QuicDNA Max

Research Programme (multi-site)

Master Protocol Version 1.0

23 October 2025

Sponsor:	**Cardiff & Vale University Health Board**
Sponsor ref:	**9118**
Funders:	**Eli Lilly and Company Ltd,** **Merck Sharp and Dohme Ltd** **Office of Life Sciences** **Menarini Stemline UK Ltd** **Illumina, Illumina Centre**
REC ref:	**TBC**
IRAS number:	**363293**
ISRCTN:	**TBC**
Q-Pulse Template Number:	**TPL/003/2**

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

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

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

Trial Sponsor:			
Name	Position:	Signature	Date
Cardiff and Vale University Health Board Sponsor Representative: **Joanne Milner**	Research Governance Manager	*Signed via email 27/10/2025*	27 Oct 2025
Director:			
Name	Signature	Date	
Angela Casbard	*Signed via email 24/10/2025*	24 Oct 2025	
Chief Investigator:			
Name	Signature	Date	
Dr Magdalena Meissner	*Signed via email 28/10/2025*	27 Oct 2025	

General Information

This protocol describes the QuicDNA Max clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR

Contact Details – Chief Investigator

Chief Investigator

Dr. Magdalena Meissner

Consultant Clinical Oncologist

Velindre University NHS Trust

Velindre Road

Whitchurch

Cardiff

CF14 2TL

magdalena.meissner@wales.nhs.uk

Co-Investigators

Sian Morgan

Consultant Clinical Scientist

All Wales Medical Genomics Services

sian.morgan22@wales.nhs.uk

Professor Richard Adams

Clinical Director

Centre for Trials Research

adamsra3@cardiff.ac.uk

Research Partners

Esther Boots, PPI Representative estherboots@hotmail.com

Nigel Pearson, PPI Representative np_buns@hotmail.com

Harry Niece, PPI Representative harry_niece@hotmail.com

Sponsor Contact Details:

Joanne Milner

Sponsor Representative

Cardiff & Vale UHB

Research.governance@wales.nhs.UK

Trial Co-ordination:

The QuicDNA Max trial is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.

For **all queries** please contact the QuicDNA team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

Main Trial Email:	QuicDNAMAX@Cardiff.ac.uk
Senior Trial Manager:	Margherita Carucci
Trial Manager:	Georgina Gardner
Data Manager:	Terri Kitson
Senior Statistician	Angela Casbard
Trial Statistician:	Jennifer Condie
Data Analyst	Lawrence Raisanen
Research Administrator:	TBC
Head of AWMGS:	Sian Morgan Email: Sian.morgan22@wales.nhs.uk

Clinical queries

All clinical queries will be emailed to QuicDNAMAX@cardiff.ac.uk

Table of Contents

Glossary of Abbreviations

AWMGS	All Wales Medical Genomic Service
CF	Consent Form
CI	Chief Investigator
CRC	Colorectal Cancer
CRF	Case Report Form
CT	Computer Tomography
ctDNA	Circulating Tumour DNA
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
CUP	Carcinoma of Unknown Primary
ddPCR	Droplet digital PCR
DNA	Deoxyribonucleic Acid
GCP	Good Clinical Practice
GP	General Practitioner
HB	Health Board
IC	Informed consent
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MDT	Multi-Disciplinary Team
NHS	National Health Service
NSCLC	Non-small cell lung cancer
PCT	Primary Care Trust
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
R&D	Research and Development
REC	Research Ethics Committee

SMG	Study Management Group
SoC	Standard of Care
SOP	Standard Operating Procedure
SR	Secondary Resistance
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHB	University Health Board
UTIGB	Cardiff University IT Department

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued		Summary of changes made since previous version

2 Synopsis

Short title	QUICDNA MAX RESEARCH PROGRAMME
Acronym	QuicDNA MAX
Internal ref. no.	9118
Funder and ref.	Eli Lilly and Company Ltd Merck Sharp and Dohme Ltd Office of Life Sciences Menarini Stemline UK Ltd Illumina, Illumina Centre **The other funders will be listed in the sub-protocols.
Trial design	Multi-centre, non-interventional, biomarker platform study
Trial participants	Individuals with radiologically suspected or confirmed advanced cancers, or those who have developed resistance to existing therapies and have radiological evidence of disease progression
Planned sample size	The sample size will be determined based on the specific tumour type, clinical setting, and research question addressed. Each tumour-specific sub-protocol will follow its own design, tailored to the scientific objectives and clinical context.
Planned number of sites	Up to 6 health boards in Wales and Velindre University NHS Trust
Inclusion criteria	Participants will be eligible for inclusion if they: • Are willing and able to provide written informed consent • Are aged 16 years or older • Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 • Have a suspected or confirmed diagnosis of cancer

