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EGG-CUP

Enabling Genomic Testing in Cancer of Unknown Primary (CUP)

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Signature Page

EGG-CUP: Enabling Genomic Testing in Cancer of Unknown Primary (CUP)

This document describes the EGG-CUP study and provides information about procedures for entering participants into it. The protocol should not be used as a guide for the treatment of participants outside of the study.

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care and the Sponsor's SOPs.

Every care was taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to all Investigators in the study as required.

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Date: 05-Jul-2024

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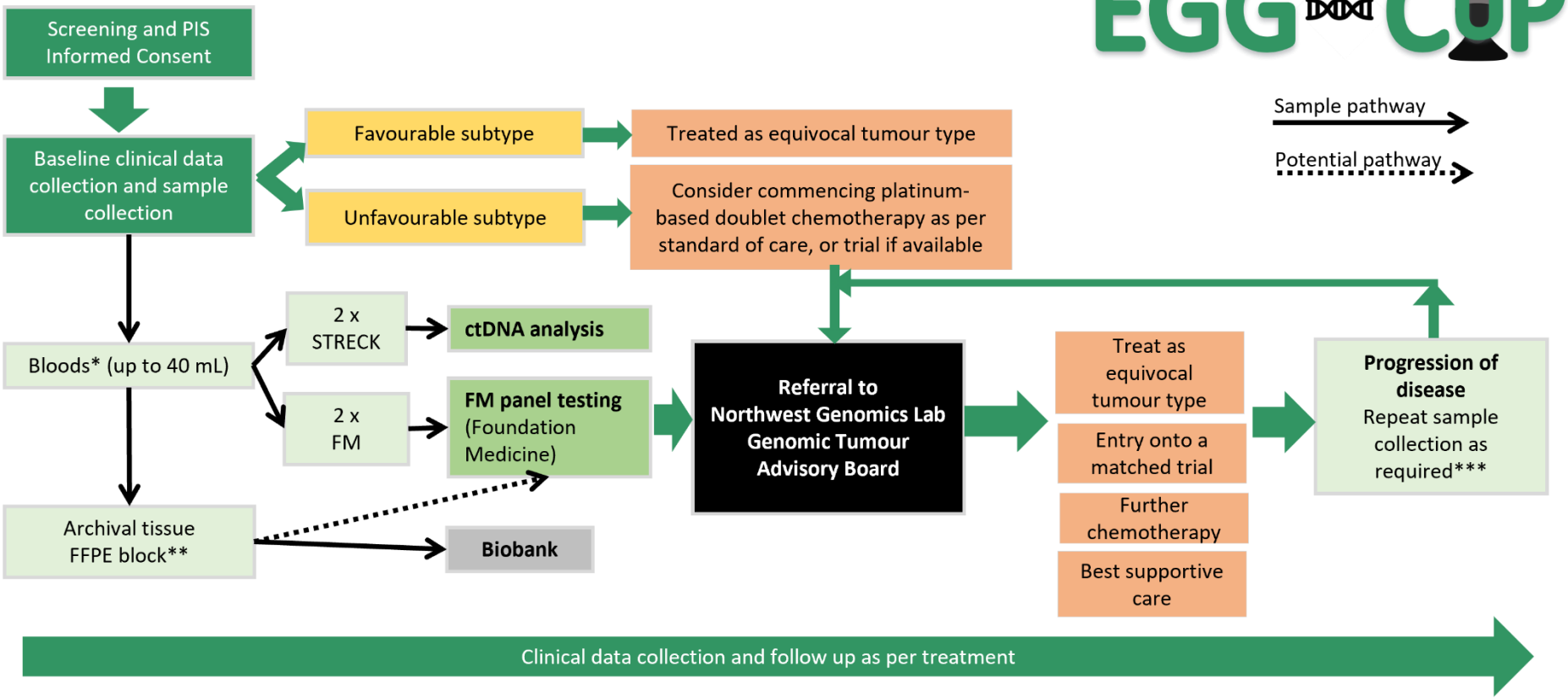
1.0 Abbreviations

AcoRD	Attributing the costs of health and social care Research and Development
AE	Adverse Event
CI	Chief Investigator
cfDNA	Circulating Free DNA
CRF	Case Report Form
CRUK	Cancer Research UK
ctDNA	Circulating Tumour DNA
CUP	Cancer of Unknown Primary
ESMO	European Society for Medical Oncology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GTAB	Genomic Tumour Advisory Board
ID	Identification
MDT	Multi-disciplinary Team
MTB	Molecular Tumour Board
NBC	Cancer Research UK National Biomarker Centre
NHS	National Health Service
NIHR	National Institute for Health Research
PIS	Participant Information Sheet
REC	Research Ethics Committee
TMG	Trial Management Group
ToO	Tissue-of-Origin
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
USM	Urgent Safety Measure
WGS	Whole Genome Sequencing

2.0 Study Summary

Title	**E**nablin**g** **G**enomic Testing in **C**ancer of **U**nknown **P**rimary (CUP)
Acronym	EGG-CUP
Study Design	An exploratory, multi-centre, clinical sample collection study
Study Participants	Adult patients with a confirmed diagnosis of CUP (please refer to section 7 for full eligibility criteria)
Planned Sample Size	100 participants
Planned Study Duration	Max study length 3 years 9 months (33 months recruitment, followed by 12 month follow up)
Study Objectives	To sequence cfDNA (or tumour tissue where there is no cfDNA yield) from patients diagnosed with CUP, in order to understand the genomic make-up of the cancer, collect samples for tissue of origin analysis, and to improve treatment stratification approaches. To assist and educate teams in directing delivery of genomic results and personalised treatments to patients with CUP.
Study Endpoints	Evaluate utility of cfDNA molecular profiling in patients diagnosed with CUP: • Percentage of patients with adequate cfDNA yields • Percentage of patients with actionable genomic alterations • Percentage of patients eligible for personalised treatment options or enrolment on a clinical trial based on the cfDNA results • Documentation and feedback of genomic results / GTAB outcomes to patients and treating teams Develop a CUP data collection repository within the NHS. Identification of biomarkers to help in the diagnosis and treatment in patients diagnosed with CUP.

3.0 Study Schema



*One tube of blood is approximately 10mls.
**FFPE blocks reflex test where blood tests do not provide results
***Repeat FM blood collection.

