The NHS-Galleri multi-cancer screening trial: explanation and justification of unique and important design issues

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Abstract

Despite there being a plethora of multi-cancer early-detection tests, NHS-Galleri (ISRCTN91431511) is the only randomized controlled trial (RCT) of a multi-cancer liquid biopsy in a screening setting thus far. The NHS-Galleri trial has generated much debate, and it has been criticized in the medical press. Some of these criticisms stem from differing opinions over the choice of primary endpoint, others from poor reporting in statements to journalists from those not directly involved in the trial. Some of the debate is positive, and relates to the speed of enrolment, and the equity in participation, which have shown what is possible in large population-based RCTs. Here we explain our reasoning for undertaking the trial and designing it in the way we did. We focus on the reason to consider multi-cancer screening and why we felt that the results from non-randomized clinical studies of GRAIL's Galleri test justified a large RCT. We also consider the very slow progress in adopting effective cancer screening historically and in reducing cancer mortality through early detection. There is a need to plan now for future research and implementation depending on the results of the trial. NHS-Galleri is the first double-blind cancer screening RCT. It also, unusually, uses late-stage cancer incidence (rather than cancer mortality) as its primary outcome.

Keywords: Advanced stage; cell-free DNA; circulating tumor DNA; health inequalities; late-stage; multi-cancer early detection; nested analyses; pilot implementation; randomized controlled trial; sensitivity; surrogate endpoint; trial design.

Background

NHS-Galleri (ISRCTN91431511) is a randomized controlled trial (RCT) designed to assess the clinical utility of annual screening with GRAIL's multi-cancer early detection test (MCED).[1] The trial commenced in August 2021. It completed recruitment in July 2022 and completed the third round of blood sample collection in July 2024. Participants are now being followed for cancer incidence. Results are expected in 2026.

There have been misunderstandings in the press over the status of a pilot implementation of MCED screening by NHS England for which a decision was made not to proceed. The pilot was never part of the NHS-Galleri trial. NHS England had made provision to run a pilot in parallel with the trial (but in different parts of the country) if early results from the trial looked to be extremely promising. There was no planned interim analysis of the trial, but it was agreed that named individuals within NHS England could receive a closed report (ordinarily only shared with the trial's Independent Data Monitoring Committee) with limited unblinded results pertaining to the first-year post randomization. It should be emphasized that the closed report did not include results on cancer mortality nor on the incidence of stage III+ cancer (the primary endpoint of the trial). Whatever the results from the first year, the trial would have (and did) continue to complete the third round of blood collection (screening) and subsequent follow-up. In the event, the results, to which we as the chief investigators are blinded, were insufficient to justify the running of a pilot screening program alongside the trial. It is reported that "the first year data showed a high level of accuracy for the test" but NHS England did not find preliminary results from the first year of the NHS-Galleri trial "compelling enough to justify proceeding straight away with a large-scale pilot program of the test in NHS clinical practice".[2] It is our understanding that the 12-month results in terms of a reduction in stage IV cancers needed to be exceptional to trigger the pilot. We think that that was never realistic due to the impact of prevalent cancers on the early results in screening trials. For instance, the National Lung Screening Trial, which demonstrated a significant reduction in lung cancer mortality

after three rounds of annual screening[3], did not find any reduction in stage IV cancer in the first round[4].

Why multi-cancer screening?

Cancer is common – about half of people will be diagnosed with cancer[5] – and nearly a quarter of deaths are from cancer. For most cancer sites, the difference in fatality from early- to late-stage is dramatic. Current screening programs target a few types of cancer which cause just 17% of cancer deaths in the UK. But each screen has a non-negligible chance of a false-positive result, and most people screened regularly for several cancer types will have at least one false-positive over their lifetime. Further, the more single cancer screening programs the less likely that any one individual will participate in all of them. A single multi-cancer test may identify many types of cancer. Provided false positives can be controlled, MCEDs offer great potential for screening. A test detecting 20% of all early-stage cancers is likely to have greater benefit than one that finds 80% of a single cancer type. But with their emphasis on specificity over sensitivity, current MCED tests would not replace colorectal, breast or lung screening – rather they would compliment existing screening programs.