	• Meet any additional tumour-specific eligibility criteria, as outlined in the relevant sub-protocols
Exclusion criteria	Participants will be excluded if they: • Are unable or unwilling to comply with study procedures • Meet any tumour-specific exclusion criteria as defined in the relevant sub-protocols
Follow-up duration	Up to three years from the time of recruitment, unless otherwise specified in the relevant sub-protocol.
Primary objective	To evaluate the utility of liquid biopsy (ctDNA) genomic profiling across a range of tumour types in patients with either suspected or confirmed advanced cancer, including those already receiving treatment *Specific or additional primary objectives will be described in the individual tumour-specific sub-protocols.*
Secondary objectives	1. To evaluate the added detection capacity of ctDNA for clinically relevant mutations not identified through tissue-based testing 2. To assess the failure rate of ctDNA testing in comparison to standard tissue molecular analysis (where tissue is available). 3. To determine the proportion of patients for whom ctDNA provides the only viable molecular profiling data due to inadequate or unavailable tissue 4. To measure the timeliness of ctDNA report delivery and its availability at the point of treatment decision-making 5. To assess whether ctDNA results can reduce the need for invasive tissue biopsy procedures 6. To quantify the frequency of failed or non-diagnostic tissue biopsies that could be mitigated through ctDNA testing

	7. To investigate the detection rate of somatic and potentially germline mutations through ctDNA, including scenarios where confirmatory testing is indicated 8. To evaluate the frequency and clinical significance of incidental germline findings identified through ctDNA testing, and to determine the proportion of patients requiring confirmatory germline testing and referral to by Clinical Genetics 9. To assess the utility of ctDNA results in stratifying patients into standard-of-care treatments, biomarker-driven clinical trials, therapies accessed through Individual Patient Funding Requests (IPFR), or compassionate access programmes 10. To evaluate clinical outcomes, including treatment response, progression-free survival, and overall survival, according to whether participants had treatment modification based on ctDNA results *Further secondary objectives and specific endpoints will be defined in each tumour-specific sub-protocol.*
Exploratory objectives	• collection of additional biological samples and associated clinical data to support future research and technological innovation, including the potential for multi-omics integration and AI-driven cancer profiling • Evaluation of novel biomarkers, emerging genomic technologies, or unanticipated research questions that arise during or after the study
Primary outcomes	*Primary outcomes tailored to specific tumour types and clinical settings will be defined in the corresponding sub-protocols.*
Secondary outcomes	*Secondary outcomes will be specified in each tumour-specific sub-protocol, according to clinical context and research objectives*

Exploratory outcomes	• Proportion of participants with additional biological samples and clinical data available for multi-omics integration and AI-driven cancer profiling • Proportion of participants with results available from additional genomic, molecular, and circulating biomarker technologies beyond ctDNA, including new assays or liquid biopsy methods introduced during the study.

3 Trial Summary & Schema

3.1 Trial Schema

Detailed trial schema specific to specific cancer type is included in the relevant sub protocols.

3.2 Trial Lay Summary

The QuicDNA Max programme is a new research programme that will explore how a simple blood test, called a liquid biopsy, can help doctors better understand and treat different types of cancer. This test looks for cancer-related DNA in the blood, which can help guide treatment decisions and track how the disease changes over time.

When cancer cells die, they get broken down and their contents, including small fragments of DNA, are released into the blood. This is called circulating tumour DNA (ctDNA). Researchers have developed a new test that looks for ctDNA in the blood and detects the multiple genetic changes leading to tumour development. Finding DNA with genetic differences aids in diagnosing the type of tumour and helps doctors determine which treatment will be most effective.

Taking a blood sample — a “liquid biopsy” — is less invasive than a solid tissue biopsy, which for some patients may be difficult or impossible. Furthermore, ctDNA test results can be available sooner compared with tissue genomic reports.

The QuicDNA Max research programme will start by focusing on the following cancers, but more will be added if funding allows:

- Lung cancer that has stopped responding to targeted treatment
- Cancer of unknown primary (when doctors do not know in which part of the body the cancer started)
- Bowel (colorectal) cancer
- Prostate cancer

Participants consenting to take part into the specific sub-study in any of the six Health Boards in Wales or Velindre Cancer Centre will be asked to donate a blood sample for ctDNA testing.

4 Background

Cancer survival outcomes and the performance of NHS cancer pathways in Wales remain poor compared with both national and international standards [1]. Emerging genomic technologies, particularly liquid biopsy, offer the opportunity to accelerate access to targeted therapies, reduce reliance on invasive diagnostic procedures, and ultimately improve cancer outcomes in Wales [2,3].

The QuicDNA study (IRAS: 328841) was initiated as a pilot to assess the feasibility of integrating circulating tumour DNA (ctDNA) testing into the routine diagnostic pathway for lung cancer. In this study, the All Wales Medical Genetics Service (AWMGS) provided genomic profiling of blood samples using its 500-gene ctDNA next-generation sequencing (NGS) panel. Preliminary results demonstrated that ctDNA testing at the point of suspicion of lung cancer can reduce the time to clinically actionable genomic results compared with standard tissue testing, thereby expediting treatment decisions for patients. Concordance between ctDNA and tumour tissue testing for actionable variants, those guiding eligibility for targeted therapies, was 98%, confirming the reliability of ctDNA testing in this setting. The QuicDNA study not only provided robust feasibility data but also enabled the clinical adoption of liquid biopsy within NHS Wales, reducing diagnostic delays and alleviating the psychological burden associated with uncertainty for patients and their families.

In May 2025, the NHSE Cancer Test Directory incorporated ctDNA multi-target NGS panel testing for patients with radiologically suspected stage III or IV lung cancer who are unsuitable for curative surgery or radical radiotherapy and who have an ECOG performance status of 0 to 3. The directory now recommends ctDNA NGS testing to detect EGFR, ALK, BRAF, KRAS p.(G12C), MET exon 14 skipping, ROS1, RET, NTRK1, NTRK2, and NTRK3. In addition, ctDNA testing is endorsed for patients with newly diagnosed non-small cell lung cancer where diagnostic molecular testing has failed and re-biopsy would otherwise be required [4].