Figure 1 - Study Schema

4.0 Background

4.1 Cancer of Unknown Primary (CUP)

Cancers of Unknown Primary are an important but historically under-researched clinical entity. Patients diagnosed with CUP have metastatic cancer at diagnosis, which is usually extensive at presentation[1]. No clear risk factors have been identified for CUP to date[1] and as most patients present with metastatic disease, early detection of patients with CUP is not possible. CUP is estimated to account for between 3-5% of all cancers and once diagnosed patients tend to have a poor prognosis. Incidence rates of CUP have fallen in recent years however mortality rates remain high. It is the 6th leading cause of cancer death in the UK and prognosis is poor with a median survival of 6-9 months[2]. There is no consensus of an 'optimal' chemotherapy regimen, and a lack of robust prognostic and predictive biomarkers to direct use of targeted or immune-based therapies.

4.1.1 CUP Diagnosis and Pathways

A CUP diagnosis is made if standard investigations fail to identify a primary site of origin of the cancer[3,4]. A clinical algorithm for the management of patients diagnosed with CUP has been developed by The European Society for Medical Oncology (ESMO) and was recently updated[5]. CUP with certain tissue-of-origin (ToO) like characteristics are seen as distinct subtypes of CUP and are amenable to therapeutic treatment based upon the suspected primary (see Table 1). When a primary cancer cannot be found patients are diagnosed with either a favourable prognosis CUP (if there is a suspected primary site) or poor prognosis CUP, based on clinico-pathological features. Subsequent treatment relies on this classification. However, in the UK the only treatment available outside the context of clinical trials remains chemotherapy or best supportive care. Research within CUP is hampered by the heterogeneity within the condition and there has been little advancement in treatments compared to other metastatic cancers. Within solid tumour types of known tissue of origin, newer therapies, including targeted therapy and immunotherapies, have dramatically improved survival[6]. The role of these novel therapies in CUP has not been well investigated but it is likely that a proportion of patients with CUP may benefit from such treatments. The genomic testing of either tissue or blood samples promises to improve outcomes for patients[7,8]. Unfortunately, without access to comprehensive genomic testing and novel biomarkers to predict tissue of origin, we will not be able to investigate whether patients with CUP also stand to benefit from a more personalised approach to their cancer management.

CUP Subtypes	Proposed Treatment
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy
Peritoneal adenocarcinomatosis of a serous papillary histological type in females (ovary-like CUP)	Optimal surgical debulking followed by platinum–taxane-based chemotherapy (addition of bevacizumab is optional) and PARP inhibitor maintenance in responding patients.
Squamous cell carcinoma involving non-supraclavicular cervical lymph nodes (Head and Neck-like CUP)	Small volume: Surgery or RT ± ChT Large volume: Surgery and/or RT ± ChT
CUP with a colorectal IHC (CK20+ CDX2+ CK7−) or molecular profile (Colon-like CUP)	Systemic treatment used for colorectal cancer
Single metastatic deposit or oligometastic disease amenable to local ablative treatment (single-site / oligometastitc-site CUP)	Ablative surgery and/or RT ± systemic therapy
Men with blastic bone metastases or IHC/serum PSA expression (prostate-like CUP)	Metastatic prostate cancer guidelines. [Androgen deprivation therapy ± RT]
Carcinoma with renal-cell histology and immunochemical profile (renal-like CUP)	TKI and ICI-based treatments. Optionally, treatment according to new kidney cancer protocol may be justifiable.
Women with isolated axillary lymph node metastasis (breast-like CUP)	Treatment according to primary breast cancer protocols.

Table 1 - CUP Subtypes

5-FU, 5-fluorouracil; ChT, Chemotherapy; CK, cytokeratin; ICI, Immune checkpoint inhibitor; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RT, radiotherapy; TKI, Tyrosine Kinase inhibitor.

Approximately 80% of patients with a diagnosis of CUP currently have an unfavourable subtype. Current treatment guidance for unfavourable CUP is primarily dependent upon prognostic indicators. For patients with adequate performance [PS 0-1, normal lactate dehydrogenase (LDH), median life expectancy of 1 year] doublet chemotherapy is generally recommended as standard of care. Currently gene expression profiling-directed therapies are not recommended outside of clinical trials. Meanwhile those with poor performance [PS 2+, elevated LDH, median life expectancy of approximately 4 months] are for best supportive care with the aim of preserving quality of life[4].

4.1.2. Cancer-type Agnostic Treatments

Molecularly targeted treatment is recommended where cancer type-agnostic therapies have been authorised as standard of care treatments. Several such targeted treatments have been approved by the FDA for cancer type-agnostic indications[9]. However, in the UK there are currently only approvals for TRK inhibitors[10,11]. This is likely to change and expand with emerging evidence from current ongoing trials investigating novel targeted treatments[12,13]. To ensure patients diagnosed with CUP can access these molecular targeted treatments they will also need access to comprehensive molecular profiling to identify the matched genomic alterations.

4.1.3 DNA Sequencing-based Molecular Targeting

Precision medicine has transformed treatment strategies in known tumour types, however, in CUP there remains an urgent need to better understand CUP molecular characteristics to establish potential roles for novel therapeutic strategies. Treatment options remain limited due to difficulties in determining the primary site of the tumour and the lack of access to validated biomarkers. The growing use of molecular profiling and subtyping across cancers of known primary type have the potential to transform the diagnosis and therapeutic management of patients with CUP. The emergence of liquid biopsies as a source of biomarkers is also gaining rapid ground and this research aims to explore the potential utility of liquid biopsies in CUP.

Liquid and tissue biopsies offer an opportunity to detect tumour molecular and immune characteristics. In the blood (liquid), this includes but is not limited to, circulating tumour DNA (ctDNA). There is emerging data investigating the area of liquid biopsy molecular testing in CUP[8]. Most previous data comes from tumour tissue profiling, despite challenges with access to tissue of sufficient quality and quantity. Small diagnostic biopsies have often undergone multiple immunohistochemistry stains prior to diagnosis and repeat biopsies are often required. Liquid biopsies have the potential to overcome some of the inherent limitations of tissue biopsy; reflecting the whole tumour burden and enable less invasive and serial sampling[14]. Where patients do have DNA sequencing results (tissue or blood), discussion at a molecular tumour board (MTB) is recommended.

