancer worry and attitudes to cancer and early detection.

Sample size

The maximum available sample size is determined by expected numbers recruited in the NHS-Galleri

Table 2 Summary of primary and secondary outcome variables

Construct	Details	Validated scale	T1	T2	T3		
					a	b	c
Primary outcomes							
Anxiety	STAI-6[25] (6 items, 4-point Likert Scale)	✓	✓	✓	✓	✓	✓
Emotional, physical and social consequences of screening	PCQ[30] (negative: 12 items, 4-point Likert Scale)	✓	✓	✓	✓	✓	✓
	PCQ[30] (positive: 10 items)	✓		✓	✓	✓	
Test-specific concern	Single item (5-point Likert Scale)		✓		✓		
Test-specific reassurance	Single item (5-point Likert Scale)		✓	✓	✓		
Changes in health behaviour	Single item for each behaviour				✓		
Secondary outcomes							
Understanding of results	Understanding of result meaning (1 item, 6 response options)	✓	✓		✓	✓	✓
	Confidence in understanding (1 item, 5-point Likert Scale)		✓	✓	✓		
Perceived risk of cancer	Affective risk (1 item, 5-point Likert Scale)		✓	✓	✓		
	Deliberative risk (1 item, 5-point Likert Scale)		✓	✓	✓		
Overall experience	1 item, 4 response options		✓				
Satisfaction with the trial	Multiple items assessing satisfaction (5-point Likert Scale):						
	Invitation; information; plan for follow-up		✓				
	Appointment, result delivery		✓		✓		
	Consultations; support during follow-up			✓			
Future intention to have a Galleri test	Single item		✓	✓	✓	✓	✓
Decisional regret	Decisional Regret Scale[33] (5 items, 5-point Likert Scale)	✓			✓	✓	✓
Fear of recurrence	Fear of Cancer Recurrence-4[34] (4 items, 5-point Likert Scale)	✓				✓	

a: Returning for second blood test; b: with cancer found; c: non-attenders.
T1, time 1; T2, time 2; T3, time 3.

trial—questionnaires are sent to all those with a cancer signal detected. Approximately 1% of the intervention arm (n~700) are expected to have a cancer signal detected. We anticipate a 50% response rate at each timepoint, resulting in data from up to 350 participants at each timepoint (if positivity rates are as expected). This sample size will allow us to estimate the proportion of participants experiencing 'very high' anxiety (using a STAI Score >49 consistent with McBride *et al*[26]) with a precision of +/−3% to 4% (based on 10%–20% experiencing 'very high' anxiety). The anticipated sample size would also give us 88% power (alpha=0.05) to detect a mean difference in STAI Score of 4 points (SD=12) between those who go on to have a cancer diagnosed and those for whom no cancer is found following further tests. To limit attrition, we invested in the design of the survey materials, offered online completion as well as paper, and sent survey reminders (at T2 and T3).

The decision to conduct 40 interviews is predominantly pragmatic, taking into consideration the expected information power of the sample.[35] Since this is the first study in this population, it is difficult to determine how heterogeneous participants' experiences will be. Qualitative interview studies relating to health tend to use between 18 and 45 interviews,[36] and so 40 interviews in total (with 20 per patient group) is expected to be a sensible and feasible number. We plan to use reflexive thematic analysis (TA).[37] Reflexive TA recognises that themes are actively created by the researcher at the intersection of data and interpretive engagement, rather than awaiting discovery. This approach means there is always potential for new interpretation and so 'attempts to predict the point of data saturation cannot be straightforwardly tied to the number of interviews' (p210).[38]

Data analysis and statistics

Survey data will be analysed in SPSS and STATA. Findings will be considered statistically significant where p<0.05; however, we acknowledge that the use of p values to indicate significance has its limitations. Confidence intervals will also be presented. If there are significant demographic differences between participants who do and do not respond to the questionnaire by sex or IMD, we will calculate and apply weights to adjust for the possibility that the sample may not represent those with a cancer signal detected in the trial in relation to sex and deprivation level. All analyses will adjust for recruitment location (ie, one of eight Cancer Alliances). Descriptive statistics will be reported for all primary outcomes and secondary outcomes at each timepoint. This will include anxiety (STAI Score and % with 'very high' anxiety), psychological consequences of screening (total score and three separate dimensions: emotional, physical and social), test-specific concern and reassurance, understanding of results, information seeking and satisfaction. Mean STAI and PCQ Scores (with SDs) will be reported by sociodemographic and other explanatory variables. Hierarchical linear regression will be used to explore relationships between explanatory variables and continuous outcomes. Similarly, stepwise logistic regression will be used to explore relationships between explanatory variables and categorical outcomes. Profile analysis will be used to explore whether combined responses (regardless of cancer diagnosis) are different at any particular point in time, that is, by testing the 'flatness' hypothesis over time (ie, time 1 (T1), time 2 (T2) and time 3 (T3)) for each outcome. The Hotelling's Trace F(df), alpha and p value will be reported. Statistical differences between those with and without cancer diagnosed will be explored using profile analysis to establish whether one result group, on average, scores differently on STAI and PCQ Scores regardless of timepoint (the 'parallelism' hypothesis) and also whether cancer patients and those with no cancer found following further tests have a similar pattern of response over the course of time (the 'levels' hypothesis).