Building on the experience, infrastructure, and outputs of the pilot, the initiative now advances to the QuicDNA Max programme. This new phase broadens the scope of ctDNA testing to include multiple tumour types and longitudinal monitoring, generating real-world evidence to support the mainstreaming of liquid biopsy testing across NHS Wales.

QuicDNA Max is also designed to strengthen the clinical and technical workforce, establish sustainable partnerships, and position Wales as a leader in precision oncology.

The initial clinical focus of QuicDNA Max will include the following cancer types:

- Lung cancer secondary resistance
- Carcinoma of Unknown Primary (CUP)
- Colorectal cancer
- Prostate cancer

Through these strands, QuicDNA Max will extend the benefits of ctDNA-based profiling beyond lung cancer, embed precision oncology into cancer pathways across Wales, and contribute to the development of a sustainable, evidence-driven genomic medicine service. While the initial focus is on the tumour types listed above, the programme is designed to be flexible and may incorporate additional cancer types in future phases, ensuring adaptability to evolving clinical needs and emerging opportunities in precision oncology.

Table 1. Advantages of ctDNA Testing

Feature	ctDNA Testing	Tissue-Based Testing
Invasiveness	Minimally invasive (blood draw)	Invasive (biopsy or surgical resection)
Turnaround Time	Rapid	Slower (2–4+ weeks), requires pathological review upfront
Sample Availability	Easily repeatable	Dependent on tumour site and procedure
Detection of Heterogeneity	Can reflect multiple tumour clones	May represent only one tumour region
Use in Monitoring	Suitable for serial testing	Not ideal for repeated sampling

5 Trial Objectives/Endpoints & Outcome Measures

5.1 Primary Objectives

To evaluate the utility of liquid biopsy (ctDNA) genomic profiling across a range of tumour types in patients with either suspected or confirmed advanced cancer, including those already receiving treatment.

Specific or additional primary objectives will be described in the individual tumour-specific sub-protocols.

5.2 Secondary Objectives

1. To evaluate the added detection capacity of ctDNA for clinically relevant mutations not identified through tissue-based testing.
2. To assess the failure rate of ctDNA testing in comparison to standard tissue molecular analysis (where tissue is available).

3. To determine the proportion of patients for whom ctDNA provides the only viable molecular profiling data due to inadequate or unavailable tissue.
4. To measure the timeliness of ctDNA report delivery and its availability at the point of treatment decision-making.
5. To assess whether ctDNA results can reduce the need for invasive tissue biopsy procedures.
6. To quantify the frequency of failed or non-diagnostic tissue biopsies that could be mitigated through ctDNA testing.
7. To investigate the detection rate of somatic and potentially germline mutations through ctDNA, including scenarios where confirmatory testing is indicated.
8. To evaluate the frequency and clinical significance of incidental germline findings identified through ctDNA testing, and to determine the proportion of patients requiring confirmatory germline testing and referral to by Clinical Genetics
9. To assess the utility of ctDNA results in stratifying patients into standard-of-care treatments, biomarker-driven clinical trials, therapies accessed through Individual Patient Funding Requests (IPFR), or compassionate access programmes
10. To evaluate clinical outcomes, including treatment response, progression-free survival, and overall survival, according to whether participants had treatment modification based on ctDNA results

Further secondary objectives and specific endpoints will be defined in each tumour-specific sub-protocol, depending on clinical setting and research priorities.

5.3 Exploratory objectives

- Collection of additional biological samples and associated clinical data to support future research and technological innovation, including the potential for multi-omics integration and AI-driven cancer profiling
- Evaluation of novel biomarkers, emerging genomic technologies, or unanticipated research questions that arise during or after the study

5.4 Primary Outcomes Measures

Relevant primary outcome measures tailored to specific tumour types and clinical contexts will be described in detail within each associated sub-protocol.

5.5 Secondary Outcomes Measures

Secondary outcomes will be specified in each tumour-specific sub-protocol, according to clinical context and research objectives

5.6 Exploratory Outcome Measures

- Proportion of participants with additional biological samples and clinical data available for multi-omics integration and AI-driven cancer profiling
- Proportion of participants with results available from additional genomic, molecular, and circulating biomarker technologies beyond ctDNA, including new assays or liquid biopsy methods introduced during the study.

6 Trial Design and Setting

The QuicDNA Max programme is a platform-based, prospective, multi-centre, exploratory diagnostic study conducted across NHS hospitals and clinics. The study is designed as an open-label, non-interventional framework with a master protocol governing multiple tumour-specific sub-protocols. These sub-protocols will address different clinical questions related to the utility, timing, and impact of circulating tumour DNA (ctDNA) testing across multiple tumour types and clinical settings, including both newly suspected and previously confirmed cancer cases. The study will evaluate ctDNA-based genomic profiling in terms of feasibility, diagnostic yield, turnaround time, concordance with tissue testing, and its impact on clinical decision-making.

The number of participants recruited will depend on tumour type, clinical setting, and specific research questions. Recruitment will follow a phased rollout across tumour-specific cohorts.