These tests also have the potential to help determine primary tissue of origin, or biomarkers that are predictive of response to certain therapies, including immunotherapy[14]. However, even though we could characterise CUP tumours by these genetic changes it is unclear if treating patients based on these predictions improves survival. The CUPSICO study [ClinicalTrials.gov identifier: NCT03498521] was a large global phase II randomised study for patients with poor prognosis CUP, which also provided access to therapeutic treatment options. Results from CUPISCO, comparing the efficacy and safety of targeted therapy or cancer immunotherapy guided by molecular testing against standard platinum-based chemotherapy were presented at the ESMO Conference 2023[15]. Although the survival data was not reported there was a significant increase in progression free survival for patients who had a molecular guided treatment versus standard chemotherapy. Further updates including survival data are eagerly awaited and this trial is likely to be practice changing. However, to participate in the trial most patients had to undergo a new fresh tumour biopsy, which is not always possible, and there was very strict eligibility criteria, so it was not possible for a large proportion of patients diagnosed with CUP to participate.

4.1.4 Future Research and Treatment

Despite significant advances and new drug development for other cancers, there are no approved targeted therapies or immunotherapies for CUP. In April 2022 whole genome sequencing (WGS) in CUP was approved and added to the NHS England Test Directory. However, despite this approval the uptake for this testing has been poor, mainly due to lack of resources on the ground to implement the testing, long turnaround time for results, and lack of fresh tissue available for the WGS. As discussed above, access to reliable tissue is difficult in patients with CUP, making researching and investigating CUP tumours difficult.

Due to the lack of research into CUP limited progress has been made to date, and therefore novel approaches to improve prognosis are desperately needed. Examining the genetic characteristics of CUP biomarkers, in both tissue and blood, could help predict response to existing or new therapies and has already been studied in multiple other cancer types[16–19].

There is also limited understanding of the diversity of genomic and epigenomic features contributing to CUP pathogenesis and progression outside of clinical sequencing panels. The influence of such features has not

been widely assessed from existing clinical trial data, nor has a clinical study been designed to identify novel genomic and epigenomic biomarkers. Therefore, there is significant value in pursuing approaches capable of identifying clinically actionable biomarkers, both for patient treatment and scientific understanding of CUP.

4.2 Rationale

Two thirds of CUP cases are from the most deprived areas of England, with incidence rates higher than average across the North-West (NW) and North-East (NE) of England (calculated by the Cancer Intelligence Team at Cancer Research UK, April 2020). It has been postulated that this disparity may be in part due to differential access to diagnostic tests although there is incomplete data in CUP reporting to evaluate inequalities in detail.

To address the regional differences in access to trials/treatments and molecular testing for patients with CUP we will focus this research across a close network of centres in the NW (including Greater Manchester, Cheshire and Merseyside, Lancashire and South Cumbria) to ensure molecular testing is made available across large and small centres in this region. Long-term we aim to initiate change in national CUP pathway guidance and streamline the diagnosis and treatment stratification for patients diagnosed with CUP across the UK. Further national projects are currently being discussed, including separately funding projects in Scotland and Wales, as their genomics medicines services are run independently to England.

This trial will use molecular characterisation in patients diagnosed with CUP to identify actionable molecular alterations, which may also give us clues to the tissue of origin. As access to good quality tissue for molecular profiling remains a huge challenge in CUP, we focus on a liquid biopsy approach to overcome this challenge. We want to understand the profile of CUP tumours in the material we collect. This project will enrol patients across all subtypes of CUP, gathering evidence for the multitude of questions that remain unanswered. We want to ensure this type of study will reach patients from NHS hospitals across regions with higher levels of socio-economic deprivation (and therefore likely have more patients diagnosed with CUP). We will offer sequencing of cfDNA to approximately 100 patients with CUP, with a focus on centres across NW England (population of 7.4 million). We want to focus only on a specific area with a high incidence of CUP to ensure we can facilitate and establish pathways across this region, to assist and educate teams in directing delivery of genomic results and personalised treatments to patients with CUP. We expect to increase the number of patients diagnosed with CUP accessing genomic testing and increase research and treatment opportunities for these patients, and hope access to these extra tests will improve identification of patients for site-specific treatments or novel treatment opportunities. We will offer support in interpreting genomics reports in collaboration with the NW Genomics Laboratory Hub, linking in with their weekly Genomic Tumour Advisory Board (GTAB)which is already established, however, underutilised in CUP.

If successful we would then look to roll this out across other areas of England as part of a national project. The NHS England Genomic Medicine Service are supportive of this research and we are collaborating with them as part of The Circulating Biomarker Genomic Network of Excellence. We need to ensure we incorporate significant genomic findings into standard of care discussions, and through the GTABs, including discussion of any potential germline findings. The genomic and longitudinal clinical data that will be collected will include multi-omic and clinical data and could be used to drive additional research in the UK. It would address an area of high unmet need and has the potential to change clinical care.

Key Objectives

- To facilitate and establish pathways to use the clinically significant genomic profiling data to assist clinicians in directing delivery of personalised cancer care and treatment options to patients diagnosed with CUP

- To enable adoption of genomic testing in patients diagnosed with CUP for better identification of patients for treatments
- To collect and analyse blood samples from patients with CUP to help identify tissue-of-origin specific biomarkers

4.3 Overall Risk/Benefit

This study has been classified as somewhat higher than the risk of standard of medical care.

Risks

1) Data/Confidentiality:

General risks associated with data collection apply. Personal patient information will be protected through pseudo-anonymisation using a unique patient identifier that will be assigned upon enrolment onto study. All data will be handled in line with the Data Protection Act 2018 and General Data Protection Regulation. Data will be stored on password protected electronic databases and source data will be stored in locked research offices within the NHS. Data will be pseudo- anonymised before transfer to external collaborators (CRUK National Biomarker Centre) using an EGG-CUP specific trial ID number.

There are some specific risks related to genomic data, please see section 9.0 for detail.

2) Procedural:

Minor risks are associated with blood sample collection such as bruising and pain. These samples will be taken by appropriately trained staff at the clinical sites according to site delegation logs.

Genetic research may result in psychological distress if results show other previously unknown conditions (e.g., hereditary conditions). All participants will receive the appropriate information about this at the time of consent and will be given the option to not have any such results disclosed. If a patient does choose to have any incidental findings reported back to them, they will be referred to a genetic counselling service as appropriate.