Qualitative data collected during the semistructured interviews will be analysed using reflexive TA. This is an interpretive approach to analysing qualitative data supporting the researcher to identify themes and patterns in the data set.[37] There are six phases of reflexive TA: familiarisation, coding, generating themes, reviewing and developing themes, refining and defining themes and producing the report. These can overlap and there is flexibility as the researchers move through these phases. The software NVivo will be used to facilitate data coding and management.

Patient and public involvement

A Patient and Public Involvement (PPI) Panel was established in May 2021. Our panel includes five representatives aged 50–70 years old and includes people with and without personal cancer experience. Our PPI Panel has supported the design and the development of the study protocol and study materials (participant information sheets, consent forms, questionnaires) and will contribute to patient/public facing dissemination. Field notes are used to record all discussions. Contributions to the materials are documented, and we will make these available in a working paper on OSF. PPI activity will be reported using the GRIPP2 checklist[39] to ensure quality and transparency.

ETHICS AND DISSEMINATION

Ethical approval for this work has been granted by the Wales Research Ethics Committee as part of the NHS-Galleri trial ethics application (Ref 21/WA/0141). The studies have also been registered on the King's Data Protection Register (ID#17436). Participants will have signed a consent form as part of the main trial that included specific consent to being contacted by KCL about future research including interviews. Return of a paper survey or completion online will be considered consent to participation in the survey. This will be made clear to participants with the following text printed in bold on the front of the questionnaires: 'By sending your completed survey to KCL, you are consenting to take part in the survey.' This consent process will also be described to participants in detail in the information sheet that is sent with the survey. Participants selected for interview will be required to sign and return a consent form before the interview takes place. Throughout the trial, a study helpline will be available to all participants, and those with a cancer signal are reminded of this when given their result. This number is also included in the information sheet and on the front of the questionnaire. Results will be disseminated via peer-reviewed publication and presentations at national and international conferences. Reporting will be supported by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[40] and COREQ (Consolidated criteria for reporting qualitative research) guidelines.[41]

DISCUSSION

The findings of this study will help to improve understanding of the psychological impact of having a cancer signal detected by MCED screening and inform the development of procedures, supporting information and interventions to minimise MCED screening-associated anxiety. Findings will inform UKNSC recommendations regarding adoption of MCED screening and will support any future roll out. We will also be able to explore whether psychological impact is pronounced in particular groups (eg, by age

or biological sex), and whether particular population subgroups may consequently require additional support if MCED testing is implemented at a national level.

Comparisons will be made with previous research in the cancer screening context. Preliminary data from the prospective Pathfinder study,[42] in the USA suggest that having a cancer signal detected through MCED screening can result in increased anxiety, relative to those that do not have a cancer signal found, but this decreased towards baseline within 12 months. This will be the first UK study to explore anxiety and other psychological outcomes in the context of MCED blood testing within an asymptomatic population. Exploring this within the trial context means that psychological outcomes can contribute to decisions about implementation, rather than being an afterthought. This is an important step in acknowledging the potential for screening to result in a range of harms, including non-physical harms.[43]

Considerable steps have been taken in the context of the NHS-Galleri trial to ensure that the recruited sample represents the wider population in terms of age and deprivation and that sufficient numbers are recruited from groups typically under-represented in clinical trials (eg, those from ethnic minority backgrounds). However, there may still be some volunteer bias particularly in the sIG(n)al study where participation requires completion of additional questionnaires, as opposed to just clinical data. In addition, though interpreters are available to those who need them in NHS-Galleri (ie, for consent and clinic visits), we have not been able to use interpreters/translations for the present substudy.

Logistical aspects of delivery (eg, how and where blood test appointments are available and how results are communicated) have the potential to influence experiences and consequently emotional responses. The way that the test has been offered in the clinical trial context may not reflect exactly how an MCED screening programme would look if implemented, so the sIG(n)al findings may not be fully generalisable to a routine context.

The trial design has also influenced the research questions for the sIG(n)al substudy. For example, findings will allow us to explore the psychological impact of particular result combinations offered within repeated MCED screening (including those who have a signal detected again in round 2 screening and those that no longer have a signal detected). However, because results are not communicated to participants who do not have a cancer signal detected in round 1 (to maintain trial blinding), we will not be able to explore the impact on those who only have a signal detected at the second screening round.

The sIG(n)al substudy has been designed to provide a holistic understanding of the broad psychological impact of MCED screening, as well as including qualitative work to explore experiences in more depth. The limited timeline for the project makes it difficult to ascertain longer-term impact on behaviour, but we will assess self-reported changes to inform further investigation of this.

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Competing interests GRAIL, LLC funds full salaries of LAVM and NS-B, as well as 20% of JW's salary via a contract with King's College London (KCL). JW is also supported by project funding from GRAIL, LLC through a KCL contract. This funding also covers article processing charges. All other authors report no conflicts of interest.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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