There is no randomisation or blinding, as all participants will undergo ctDNA blood testing in parallel with standard care. Comparison with tissue biopsy data, where available, will serve as the internal control.

6.1 Risk Assessment

A specific Trial Risk Assessment will be completed for each sub-protocol to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to standard practice
- How the risk will be minimised/managed

The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 22.1).

7 Site and Investigator Selection

This QuicDNA Max programme will be carried out at participating sites within NHS Wales with the potential for English sites to participate, if laboratory capacity allows. All sites who are interested in participating in a specific sub-study will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the study.

Before any site can begin recruitment, a Principal Investigator (PI) at each site must be identified. The following documents must be in place and copies sent to the QuicDNAMax@Cardiff.ac.uk study email account (see contact details on page 4):

- The confirmation of Capability &Capacity from the site's R&D Department following sharing of local information pack
- Favourable opinion of Main Ethics committee
- A signed Trial Agreement

- Current Curriculum Vitae (CV) and GCP training certificate of the PI
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper

Further documents may be required in the specific sub-protocols.

Upon receipt of all the above documents and following attendance at the site initiation which will be conducted via Teams online, the Trial Manager (TM) will send written confirmation to the PI/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive anything relating to trial intervention and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

8 Participant Selection

Participants are eligible for the study if they meet all the inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before registration.

8.1 Inclusion Criteria

Participants will be eligible for inclusion if they:

- Are willing and able to provide written informed consent
- Are aged 16 years or older
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2
- Have a suspected or confirmed diagnosis of cancer

- Meet any additional tumour-specific eligibility criteria, as outlined in the relevant sub-protocols

8.2 Exclusion Criteria

Participants will be excluded if they:

- Are unable or unwilling to comply with study procedures
- Meet any tumour-specific exclusion criteria as defined in the relevant sub-protocols

9 Recruitment, Screening and Registration

9.1 Participant Identification

Participants will be identified primarily by members of their existing clinical care teams. This includes consultants, doctors in specialty training, research nurses, and clinical nurse specialists who are directly involved in the diagnostic or treatment pathways of participants with suspected or confirmed cancer.

Identification will take place during routine clinical care within NHS hospitals and clinics across Wales with the potential for English sites to participate, if laboratory capacity allows.

Identifiable participant information will only be reviewed by healthcare professionals already responsible for the participant's care. Participants will be pre-screened against eligibility criteria through standard clinical documentation and multidisciplinary team (MDT) discussions. Clinicians will determine their suitability for inclusion.

The sources of identifiable information used for eligibility screening will include routinely collected clinical records, such as diagnostic imaging, histopathology reports, clinic letters, and electronic patient records. All such data will be accessed only by members of the clinical team with legitimate access.

If an individual meets the inclusion criteria, the initial approach will be made by a clinician directly

involved in their care, who will provide study information and a copy of the PIS and ICF and offer the opportunity to participate. The patient will be given adequate time to consider the study and given the opportunity to ask further questions. If the patient expresses interest, informed consent will be obtained by a member of the research team or delegated clinical staff trained in Good Clinical Practice (GCP).

Eligibility will be confirmed by the responsible treating clinician, typically a consultant or specialist involved in the diagnostic or oncological management of the participant.

9.2 Screening Logs

A screening log of all ineligible and eligible but not consented/not approached individuals will be kept at each site so that any biases from differential recruitment can be detected. When at site, logs may contain identifiable information, but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the QuicDNAMax@Cardiff.ac.uk periodically or when requested (see section 19 for further detail on data monitoring/quality assurance).

9.3 Recruitment Rates

Recruitment targets and rates will vary depending on tumour type and outlined in each tumour-specific sub-protocol. Estimated accrual per site and timelines will be defined within each sub-study.

9.4 Patient Enrolment

9.4.1 Informed Consent and Ethical Considerations

All patients enrolled in QuicDNA Max must provide written informed consent using the study Consent Form (CF), which follows the Participant Information Sheet (PIS). The consent process will be led by the Principal Investigator (PI) or a suitably qualified and GCP-trained member of the research team delegated by the PI.

Patients will be given sufficient time after the initial invitation to consider participation. Consent must be obtained before any procedures undertaken solely for research purposes. Patients will be given study team contact details for further questions.

Once signed, a copy of the consent form will be given to the participant, the original will be kept in the Investigator Site File (ISF), and another copy filed in the participant's hospital records. The right to refuse participation or to withdraw at any time, without giving a reason or affecting clinical care, will be respected.

Participation is voluntary and will not affect standard care, other trial eligibility, or access to treatments.

9.4.2 Genomic Results and Disclosure

As QuicDNA Max includes ctDNA (blood-based) genomic profiling, the study may generate results relevant to treatment as well as incidental findings. Patients will receive information before consent to understand these issues and may choose whether they wish to receive certain categories of results. Clinical Scientists performing genomic interpretation and reporting will align their practice to appropriate literature and guidelines.

The study will adopt a flexible-default model of consent (Table 1), where results directly relevant to the participant's cancer ("cancer of interest") will always be disclosed. Results unrelated to the participant's cancer, but with potential medical or familial significance, will be disclosed by default but patients may decline.

Any other or unanticipated findings that fall outside these categories will be considered on a case-by-case basis by the Trial Management Group (TMG), which will determine the appropriate approach to disclosure.