Benefits

Although the objectives of this study are not directly therapeutic and therefore may not have a direct benefit for all participants, it is anticipated that the results from the tests may help direct some participants onto a suitable treatment option. There is also the benefit of increased knowledge about molecular changes in their cancer which some patients may also find useful.

The data collected from this project will help to develop the understanding of CUP, in particular the discovery of clinically relevant biomarkers to assist with the diagnosis and treatment stratification for patients, thus aiming to improve access to targeted therapies for this patient group with currently limited options. This information will be made widely available following relevant publications.

5.0 Research Question

5.1 Primary Objective

- To utilise cfDNA from a liquid biopsy to understand the genomic make-up of the cancer

5.2 Secondary Objective(s)

- To establish a genomic reporting mechanism whereby clinically relevant and potentially 'actionable' abnormalities found during sequencing/molecular characterisation can be reported to patients and treating teams
- Collect evidence investigating the most effective way to stratify patients with CUP onto treatment
- To facilitate and establish pathways (in the NW of England) to use the clinically significant genomic profiling data to assist clinicians in directing delivery of personalised cancer care and treatment options to patients diagnosed with CUP

5.3 Exploratory Objective(s)

- Identify tissue-of-origin specific biomarkers in liquid biopsies from patients with CUP
- To understand whether liquid biomarkers in CUP can be used to stratify patient management and give prognostic information

5.4 Primary Endpoint/Outcome Measure

Evaluate the utility of cfDNA molecular profiling in patients diagnosed with CUP as determined by:

- Percentage of patients with adequate cfDNA yields
- Percentage of patients with actionable genomic alterations
- Percentage of patients eligible for personalised treatment options or enrolment on a UK based clinical trial because of the cfDNA results

5.5 Secondary Endpoint/Outcome Measure

- Documentation and feedback of genomic results/GTAB outcomes to all patients and treating teams
- Routinely incorporate molecular genomics as standard of care in patients diagnosed with CUP (working with the NHS England Genomic Medicine Service)
- Develop a data collection repository and readily available information on trials/treatments for patients diagnosed with CUP

5.6 Exploratory Endpoint/Outcome Measure

- Development of novel biomarkers to help in the diagnosis and treatment of patients diagnosed with CUP

5.7 End of Study Definition

Unless early termination is required, the end of study is defined as the end of samples analysis. The last patient last visit will occur 12-month post baseline visit. Progression samples can be collected up to 12 months after the baseline visit. There is a 6-week turnaround time for samples to be sent, processed and results to be reported.

6.0 Study Procedures

6.1 Overview

This is a multi-site study based in the NW of England, recruiting up to 100 patients diagnosed with CUP.

Study participants will be identified from local or central CUP MDT discussions. Members of the study team will identify eligible patients who voluntarily agree to be enrolled in this trial. The process of informed consent will include counselling about risks and benefits of genomic sequencing results in which patient can choose a priori whether to receive the result of genetic analysis.

Sequential blood samples will be collected to investigate biomarkers. Where circulating tumour DNA is not found an archival tumour block from previous diagnostic biopsies may be sent for testing. We intend for all samples to be obtained through minimally invasive collection.

Each collected biospecimen will be pseudo-anonymised and assigned with an identification (ID) number, which will be used by laboratory staff. Links between study ID number and clinical data will be held within secure, password-protected computers. Only key personnel with the need to link biomarker data with clinical data for clinical decision-making will have access to this database. Samples will be distributed to analysing laboratories in accordance with participating sites standard-operating procedures. Upon completion of analyses or at the end of the study, any leftover samples will be returned to their local institution and stored according to the biobank ethical approvals and guidelines.

6.2 Study Schedule

The study will consist of the following visits:

	Baseline	First treatment progression within 12 months of baseline[1]	Follow up 6 months (± 2 weeks)[2]	Follow up 12 months (± 2 weeks)[2]
Patient Consent	X			
Medical History	X			
Blood Sample[a]	X	X[b]		
Archival Tumour Tissue Retrieval[a]	X			
Clinical Data Collection[c]	X	X	X	X
SAE Reporting[d]	X	X	X	X

Table 2 - Study Schedule

1 Only collect samples and data at the first treatment progression following baseline. Progression sample collection must occur within the 12 month follow up period.

[2] Data collection is to be completed within 2 weeks of the scheduled timepoint. Data collection can occur earlier if the participant is known to have deceased prior to this date.
a Please see section 6.2.4 for detail on sample collection.
b Please see section 6.2.4. for detail on sample collection. Sample to be collected at the discretion of the participant and principal investigator.
c Please see section 9.0 for detail on clinical data collection. Genomic Tumour Advisory Board outcome data are to be entered within 6 weeks of the baseline visit.
d Please see section 10.8 for detail on SAE reporting

6.2.1 Screening Assessments

Participants must meet eligibility criteria to enrol into the study. All mandatory data must be available and/or collected at the baseline visit.

6.2.2 First Treatment Progression within 12 Months

Participants who start a new line of treatment after the baseline visit are eligible for repeated ctDNA sample collection upon progression, where progression occurs within 12 months of the baseline visit. Collection of a progression sample is at the discretion of the participant and principal investigator. All mandatory data must be available and/or collected at this visit.

6.2.3 Follow-up Assessments

Participants are scheduled to have a both a 6 month and 12 month follow up relative to baseline visit. All mandatory data must be available and/or collected at this timepoint. The follow up timepoint does not require an in-person clinic visit as all mandatory data can be obtained from either telephone contact, medical note review or contact with the GP. Sites should attempt to establish contact with the participant within ±2 weeks of the scheduled date. If patients are not contactable within this period, the most recent data should be obtained from the medical record and/or contact with the GP. Participants will be considered lost to follow up if there is no new data since baseline/the previous follow up timepoint. The next follow up clinical research form can be completed earlier than the scheduled timepoint where the participant is known to have deceased and all mandatory data is available.

6.2.4 Sample Collection

Samples will be collected as shown in Table 3 below.