Blood tests analyzing cell-free DNA (cfDNA) for biomarkers of cancer have received great interest. The larger the tumor burden (both macro and microscopic) the more cfDNA will be shed.[6-8] Similarly, the greater the cell turn-over, proliferation and underlying genome instability, the more cfDNA will be shed. Thus, the sensitivity of a cfDNA-based test will likely increase with tumor size and aggressiveness.

There are great inequities in cancer control globally both between and within countries. In high-income countries, that often translates to more later stage cancers in those who are more deprived, and often those from ethnic minorities. Since those who are currently diagnosed late have the most to gain from screening, multi-cancer screening has the potential to reduce inequalities. However, within countries, cancer screening coverage is lowest in those who are most

disadvantaged. Thus, ironically, introducing a new cancer screening program could exacerbate inequalities. But increased health inequalities is by no means inevitable[9]. A focus on reducing inequalities requires quality management and targeted communication strategies to reach those with the greatest need.

Why an RCT?

By 2020, GRAIL had evaluated Galleri, a locked test (assay and algorithm), in clinical studies. The test was only rarely (0.5%) positive on bloods from people without cancer but was positive in about half (51.5%) of patients (already diagnosed) with a mix of stages and over 50 different cancer types[10]. Sensitivity increased with stage (17%, 40%, 77% and 90% for stages I, II, III, and IV, respectively). Stage-specific sensitivities were higher for 12 pre-specified cancers responsible for >60% of UK cancer deaths (37%, 70%, 87% and 93%).[11] Sensitivity for some stage II cancers were higher: 80% for lung, 85% for colorectal, 65% for esophagus; but only 5% for prostate. When positive, Galleri correctly identified the site of origin (on the first attempt) in 88.7% of cancers. In a prospective longitudinal study, PATHFINDER, the (original version of the) Galleri test led to the diagnosis of 36 cancers in 35 patients.[12] Over the following 12 months, there were a further 86 cancers in test negative individuals, corresponding to a "sensitivity" of 29.5% (95% confidence interval 22-38%). However, only 9 (10.4%) of the 86 "interval" cancers were stages III or IV, and 38 were screen-detected (with a different screening test).[12]

At the end of 2020, we felt that the performance characteristics estimated from retrospective clinical studies justified evaluation of clinical utility in a prospective RCT. Modelling suggested that the impact of screening on prevention of late-stage cancer and reduction in cancer mortality could be substantial[13]. But we had no empirical evidence that there would be any clinical benefits from annual screening. NHS-Galleri was designed to provide that evidence.

Alternative designs were briefly considered but quickly rejected. A single arm prospective trial (such as PATHFINDER[14]) has a role in demonstrating that testing asymptomatic individuals can

detect cancer and to empirically validate the positive predictive value in a screening population. It also provides data on the stage distribution of screen-detected cancers. But this would not be sufficient to demonstrate clinical benefit of screen detection, nor would it be sufficient to justify a screening program. Similarly, although it might be possible to demonstrate impact on cancer mortality through a well-designed large-scale pilot implementation, we did not feel that the evidence justified such a pilot.