Table 2: Flexible-default model of consent in QuicDNA Max

Result type	Default action	Decline Results?	Notes
Cancer of interest (results with direct impact on treatment)	Always disclose	Not flexible	Guides therapy or trial eligibility
Familial cancer risk (findings relevant for relatives)	Disclose	Flexible	Participants may decline
Other medical conditions (not related to current cancer)	Disclose	Flexible	Clinically significant, but optional
Uncertain significance	Do not disclose	Not flexible	Mutation role unknown
Other/unanticipated findings	TMG decision	Case by case	Outside predefined categories

9.4.3 Content of Consent

The consent form will cover:

1. Collection of blood samples for ctDNA and related biomarker analyses
2. Risks and benefits of genomic testing
3. Secure storage and controlled access to patient data
4. No guarantee of clinical benefit from genomic profiling
5. Mandatory disclosure of results relevant to the patient's cancer; optional disclosure of other clinically significant findings
6. Referral to genetics services if germline findings of concern are identified
7. Clarification that treatment decisions remain at clinician discretion

8. Ongoing access to medical records and follow-up for up to three years, with possible phone contact for updates
9. Contact for new clinical trial opportunities arising from genomic results
10. No cost or payment to participants
11. Choice to receive results that do not have direct impact on the care of current cancer but may have significance to biological family members or may have potential medical impact to participant
12. Use of blood samples for genomic research in collaboration with NHS, academic, and commercial partners. Samples will not be sold and will be pseudonymised where possible.
13. Genomic data may be shared on secure public repositories without patient identifiers, but with basic demographic and clinical information
14. Consent to collect NHS Numbers and selected identifiers (initials, partial date of birth (month and year), NHS Number) to enable long-term follow-up using routinely collected NHS data for study objectives and related ancillary research. Identifiers will be securely stored at Cardiff University

9.4.4 Optional and Continuing Consent

Patients may consent to optional components (e.g., additional blood samples for storage in a Sponsor-approved biobank for future not-for-profit biomarker or genetic research). Preferences may be amended during the study.

Re-consent may be sought if clinically appropriate (e.g., re-referral to a trial). If participants progress on treatment, further blood samples may be collected, recorded in clinical notes, within protocol-defined limits.

9.5 Registration

Participant enrolment for this study will be using the QuicDNA Max study web-based system. Details of how to access the system will be supplied to Investigators as part of the trial set-up.

If any problem with the web-based system, sites are recommended to contact the trial team QuicDNAMax@Cardiff.ac.uk

10 Withdrawal and Lost to Follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time for any reason or be withdrawn from the study at the discretion of the investigator, e.g. should any untoward effect occur. The participants care will not be affected at any time by declining to participate or withdrawing from the study. In addition, a participant may be withdrawn by the investigator or the Sponsor if enrolment into the study is inappropriate, the study plan is violated, or for administrative reasons.

A participant must be discontinued from the study for any of the following reasons:

- Participant's decision to withdraw consent
- Investigator's decision to withdraw the participant
- Non-compliance with study procedure requirements
- Administrative reasons

If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to what aspect of the study the participant is withdrawing from. These aspects could be:

1. Withdrawal from samples collection

   Any samples that are taken prior to the date of withdrawal are to be kept (unless the participant has specified a wish for the samples to be destroyed – see Withdrawal level 3 below). Any samples that arrive at the laboratory that have been taken after the date of withdrawal should be destroyed by the laboratory and noted on the sample destruction log.

2. Withdrawal from further data submission

   Participant may withdraw consent for any further data to be submitted. Data available in participant notes up to the date of withdrawal may be submitted, but no further data can be collected by, or submitted to, the CTR.

3. Withdrawal from any previous sample to be used

   Participants may request that all previously collected samples are destroyed to prevent use in future research, though it may not be possible to retrieve samples already donated for future research, e.g. if samples have been anonymised. Upon notification of a participant withdrawal via the relevant CRF form in the database, samples should be destroyed by the laboratory and noted on the sample destruction log.

For participants who consent and subsequently withdraw, the QuicDNA Max Withdrawal of Consent Form should be completed by the participant and signed by both the participant and the PI or a member of the trial team who has been delegated by the PI to undertake this activity. One copy of the Withdrawal of Consent Form will be given to the participant, the original copy will be kept in the Investigator Site File -ISF), and a further copy will be kept with the participant's hospital notes.

Completed participant withdrawal forms should not be sent to the CTR, since they will contain participant identifiable information. The participating site should advise the CTR of this withdrawal by completing the relevant Withdrawal form on the database.

Any queries relating to potential withdrawal of a participant should be forwarded to QuicDNAMax@cardiff.ac.uk

10.2 Lost to follow up

Participants who cease to attend the standard of care follow up visit prior to the end of the follow-up period will be classed as lost to follow up, if we do not have confirmation of death. Every effort will be made to obtain follow-up information on these participants, unless they have completely withdrawn from the study. Participants will be contacted by their local research team by telephone or letter. If

the participant is alive but not compliant with the protocol requirements, the minimum information the local research team will aim to collect is: date of disease progression and date of death. Participants lost to follow up will be replaced only if the primary endpoint is not evaluable.

Any missing data in our database will be verified by routine data available via Digital healthcare Wales if consent obtained by participants.

11. Trial Procedures

Study procedures will be performed at the screening/baseline visit by the PI or qualified designee.