	Baseline	Progression
2x STRECK tube (blood sample)[1]	X	
2x FM (blood sample)[1]	X	X
Archival tissue	X[a]	

Table 3 - Sample Collection

[1] Up to 10ml of blood per tube

[a] Where FM liquid biopsy test fails to meet the supplier's quality controls for testing and/or no cfDNA yield, archival tissue can be sent for testing. Where available, archival tumour blocks will be sent to The Christie. Following the end of the study these samples will be retained for future research under a HTA licence.

FM liquid biopsy samples will be sent to collaboration research laboratories at Penzburg, Germany (or Boston, USA as a back-up) for ctDNA analysis.

STRECK blood samples will be processed to double spun plasma and stored for circulating free DNA extraction, methylation profiling and tissue-of-origin classifier predictions (CUPiD)[20]. This will be undertaken by the CRUK National Biomarker Centre (NBC).

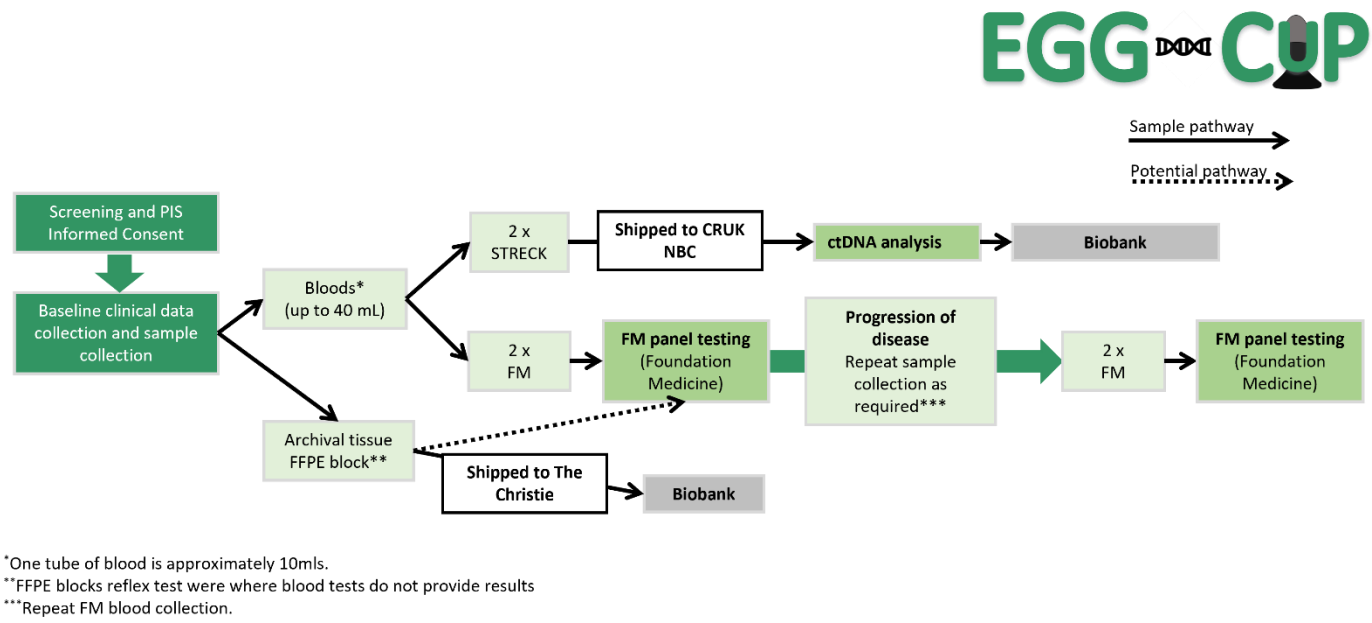
Blood sample collection for Foundation Medicine

- Foundation Medicine will supply sample selection kits
- Each kit will contain 2 x 'Roche Cell-Free DNA (cfDNA) blood collection tubes
- Blood specimens will not be returned, remaining blood or plasma not placed into testing is discarded in accordance with local practice.
- Typical turnaround time is approximately <2 weeks from receipt of specimen (see lab manual)
- Further detail on the collection and shipment of these samples can be found in the sample collection kit

Sample collection for plasma

- 2 x STRECK tubes will be supplied by CRUK National Biomarker Centre (NBC) and distributed by The Christie.
- STRECK samples will be shipped to NBC for processing into to double spun plasma and storage.
- Further details can be found in the laboratory manual.

Samples will be retained by the research team for no longer than 12 months after the end of study date, to allow for verification or quality checking of the research data. After this period legal authority to hold any human tissue under the ethical approval for this project will expire and samples will be held under HTA license.



*One tube of blood is approximately 10mls.
**FFPE blocks reflex test were where blood tests do not provide results
***Repeat FM blood collection.

Figure 2 - Sample Flow

7.0 Recruitment and Selection of Study Participants

Potential study participants will be identified and assessed through discussions at local CUP MDTs.

7.1 Informed Consent

All potential study participants will be provided with a participant information sheet (PIS) and invited to voluntarily consent to participate in the study. It should be made clear to the potential study participant that consent is voluntary and can be withdrawn without giving reasons and without prejudicing their ongoing/future care.

Potential study participants will be given adequate time to consider participation in the study before consent is elicited. When all queries have been addressed and the research team is confident that the participant understands the study and all requirements, participants will be consented to participate.

Consent will be taken by a researcher who is appropriately trained and who has been delegated by the PI to undertake this activity (and this is clearly documented on the delegation log). No study-related activities can be undertaken prior to consent.

The original, signed copy of the participant information sheet and consent form(s) will be retained in the Investigator Site File, with a copy in the participant notes. A copy will also be given to the participant.

After consent has been obtained, the participant will be formally assessed for eligibility for the study at the screening visit against inclusion and exclusion criteria of the study protocol.

7.2 Participant Selection Criteria

All participants must meet all the inclusion criteria and none of the exclusion criteria for this study at the time of registration. Eligibility waivers will not be used under any circumstances.

All study participants must have a histological confirmed diagnosis of CUP based on the clinical, radiological, and pathological review at a local or regional CUP MDT and the ESMO Clinical Practice Guidelines for CUP (see Appendix 2)[5]. Favourable and unfavourable-risk CUP subsets are eligible. The population to be included in this study corresponds to patients with CUP of epithelial origin for whom a likely tissue of origin cannot be determined. All tests/examinations performed to ascertain the diagnosis of CUP and exclude a tumour of known origin (following ESMO guidelines) will be available and entered onto the study clinical research form (CRF). Any primary origin suggested by the clinical presentation or pathology work-up should be formally excluded prior to confirming a CUP. Participants will have undergone these procedures prior to the study as part of their routine care.