Sensitivity:

Whilst it is desirable for a screening test to have high sensitivity for early-stage disease, it is not necessary. Screening with the guaiac fecal occult blood test has reduced colorectal cancer mortality in many countries despite a sensitivity of only 40-70%. By comparison, the sensitivity of Galleri to detect (already diagnosed) colorectal cancer was 82%: 43% for stage I and 85% for stage II.[10]

A single-cancer test with 100% sensitivity for the targeted cancer would be unlikely to have an all-cancer sensitivity of more than 10-30% in a screening population. For instance, in the UK, breast cancer accounts for about 30%, and bowel cancer for about 11%, of all cancers; and 32% of all cancers diagnosed in NLST (a trial targeting individuals with high lung cancer risk) were of lung cancer.[15]

The usefulness of cancer screening depends on its benefits and harms. The higher the sensitivity to potentially fatal cancers the better, but the potential impact of population screening with an MCED of modest sensitivity may still be substantial. Using published site- and stage-specific sensitivities for Galleri, and the site- and stage-specific fatality, modelling predicts that annual screening could over the long-term prevent 17% of cancer deaths in screened individuals.[16] 17% was the smallest modelled reduction from all the scenarios considered and included allowance for the stage-specific hazard ratio of a screen-detectable cancer being three times that in a cancer that is not screen-detectable. It does, however, apply only to those who comply with annual screening.

Such a reduction is by no means certain, but the potential necessitates generation of high-quality RCT evidence to determine whether it can be achieved. A more recent microsimulation model of 14 solid tumor cancer types predicted an 18% reduction in cancer mortality over a 10-year horizon in the general US population.[17]

A 17% reduction in cancer deaths would be transformative. By comparison, initiatives based on accelerating diagnosis in symptomatic patients have had at most modest impact on mortality. Trends in cancer mortality between 1993 and 2018[18] provide no indication of an accelerated decline following the introduction of two-week wait referrals for suspected cancer in 2000.

We note that the modelled 17% reduction in cancer mortality is after several years of annual screening. We anticipate a much smaller effect within a year of the first (prevalent) screen because most cancer that result in death within a year of randomization will have already been advanced at the time of the first blood draw and screening may have been offered too late to make a difference.

The lack of sensitivity of Galleri to non-aggressive cancers such as thyroid, low-grade prostate, and screen-detected ER-positive breast[10] means, together with the above mentioned correlates of ctDNA shedding (tumor burden, proliferation and genome instability), that we are less concerned about the potential for overdiagnosis. Although there could be some overdiagnosis of hematological cancers. NHS-Galleri will study overdiagnosis. Five years after the last participant was randomized, we will test the stored baseline sample from control-arm participants who have been diagnosed with cancer. We will then compare the cumulative incidence of “baseline test-positive cancers” between the arms. We anticipate an initial excess in the screening-arm, due to earlier diagnosis, that will decrease over time. By restricting analysis to the small proportion of participants who may have been over-diagnosed from their baseline screen, we greatly improve the power to study overdiagnosis.[19]

Specificity:

Some commentators have questioned the practicality of extensive investigation of positive Galleri tests. With annual screening from age 50-77 (close to 100% uptake and 99.5% specificity), there would be ~100,000 individuals with a false-positive screen in England each year.[20] However, in 2022/23 there were 2.98 million urgent referrals for suspected cancer (an increase of 147,960 from the previous year) and 94% of these did not lead to cancer diagnosis.[21] 100,000 additional negative investigations, whilst substantial, is less than 4% of the current total. If such an increase were to result in 10% reduction in cancer mortality, it would be worthwhile.

Galleri's specificity of 99.5%[10] compares favorably with that of other screening tests. In the UK, the specificity of bowel screening FIT is about 94%[22] and the specificity of mammographic screening is 90-98%. Equivalently, 12 of every 200 people screened by FIT have a false positive test compared with 1 in every 200 with Galleri.

Precautionary principle

A balance is needed between the precautionary principle (i.e., screening should not be introduced until proven to cost-effectively do more good than harm) and guarding against the "perfect" becoming "the enemy of good" (i.e. rejecting or delaying the introduction of a good screening program because the evidence whilst strong is not overwhelming). Historically, it has taken 10-15 years from publication of RCT evidence of a benefit to complete roll-out of a cancer screening program. For instance, in 1996[23,24] two RCTs showed screening by fecal occult blood testing reduced mortality from colorectal cancer. A national Bowel Cancer Screening Program was introduced in 2006 and completed roll-out in 2010.[25] UK bowel screening was predicted to prevent ~2000 deaths/year.[26] If screening had been safely and efficiently rolled-out 10-years earlier some 20,000 deaths would have been avoided. More needs to be done to accelerate national uptake of cost-effective screening[28]. A first step would be to accelerate the generation of quality evidence.