11.1 Screening and Baseline assessments/procedures

Written informed consent will be obtained before any study-specific procedures are undertaken.

The key procedures undertaken and data recorded at the screening and baseline visit are:

- Informed consent
- Inclusion/exclusion criteria
- Registration
- Demographics
- Medical history
- ECOG performance status
- Radiological assessment of disease by CT scan
- Up to 40ml Study blood sample collection
- SoC tumour tissue sample collection (depending on sub-study protocol requirements)

Further assessments specific to each tumour type are listed in the relevant sub-protocols.

11.2 Follow-up assessments

- Participant's status (alive or deceased)
- Treatment received

- CT scan response

Further assessments specific to each tumour type are listed in the relevant sub-protocols.

12. Central monitoring

Sites may be requested to submit staff delegation logs and screening logs to the QuicDNA Max trial manager at the frequency detailed in the study monitoring plan or on request. These will be checked for consistency and completeness.

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the registration form will be undertaken by an appropriately trained study team member following registration.

Sites will be expected to maintain oversight of study documentation held within the Investigator Site File (ISF). Checklists detailing the current version/date of version-controlled documents will be provided for this purpose. The trial manager may request documents from the ISF at any time.

Details relating to the informed consent process will be collected on the registration form and are subject to review by the trial manager as part of patient eligibility. A copy of the consent form for each patient entered onto the trial must be submitted to the Centre for Trials Research (Cardiff University) for verification (see Section 9.4). These will be checked for completeness and accuracy, including: correct version of the form used, patient initials in every box, patient name and signature, patient (or representative) personally completed date of signing, and confirmation that the person taking consent has signed/dated and is listed on the delegation log as performing this duty.

13 Statistical Considerations

13.1 Sample Size

As QuicDNA Max is a platform, non-interventional study, a formal statistical sample size calculation is not applicable to the overall master protocol. Instead, sample sizes will be determined for each tumour-specific sub-protocol, considering clinical feasibility, participant flow, and the specific objectives and outcome measures of each sub-study. Where applicable, individual sub-protocols will

include a statistical justification for their target sample size based on primary endpoints relevant to that tumour type or clinical setting.

13.2 Missing, Unused & Spurious Data

Detail provided in the Statistical Analysis Plan (SAP) for each sub protocol. As this is a non-interventional study with descriptive analyses of real-world practice, missing data will not be imputed. All participants are expected to receive a ctDNA blood test; the number and reasons for any missing ctDNA tests will be reported and tissue biopsy data will be reported where available. The number and proportion of missing demographic and clinical characteristics will be reported. Analyses will be presented for participants with available data, and the number and proportion of missing values will be reported. Where possible, missing data will be obtained from routine data available via Digital healthcare Wales if consent obtained by participants.

13.3 Procedures for Reporting Deviation(s) from the Original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

13.4 Termination of the Study

As this is a diagnostic, non-interventional platform study, early termination of specific sub-protocols or the overall QuicDNA Max programme may be considered if the clinical utility of the ctDNA test under investigation has been sufficiently demonstrated and the test is subsequently incorporated into national guidelines or the National Cancer Test Directory. In such instances, further data collection may no longer be scientifically justified.

The decision to discontinue any part of the study on these grounds will be made in agreement with the Sponsor and relevant oversight bodies, such as the Trial Steering Committee (TSC), and will be communicated to regulatory authorities and ethics committees as appropriate.

13.5 Inclusion in Analysis

All participants who provide valid consent will be included in the primary analysis population. Additional analyses may be conducted on subgroups, such as those with matched tissue samples, those with actionable genomic findings, or those with complete follow-up data. Analyses will be conducted according to predefined criteria outlined in each tumour-specific sub-protocol. Participants for whom no usable data is obtained will be excluded from analysis. will be included in the primary analysis population. Additional analyses may be conducted on subgroups, such as those with matched tissue samples, those with actionable genomic findings, or those with complete follow-up data. Analyses will be conducted according to predefined criteria outlined in each tumour-specific sub-protocol. Participants for whom no usable data is obtained will be excluded from analysis.

14 Analysis

14.1 Main Analysis

A detailed statistical analysis plan will be prepared for each sub protocol, specifying the planned analyses for the primary, secondary and exploratory outcomes. Descriptive statistics will be provided for baseline demographics and clinical characteristics and all feasibility, utility and clinical outcomes of ctDNA testing, with comparisons to tissue biopsy data where available. Analyses will be conducted on participants with available data for each outcome, with the number and proportion of missing values reported. Incidental findings will be line listed, and the number of affected participants will be reported. Categorical data will be summarised by frequencies and proportions. Continuous data will be summarised by mean and standard deviation, if data are normal, or median and Interquartile Range, if data are skewed. Where appropriate, results will be presented with 95% confidence intervals. Exploratory analyses may compare ctDNA and tissue biopsy outcomes (where both are available) using appropriate statistical methods, such as chi-square tests for categorical variables and t-tests for continuous variables. All analyses will be conducted using the statistical software Stata version 18 or higher.

14.1.1 Sub-group and Interim Analysis

Exploratory sub-group analyses (e.g. by cancer type or treatment status) will be detailed in sub-protocols. Interim analyses may be performed to assess feasibility, assay performance, or recruitment progress, but will not influence trial continuation decisions unless specified.