7.3 Participant Inclusion Criteria

Participants are eligible to be included in the study only if **ALL** of the following criteria apply:

1. Aged 16 years or over.
2. Written informed consent according to GCP and national regulations.
3. ECOG Performance status 0-2
4. Confirmed diagnosis of CUP as per the ESMO guidelines (described above). Patients must have;
    a. The local pathology report confirming compatibility with CUP diagnosis and the associated slides used for the diagnosis.

   b. Discussion at a local CUP MDT confirming diagnosis.
5. Availability of archival tumour histological report
6. Willingness to provide blood samples on up to two occasions during the study.

7.4 Participant Exclusion Criteria

Participants are excluded from the study if **ANY** of the following criteria apply:

1. Patient with an immunohistochemistry profile and radiological appearances that provide a definitive clinical indication of a primary cancer with a specific treatment.
2. Known HIV, Hepatitis B, C positive, due to the difficulties in handling high-risk specimens.
3. Patients who are unable to provide fully informed written consent.
4. Presence of any medical, psychological, familial or sociological condition that, in the investigator's opinion, will hamper compliance with the study protocol and follow-up schedule.
5. Bleeding diathesis (patients' on anticoagulation are permitted to enter the trial if anticoagulation can be safely managed to enable blood sampling)
6. Conditions in which blood sampling may increase risk of complications for the patients and/or investigator.

7.5 Study Payment

Participants will not receive any payment, nor be compensated for travel expenses related to the study.

7.6 Participant Registration

Potential participants will be registered with the coordinating centre using REDCap. REDCap will assign an ID number and the site will complete the expected date of consent and baseline visit. For participants that do not consent to the study, the ID number will be discontinued. If a participant declines the study and later reconsiders a new ID number will be assigned.

After consent has been obtained, the participant will be formally assessed for eligibility for the study against inclusion and exclusion criteria of the study protocol. Eligibility must be determined by the principal investigator or an appropriately trained and delegated member of the clinical research team. Sites will complete the eligibility criteria checklist and confirm the date of consent and baseline visit within REDCap to enrol the participant. If a patient does not meet the eligibility criteria at screening the ID number will be discontinued. A new ID is to be assigned if the patient repeats consent and screening for the study.

Participating sites will maintain a screening and enrolment log to document the number of participants approached and reasons the participants were not enrolled, making specific mention of any inclusion criteria not met or any exclusion criteria met.

The master list will be stored in a secure location and access will be restricted to authorised personnel.

7.7 Discontinuation of Participants

Specific reasons for discontinuing a participant from study procedures are:

- Investigator decision.
- Oversight committee recommendation/ decision.
- Safety reasons.

- Severe non-compliance to protocol as judged by the investigator and/or sponsor.
- Participant's decision to withdraw (see section 7.8).
- Completed visits up to the End of Trial time point.

7.8 Withdrawal of Participants

If at any time a participant expresses a wish to withdraw consent for ongoing study participation the following procedures will be observed:

1. Withdrawal of consent will be clearly documented in the study documentation and the study participant's medical record.
2. No further clinical data will be collected from the study participant. However, existing clinical data held will be retained and may still be used in future research by researchers who have a legitimate interest in the study data.
3. Samples will be retained and included in analyses unless the participant requests them to be destroyed. Samples not already processed/analysed will be destroyed upon request, samples already resulted will remain in the trial data set. It is the responsibility of the participating sites' research team to ensure that participant's wishes are met.
4. The study participant's privacy will be respected and preserved.

If a participant consents to the study but subsequently becomes unable to give consent, they will be withdrawn from the study and no further information or samples will be collected. Previously obtained data and samples will still be used in the study.

8.0 Statistics and Data Analysis

8.1 Sample Size

We expect up to 100 patients to consent prospectively over this time period across the 6 named sites open to recruitment. Each site will initially be given 15 slots to allocate, with any further slots allocated upon agreement with sponsor and CI. The nature of CUP and likelihood of many different tumour types being represented justifies as large a sample size as possible, however we are also only able to obtain funding for molecular testing for the patient numbers quoted. From discussions with sites across the NW we anticipate this will be achievable over a 24-32 month period. Descriptive statistics will be used to understand how recruitment, screen failures, and barriers to genomic testing vary by NW region; and also to describe age, ethnicity and socioeconomic deprivation across these regions. These analyses are exploratory in nature so there are no formal power calculations.

8.2 Recruitment Rate and Interim Analysis

We intend for there to be up to 6 recruiting centres for this study situated across the Northwest of England. From the study start date we aim to recruit 100 patients. The centres will attend a monthly teleconference to discuss the screen fail and consent rates. From previous experience of recruiting CUP participants to a similar study [CUP-COMP, NCT04750109] we anticipate 1 participant to be recruited per site every other month. If some sites are not recruiting the numbers of patients anticipated other sites may be allocated extra slots. There is no planned interim analysis.

Time after study start	5 months Set up phase [1 site added per month]	Month 20 Mid-trial timepoint [Last site to open recruiting for 14 months]	Month 33 [End of recruitment]
Sites	1-6	6	6
Recruited participants	11-12	54-57	93-100

Table 4 – Projected Recruitment

We anticipate that approximately 15-20% of baseline ctDNA blood samples will not identify any mutations in the blood for one of the following reasons:

a) Sample testing incomplete
    a. Insufficient sample volume
    b. Loss of sample due to handling or shipment issues
    c. Sample fails pre-testing quality control
    d. Sample fails post-testing quality control
b) Little to no circulating tumour DNA identified in the blood sample

For participants where no mutations are identified from the blood test, analysis of archival tissue will be available. The success of archival tissue testing depends upon there being enough tissue of sufficient quality remaining. Instructions will be provided to sites in the laboratory manual to help determine which samples are appropriate for testing.

We will analyse the data comparing tissue to cfDNA testing as part of the CUPCOMP study (mentioned above), and in EGGCUP we will calculate the percentage of patients with adequate cfDNA yields and the type of genomic alteration discovered, and correlate with survival outcomes. Each high confidence genomic alteration that passes mutation filtering steps will be annotated using OncoKB to determine likelihood of being

oncogenic and potential actionability. Further external funding could be applied for at the end of this study dependent on the results.