A UK MCED screening program might involve collection of plasma from 5-18 million people each year (depending on age-range and frequency of screening) and the management of 50,000 – 200,000 positive results. That will be a substantial undertaking. We should be thinking about that challenge now. There are many blood-based MCED tests being developed or evaluated for screening. If one is shown to substantially reduce cancer morbidity and mortality with very little harm, we will want screening to be rolled out quickly and efficiently whilst ensuring that all sections of society benefit. Even a two-year delay in implementation could result in an additional 28,000 cancer deaths in the UK alone.

An independent health economic analysis of the NHS-Galleri trial is planned. Cost-effectiveness is outside of the scope of this paper, but others have estimated an incremental cost-effectiveness ratio (ICER) of $66,000 per Quality Adjusted Life Year (QALY) (range $49,000-$116,000 depending on assumptions) based on annual screening with a test that costs $949.[27] It seems likely that the cost of liquid biopsies will fall exponentially over the coming decade. With apologies to health economists, we offer this crude calculation as to at what price per test, multi-cancer screening might be cost-effective. We assume there is no impact on the cost of cancer treatment (others have estimated a saving of $5241 per person screened annually from age 50 to 79 primarily based on a reduction in stage IV cancer which is extremely expensive to treat in the US[27]), and a willingness to pay is £30,000 per QALY (noting that a threshold of $100,000/QALY is often used in North America). If, on average, screening those aged 50-79 yielded 10 QALYs per cancer death avoided, then one would need to prevent one death for every 2000 screens (i.e., 50 per 100,000) to make it affordable at £150/test. Cancer mortality aged 55-84 is about 800/100,000/year, so screening at £150/test would need to prevent about 6.25% (50/800) of cancer deaths. On the other hand, if annual screening prevented 17% of cancer deaths, the test could cost up to £400 and still meet the willingness to pay threshold. A more expensive test might only be used every 18 months or biennially or might be restricted to a narrower age-group. Some will consider these speculations as premature and too rosy. But it is only through a trial that we will be able to better estimate the likely impact on QALYs.

Trial design

There are two aspects of the NHS-Galleri design that are unusual. It is the first double blinded cancer screening trial; and the primary endpoint is incidence of advanced stage cancer (most cancer screening trials use cancer-specific mortality).

Blinding:

In drug trials, blinding is the gold-standard. In NHS-Galleri, randomization takes place after participants give their first blood sample; they are only unblinded if they are in the intervention arm and their test is positive. Thus, participants are invited to return for annual blood samples without knowing which arm they are in. Previous cancer screening trials have not attempted blinding either because of concerns about placebo tests/scans or because those randomized to control do not even realize that they are part of a trial (Zelen design).

Nevertheless, NHS-Galleri has been criticized because it will not permit evaluation of change in behavior following a negative screen.[28] However, it is not possible to estimate the impact of a negative *routine* screen on behavior from an RCT of an *experimental* screening test. In routine screening, participants are told that there is strong evidence that the benefits outweigh the harms and that a negative screen means "low-risk not no-risk".[29] By contrast, trial participants are told that the screening test may or may not work.

There are, however, advantages of collecting and storing blood from control-arm individuals. Thanks to blinding, randomization can only influence mortality in those with a positive screen. At 5 years, we will test all stored samples from controls who have died of cancer. By focusing on cancer deaths in those with a positive Galleri test, we have good power to study cancer mortality.[19,30] There is no need to test all control samples because we aim to show a reduction in "cancer deaths with a positive sample amongst all those randomized" rather than "cancer deaths amongst those with a positive sample".