14.2 Cost Effectiveness Analysis

If specified in the sub-protocol, cost-effectiveness analysis may be conducted to evaluate the economic impact of ctDNA testing, if more funding is secured. More details will be added to the specific sub-protocols.

15 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

Source documents include, but are not limited to, hospital records (from which medical history may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). CRF data will be entered onto a CTR web-based data recording system, which is a secure encrypted system accessed by an institutional password. Sites will retain all original source data from these investigations for future reference. On all study-specific documents, other than the signed consent form and the genomic reports, the participant will be referred to by the trial participant ID, not by name.

15.1 Completion of CRFs

Electronic CRFs

It is intended to develop data recording for this study as a web-based system. This is a secure encrypted system accessed by an institutional password and complies with the General Data Protection Regulation standards.

A user password will be supplied to investigators upon completion of all processes required prior to opening. Participating sites will be provided with training and instructions on how to complete and return the CRFs. The CTR will send reminders for any queries and overdue data that has not been entered onto the study database. It is the site's responsibility to submit complete and accurate data in timely manner.

If any problem with the web-based system, sites are recommended to contact the trial team QuicDNAMax@Cardiff.ac.uk

Paper CRFs will remain in use as back up to the database, in case there was ever a malfunction, or any reason data could not be directly entered into the eCRF.

16 Further research

Although not all translational experiments can be pre-specified within the QuicDNA Max programme, future research will be guided by tumour type, emerging clinical relevance, and the development of new genomic technologies. Future research may also include a data utility comparison of QuicDNA Max clinical trial data with routinely available data. All future analyses will be conducted in accordance with participant consent and ethical approvals. Research will focus on understanding ctDNA-detected genetic alterations that may predict treatment response, resistance mechanisms, or participant prognosis, and will support continued innovation in precision oncology.

17 Protocol/GCP Non-Compliance

The PI should report any non-compliance to the study protocol or the conditions and principles of GCP to the CTR in writing as soon as they become aware of it.

18 End of Trial Definition

For the purposes of Research Ethics Committee approval, the end of the study is defined as the date of last data capture. Date of final data capture is defined as the act of entering the final data onto the study database.

CTR on behalf of Sponsor must notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

19 Archiving

The electronic Trial Master File (TMF) containing essential documents and data will be archived to Cardiff University file stores, within a restricted secured environment, which is accessible by the Electronic Archivist only. The archive data will be subject to standard Cardiff University Back-up procedures and therefore more than one copy of the data is retained, retrievable from backup and managed by Cardiff University IT Department (UTIGB). This will be stored for a minimum of 5 years after End of Study has been declared. The CTR will archive the TMF on behalf of the Sponsor. The Principal Investigator is responsible for archival of the Investigator site file (ISF) at site as outlined in the Site Agreement. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

20 Regulatory Considerations

20.1 Ethical and Governance Approval

This protocol has approval from a Research Ethics Committee (REC) that is legally “recognised” by the United Kingdom Ethics Committee Authority for review and approval.

This study protocol has been submitted through the Integrated Research Application System (IRAS) to Health Care Research Wales (HCRW) and has approval from Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

Confirmation of capability and capacity to support the study will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

Substantial amendments to this Protocol must be approved by the REC responsible for the study before the implementation of the amendments. Minor amendments will not require prior approval by the REC.

If the study is temporarily halted, it will not be recommenced without reference to the REC responsible for the study.

The REC will be notified within 90 days of trial completion. If the study is terminated early, the REC will be notified of this within 15 days.

A summary of the clinical trial report will be submitted to the REC responsible for the study within one year of the end of trial.

20.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 2018. The data custodian and the translational sample custodian for this study is the All Wales Genomic Services and Centre for Trials Research.

Once enrolled, participants will be assigned a unique trial ID which will be used, in addition to their initials and month and year of birth, throughout their participation in the study to link trial data. All staff involved with the study will comply with the requirements of the Data Protection Act 2018. For genomic reporting purposes, both blood samples for ctDNA and SoC tumour tissue samples together with associated data cannot be anonymised when collected by the study Sponsor, approved laboratories either in UK (for example the All Wales Medical Genomics Service (AWMGS) laboratory, based in Cardiff) or abroad. CTR will provide the laboratories with a list of the QuicDNA participants

trial ID and partial date of birth and NHS number that the laboratory staff will link to the samples. All reports issued by the laboratories to CTR will contain only pseudonymised data.

Representatives of the Sponsor or regulatory authorities will be given access to study data and study documents (at sites or the CTR) for monitoring or inspection purposes. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

20.3 Indemnity

- Non-negligent harm: This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.
- Negligent harm: In accordance with Technical Note 12 Indemnity for Clinical Research for research Sponsored by a Welsh body, Welsh Risk Pool Services provides indemnity cover against successful negligence claims arising from the management and conduct of the study. Where NHS employees are responsible for the design of a study, indemnity cover will also be provided for negligent harm arising from the study design. Cardiff and Vale University Health Board does not accept liability for any breach in the other NHS Organisations duty of care, or any negligence on the part of employees of these NHS Organisations

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

20.4 Trial Sponsorship

Cardiff and Vale University Health Board will act as Sponsor for the whole research programme. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor has/will be delegating certain responsibilities to Cardiff University/CTR(CU), the CI, PI, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

20.5 Funding

The QuicDNA Max programme is funded by integrated governmental, industry and charity grants. A list of all funders will be retained in the Trial Master File.