9.0 Data Management

Potential study participants, with a confirmed diagnosis of CUP at the local CUP MDT, will be brought to the attention of the local clinical research team. A unique screening number will be generated by the local research team which will be used to pseudonymise potential participants until registration is confirmed. The coordinating centre will be notified of consent being offered to potential participants. After consent has been obtained, the participant will be formally assessed for eligibility for the study against inclusion and exclusion criteria of the study protocol. Participants who are eligible will be registered with the coordinating centre with the next sequential trial ID number. Clinical data will be obtained from potential participants by authorised and appropriately trained members of the clinical research teams at participating centres. Participants data will be collated by members of clinical team with legitimate access to the participants medical records. Data will be pseudo-anonymised and coded appropriately by a member of the clinical team and therefore clinical information will be rendered non-identifiable for researchers.

Samples will be pseudo-anonymised to researchers. It is proposed that linkage of clinical data to tissue samples holds no risk to participants. Local and national procedures and policies in place will be applied to all personal data to ensure confidentiality and compliance with data protection laws.

Mandatory clinical data that must be available;

- DOB
- Gender
- Ethnicity
- Date of onset of symptoms
- Date of referral to secondary care
- Date of diagnosis
- Date of biopsy
- Site of biopsy
- Disease sites/burden of disease
- Height/Weight
- Past medical history/Co-morbidities
- Medications
- Family history of cancer
- Smoking History
- Histology, including cellularity of tissue and immunohistochemical (IHC) analysis.
- Pseudo-anonymised pathology report
- Pseudo-anonymised radiological report (CT scan or PET/CT scan)
- Blood parameters, to include Full blood count, Albumin, C-reactive protein, Liver function tests, adjusted calcium, Blood glucose, Lactate dehydrogenase and tumour markers where performed.
- Treatment type (Surgery/Radiotherapy/Chemotherapy/Other) and dates
- Date of treatment
- Date of progression
- Outcomes (date of progression/date of death)
- Genomic Tumour Advisory Board (GTAB) Meeting Outcome(s)*

**Meeting outcome is to be entered into the eCRF within 1 of the scheduled GTAB meeting.*

Such data will only be used to facilitate clinical and translational research and will be stored in secure computers and will be protected by data confidentiality legislation.

Genomic data confidentiality: DNA samples will be evaluated by sequencing in order to identify "actionable" aberrations and to provide a molecular profile of individual cancer specimens. Additional analyses may be performed on tumour or circulating biomarkers to identify potentially actionable molecular aberrations or biomarkers relevant to the use of immunotherapy treatment. All samples will be pseudo-anonymised and the link between the samples ID and patients' identifiable data will be stored in secure, password-protected computers. Clinical data will be handled according to the Data Protection Act 2018 and in accordance with the principles of GCP. The sequencing database will initially be separate from the clinical/sample database and access to one database will not provide automatic access to the other. In the global joint endeavour to understand the molecular basis of cancer, secondary research use maximises scientific utility and promotes the achievement of public benefit. Patients will be asked to consent to sharing of their anonymised data.

Sequencing results and disclosure: The molecular profiling analyses of each patient will be reviewed in the NW Genomics Laboratory Hub Genomic Tumour Advisory Board (GTAB) meetings who will provide oversight on the nature, clinical significance and the relevance of the results and will inform the local CUP team of any "actionable" mutations/aberrations, which could be useful to direct selection of a targeted therapy treatment for that patient. A form will be completed for each patient that needs discussing at the GTAB (See lab manual) and the site will need to ensure a representative is available at meetings where their patients are discussed.

9.1 Case Report Forms

Participating sites are responsible for maintaining source data for their study participants and for transcribing this into the eCRF. The Principal Investigator is responsible for ensuring the accuracy, completeness and legibility of the data recorded in the CRFs. Only the investigator and authorised personnel who have signed the delegation log should record or amend data in the CRFs.

9.2 Data Storage

Participant's notes, and study files will be held in a secure storage area with limited access. Computers used to collate data will have limited access measures via usernames and passwords.

9.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related audits and inspections. Informed consent will be obtained to cover this activity.

Once the project is completed and data has been published anonymised data will be made available to broader communities in the UK and globally to help drive innovation and research in CUP.

9.4 Confidentiality

All Investigators and site staff involved with the study must comply with the requirements of The Data Protection Act 2018 and General Data Protection Regulations 2018 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Any personal data recorded will be regarded as confidential, and any information which would allow individual participants to be identified will not be released into the public domain.

9.5 Archiving

Essential documents will be maintained securely stored and access restricted to authorised personnel. Essential documents are documents that individually and collectively permit evaluation of the conduct of the study and substantiate the quality of the data collected.

Essential documents, including personal data will be stored at an approved external storage facility for 5 years after the end of the study.

At the point where it is decided that the study documentation is no longer required, the sponsor will authorise the destruction of all essential documents related to the study.

10.0 Administrative and Regulatory Details

10.1 Study Sponsor

The Christie NHS Foundation Trust will act as the sponsor for this study. Delegated responsibilities will be assigned to the Chief Investigator and the EGG-CUP research team to manage the study on behalf of the sponsor.

10.2 Peer Review

A detailed research project outlined has undergone high-quality peer review as part of the NIHR Advanced Fellowship Award process. The NIHR clinical research network confirms that no additional peer review would be required for adoption to the NIHR portfolio. It also has full support from the CUP Foundation: Jo's friends, the only CUP charity in the UK and the World CUP Alliance.

10.3 Funding Body

This study is funded by the NIHR [NIHR Rosetrees Trust Advanced Fellowship, NIHR303220]. As per the research collaboration agreement, F. Hoffmann-La Roche will provide a one-off support service support contribution for the delivery of the study as well as provide tests at no cost.

This study has been costed in accordance with DH guidelines: Attributing the costs of health & social care Research & Development (AcoRD).

The study has been submitted for adoption on the NIHR portfolio providing access to service support costs.

10.4 Ethics Approval

No participants will be entered onto the study before ethical approval has been confirmed. The study protocol has received the favourable opinion of the HRA Ethics Committee North West - Haydock Research Ethics Committee for the study protocol, informed consent forms and other relevant documents.