Trial endpoint:

Traditionally, trials of screening for invasive cancer use target-cancer mortality as the primary endpoint.[31] Increasingly, people are concerned that using cancer-specific mortality as the only primary endpoint is too slow and too blunt an instrument[32]. Whilst the primary endpoint of NHS Galleri is advanced stage cancer, cancer mortality will be reported two years later. This acknowledges that it is theoretically possible for a screening test to reduce late-stage cancers without impacting on cancer mortality. That could happen for a variety of reasons. (i) Screen-detected cancers could be "born to be bad". That is, despite being diagnosed at an early stage, these cancers are highly aggressive and do not respond to treatment. (ii) Earlier initiation of treatment for screen-detected cancers makes no difference – the patient will die on the same date whether diagnosed via screening or later via symptoms. This might arise if there is little difference in survival between early and late-stage cancers: with either poor survival even of early-stage cancer or excellent survival even of late-stage cancer.

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)[33], UK Flexible Sigmoidoscopy Trial[34], the Telemark trial of flexible sigmoidoscopy[35], and the lung component[36] and the ovarian component[37] of the US Prostate, Lung, Colorectal and Ovarian (PLCO) trial all took at least 15 years to publish the impact of screening on cancer mortality. The National Lung Screening Trial (NLST) took 9 years[3]. With cutting-edge technologies, screening (and treatment) will have advanced over such a period and a definitive answer regarding the trial intervention will no longer be of relevant. Negative trials about chest X-rays for lung cancer screening, tell us nothing about low-dose CT. The trials of mammographic breast screening were (mostly) conducted when treatments for both early and late breast cancers were very different from those used today and, at all stages, 5- and 10-year relative survival were far worse than they are today. Thus, the mortality advantage of diagnosing a breast cancer at stage II rather than at stage III will be very different than in the trials and it is not possible to directly infer the mortality benefits of screening. The rapid pace

of advances in liquid biopsies makes the case for accelerated research programs. Carrying out different studies in parallel (rather than in series) will help, but we also need to consider alternative endpoints that provide a good reflection of a meaningful outcome.

The reasons for use of stage III+IV cancers as the primary endpoint are:

1. Modelling suggests that if Galleri screening reduces cancer mortality, it will work *primarily* by preventing cancers from progressing to stage III or IV.[38]
2. Meta-analyses[39,40] of cancer screening trials show that the reduction in the incidence of advanced cancer in each trial is correlated with the reduction in cancer mortality in that trial. Although the authors of these two meta-analyses disagree on the interpretation of those findings, when combining results from RCTs of several types of cancer screening, there are only a few outliers to the general trend.[41] Thus, the evidence to date, is that a statistically significant reduction in all stage III+ cancers will only be observed if screening causes a reduction in cancer mortality. There are concerns that these old trials were mostly based on imaging or protein biomarkers whereas Galleri is looking for circulating tumor DNA. Since shedding of DNA is a hallmark of an aggressive cancer, there is concern that cancers screen-detected by Galleri are "born to be bad" and even those diagnosed at an early stage will be rapidly fatal. Although, stage-for-stage cancers detectable by Galleri have worse prognosis that those that are not detectable, there is no suggestion that their survival is any worse than observed in SEER as a whole.[42]
3. A trial powered to study cancer mortality would need to be substantially larger, would require at least a further two years of follow-up after the last screen and would likely require an additional two rounds of screening. For instance, Hu, Prorok and Katki propose a trial in 200,000 people lasting 7-9 years with 5 annual screens.[43] By comparison NHS-Galleri randomized 140,000 people with 3 annual screens and will publish approximately 4 years after starting.