21 Study Management

21.1 Study Management Group (SMG)

The Study Management Group (SMG) will oversee the operational management of the QuicDNA Max programme. This group will include the Chief Investigator, four Co-Chief Investigators, co-investigators, the CTR Trial Statistician, CTR Trial Manager, and at least one public/consumer representative.

In addition to the central SMG, tumour-specific sub-SMGs will be established to address the clinical and operational aspects of each sub-protocol. These sub-SMGs will meet separately and led by the designated tumour-specific co-Chief Investigator (co-CI).

All SMG and sub-SMG members will adhere to defined roles and responsibilities, as outlined in the SMG Charter, which each member will be expected to sign.

21.2 Trial Steering Committee (TSC)

The TSC will be a committee of independent members providing overall supervision of the trial. The role of the TSC is to act on behalf of the Sponsor, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent chairperson. The TSC will meet at least annually when it will consider the trial team reports and new information which has arisen and recommend appropriate action.

The Committee's terms of reference, roles and responsibilities will be defined in a charter. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

21.3 Data Monitoring Committee (DMC)

Not applicable to this study

22 Quality Control & Assurance

22.1 Monitoring

The clinical study risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the QuicDNA Max study.

Monitoring levels will be employed and are fully documented in the study monitoring plan for each sub protocol.

Investigators should agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

Further monitoring activities may be required for the specific sub-protocols.

22.2 Audits and Inspections

The study is participant to inspection by REC as the regulatory body.

The study may also be participant to inspection and audit by Cardiff and Vale University Health Board under their remit as Sponsor.

23 Publication Policy

A publication plan will be written. All publications and presentations relating to the trial will be authorised by the SMG.

Data from all sites will be analysed together and published as soon as possible. Individual participating PIs may not publish data concerning their participants that are directly relevant to questions posed by the study until the study team have has published its report.

The main study results will be published in the name of the trial in a peer-reviewed journal on behalf of all collaborators. The manuscript will be prepared by a writing group that may also include high accruing clinicians and/or other people who contribute to the trial. All participating centres and clinicians will be acknowledged in this main publication together with appropriate staff from the CTR.

All publications should include a list of participating PIs, and if there are named authors, these should include the CI, Co-Investigators, Trial Manager, and Statistician(s) involved in the study, as agreed by the CI and Director of CTR. If there are no named authors, a writing committee will be identified.

24 Sub-protocols for specific tumour type

- Lung Cancer
- Cancer of Unknown Primary (CUP)
- Colorectal Cancer
- Prostate Cancer

25 References

1. CRUK, *Lung cancer statistics*. 2018, Cancer Research UK: http://www.cancerresearchuk.org.
2. Wang, M., R.S. Herbst, and C. Boshoff, *Toward personalized treatment approaches for non-small-cell lung cancer.* Nat Med, 2021. **27**(8): p. 1345-1356.
3. Shah, M., et al., *US Food and Drug Administration Approval Summary: Elacestrant for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, ESR1-Mutated Advanced or Metastatic Breast Cancer.* J Clin Oncol, 2024. **42**(10): p. 1193-1201.
4. She, W., Y. Garitaonaindia, and Y. Lin, *The latest advances in liquid biopsy for lung cancer-a narrative review.* Transl Lung Cancer Res, 2024. **13**(11): p. 3241-3251.
5. Wales Cancer Network, *A Cancer Improvement Plan for NHS Wales*. 2023-2026, Wales Cancer Network.
6. Welsh Government, *Genomics Delivery Plan for Wales*. 2022-2025, Welsh Government.
7. Advanced Therapies Wales, *Delivery Plan for Advanced Therapies in Wales*. 2024; Available from: https://advancedtherapies.wales/delivery-plan-for-advanced-therapies-in-wales/.
8. Welsh Government, *The Diagnostics Recovery and Transformation Strategy for Wales*. 2023-2025, Welsh Government.
9. Greystoke A, M.M., Morgan S, Bhatnagar P, Armstron C, Barrnet J, Roberts P, Ryves P, Popat S, Januszewski A, Madley L, Winter H, Steer H, Farn D, Murrel A, Taylor S, *The Liquid Experience: From Research to Reality. What have we learnt from the lung liquid biopsy pilots in England and Wales?* 2024, Roche.
10. CRUK. *Cancer of unknown primary statistics*. 2019; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cancer-of-unknown-primary#heading-Zero.
11. Conway, A.-M., Robinson, M., Concannon, M., Clive, S., Tillett, T., Shiu, K.-K., Medley, L. C., Dasgupta, S., Ahmed, E., Warrington, K., Zair, Z., Gillham, T., Davis, A., Scott, J.-A., Taylor, A., Stares, M., Mitchell, C., Oliveria, P., Burghel, G., Cook, N, *CUPCOMP: A multi-site UK trial in carcinoma of unknown primary: A comparison across tissue and liquid biomarkers.*, in *American Society of Clinical Oncology*. 2024, ASCO: Chicago.
12. Krämer, A., et al., *Molecularly guided therapy versus chemotherapy after disease control in unfavourable cancer of unknown primary (CUPISCO): an open-label, randomised, phase 2 study.* Lancet, 2024. **404**(10452): p. 527-539.
13. https://www.england.nhs.uk/publication/national-genomic-test-directories/