4. We will study the numbers who either die of cancer or are diagnosed with stage III and IV cancer in a sensitivity analysis. This endpoint might be called death-updated stage[44].
5. The main outcome is advanced stage at 3 years. However, everyone will be followed at least until 5 years after the last participant was randomized at which point the trial will be analyzed in terms of cancer-mortality.

If there is both a statistically and clinically significant reduction in advanced stage, and if other safety and health-economic criteria are met, we anticipate there will be a pilot implementation of a Galleri-based screening program. Importantly, if there is a statistically significant reduction in advanced cancer at 3 years, but no reduction in cancer mortality at 5 years (using the nested analysis), such a pilot should not lead automatically to a screening program. Rather one would need to synthesize the evidence from a variety of studies to determine whether it is the reduction in advanced stage cancer or the absence of reduction in cancer mortality that is the aberrant result. But if the results are consistent, by acting on the 3-year results, society will have gained two years, and many thousands of people will have been prevented from dying from cancer.

It has been suggested that waiting two-years for the mortality outcomes would be sensible. We do not agree with this. What is gained by waiting for mortality? Whether or not we wait, we would want to run a very large screening pilot. Such a pilot would be substantially, cheaper per 10,000 people screened than an RCT. The safety (in terms of harms) will already be established from the RCT (there will be very little additional evidence on harms from the additional follow-up because most harms from screening are almost instant). If screening has substantial harm, there will be no pilot. Pilots of cancer screening in the UK have not inevitably led to immediate roll-out of that screening (use of HPV testing to triage low-grade cytology is a case in point). If the pilot is well designed, it will provide considerable additional data on mortality. Had the trial been designed to study mortality as the primary outcome, we agree with Hu et al[40] that it would have need to be 50% larger and to run for an additional 3-4 years (not simply an additional 2 years).

Provided the trial is not adversely affected by lack of adherence with annual testing, a negative result in terms of advanced stage will imply that, at best, the clinical benefit of annual screening with the Galleri test is modest. By showing in just over four years that annual screening with Galleri provides insufficient clinical benefit, we will limit investment in this one trial and allow the cancer screening community to move on and consider trials of newer more sensitive MCED tests much sooner than had we waited for a trial powered for a mortality endpoint that would likely have taken a further three years.

Conclusion

The only way to know whether regular screening with an MCED can reduce cancer morbidity and mortality is through a well-designed and executed RCT. However, in our opinion, traditional approaches have not necessarily always served society well. Pragmatism demands that we consider new designs. NHS-Galleri is uniquely placed to provide early answers to important questions related to the benefits and harms of MCED screening, using innovative and robust study designs.

Data availability

Not applicable – no data were generated or analyzed for this manuscript.

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Conflicts of interest

The authors of this paper are the joint chief investigators and the lead statistician on the NHS-Galleri trial. In that capacity, they speak regularly with GRAIL. The trial is run by the Cancer Prevention Trials Unit (CPTU) which is completely independent of GRAIL but receives funding from GRAIL via its host institution to run this trial. When the trial started CPTU was hosted by King's College London; it is now part of Queen Mary University of London. The trial has an Independent Data Monitoring Committee and a Trial Steering Committee with an independent chair and majority membership that is independent of the trial team and GRAIL.

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Author contributions

PS wrote the original draft. All authors contributed to the conceptualization, verification, and review and editing of the manuscript

Ethical considerations

The NHS-Galleri trial is conducted according to the guidelines of the Declaration of Helsinki. It received ethical approval from Wales Research Ethics Committee 1 (Ref: 21/WA/0141). It also received Health Research Authority (HRA) approval with support from the Confidentiality Advisory Group (Ref:21/CAG/0056), under Regulation 5 of the Health Service Regulations 2002 (Section 251 support), for NHS Digital to send out invitation letters to eligible invitees to seek consent.

Consent to participate

Not applicable for this paper. All participants provided written informed consent before participation in the NHS-Galleri trial.

Consent for publication

Not applicable

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