All participating sites must undergo site specific assessment of capacity and capability prior to their participation in the study. All investigators and key study personnel will be appropriately trained in GCP.

The study will be conducted in accordance with, but not limited to, the Human Rights Act 1998, The Data Protection Act 2018, General Data Protection Regulations 2018, Freedom of Information Act 2000, the Human Tissue Act 2004 and the UK Policy Framework for Health and Social Care Research as amended from time to time.

Where participants agree to take part in the study, they will be informed of how data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with The General Data Protection Regulation (GDPR) (EU) 2016/679. As the sponsor of the study is a non-commercial organisation the legal basis for the handling and processing of data is 'task in the public interest.'

Annual progress reports will be submitted to REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

10.5 Participant and Public Involvement

Patient representatives from our local CUP patient engagement group ["CUP Club"], the CUP foundation Jo's Friends, and the World CUP Alliance have been involved in aspects of trial design, documentation review and plans for dissemination of results. They have also contributed to the development of patient information documents.

10.6 Study Monitoring

The study will be monitored by the sponsor, in accordance with the trial risk assessment through the completion and review of Sponsor Oversight Activity Reports (SOARs), Annual Progress Reports and Trial Management Oversight Committees. The study will be subject to The Christie Research division's audit programme. In order to provide assurance of the conduct of research activities and compliance to regulatory governance and Trust SOP's, a programme of audit will be developed on an annual basis. Priority for the selection of studies for auditing will be made on the basis of risk assessment of their Static (e.g. study design) and Dynamic Risk Factors (e.g. number of participants recruited or number of non-conformances reported); as well as the capacity of the Quality team. Audits will be conducted in accordance with the Trust SOP and Quality Management systems.

10.7 Protocol Compliance

The study protocol must be adhered to at all times. Intentional deviations from the protocol are not permitted under any circumstances.

The research team will record technical/minor deviations in the study records. Such deviations will include isolated issues that do not put participants at risk of harm nor risk credibility of data; e.g. a single missed visit window.

The sponsor will be notified of other deviations significantly impacting the risk profile of the study or significantly interrupting study services or supplies via: the-christie.sponsoredresearch@nhs.net. The Chief Investigator should also be notified.

Identified or suspected serious breaches of the study protocol or principles of GCP will be notified to the Sponsor's Operational Director of Research or Quality Manager via the-christie.breaches@nhs.net

10.8 Safety Reporting

10.8.1 Terms and Definitions

10.8.1.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant who has undergone a research procedure, including occurrences which are not necessarily caused by or related to that procedure.

10.8.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is defined as an untoward occurrence that:

a) Results in death;
b) Is life-threatening;

c) Requires hospitalisation or prolongation of existing hospitalisation;
d) Results in persistent or significant disability or incapacity;
e) Consists of a congenital anomaly or birth defect; or
f) Is otherwise considered medically significant by the investigator

10.8.2 Notes on Adverse Event Inclusions and Exclusions

Adverse events which do not meet the criteria to be reported as an SAE are to be excluded. Serious adverse events are to be reported from the time of participant consent to the last study visit. Serious adverse events or hospitalizations secondary to other causes as judged by investigators to be unrelated to the research procedure (e.g. the anticancer treatment the patient may be receiving) will not be considered an SAE for this study. Reported SAEs will be followed up until resolution of the event.

10.8.3 Evaluating Serious Adverse Events

The AE will be assessed for seriousness, causality and expectedness by the principal investigator or a delegated co-investigator at the relevant site. All SAEs are to be encoded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

SAEs will be submitted to the Chief Investigator within 24 hours of the site becoming aware of the event. SAEs must be reported using the paper SAE reporting form located in Appendix 2. Upon receipt, the Chief Investigator will review the event and the following will be considered.

- Whether there is a causal link with the study intervention
- Whether the event is or is not expected

The outcome of the assessment will be documented and filed in the trial master file.

10.8.4 Reporting of Serious Adverse Events

An SAE occurring to a research participant will be reported to the REC where in the opinion of the Chief Investigator the event was:

- “Related” – that is, it resulted from administration of any of the research procedures, and
- “Unexpected” – that is, the type of event is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs will be submitted to the REC within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website.

A copy of the complete report and the REC acknowledgement will be forwarded to the sponsor using the-christie.safety@nhs.net

10.9 Study Oversight

A weekly Genomic Tumour Advisory Board (GTAB), for reviewing sequencing results, is already established by the NW Genomics Laboratory Hub. Please see section 9.0 for detail.

A Trial Management Group (TMG) will be established and will include those responsible for the day-to-day management of the study including the Chief Investigator, site Principal Investigators and study managers

as detailed in the key contacts section of this protocol. The TMG will meet monthly to review recruitment and ensure the safety of study participants.

A Trial Steering Group (TSG) will be established to monitor ongoing progress of the trial. The purpose of these meetings will be to discuss the overall results and scientific merit of the study to date, highlight any areas of concern and/or issues, review resource and ongoing capacity and capability, and review any amendments. The TSG will consist of the Chief Investigator, Study Manager, site Principal Investigators, representative from Cancer Research UK National Biomarker Centre, the Sponsor and an external independent investigator with relevant research expertise in the field of Cancer of Unknown. This group will meet quarterly.

10.10 Protocol Amendments

Any changes in research activity will require an amendment and will be initiated by the CI. Proposed changes must be submitted in writing to the sponsor. The amendment will be categorised as substantial or non-substantial.

Any required changes to the documents that supported the original ethical approval will be submitted as an amendment to the appropriate ethical and regulatory authorities by the research team, following the UK process for handling amendments. Substantial amendments will not be implemented until REC and HRA, if applicable grant approval.

The research team will notify participating sites of all amendments. In accordance with the HRA amendments process, it is assumed that a participating site will implement the amendment unless communication to the contrary is received within 30 days of submission of the amendment to participating sites.

An Urgent Safety Measure (USM) may be put in place with immediate effect without gaining prior authorisation in order to protect participants from any immediate hazard to their health and safety. A discussion will take place within REC to agree timelines for the amendment submission. This discussion will be documented within the study file.

The research team will maintain an amendment history log to ensure that the most recent version of the protocol and supporting documents are used at all times.

10.11 Liability and Indemnity

As the sponsor is an NHS organisation the NHS indemnity scheme will apply in the event of harm to participants arising from the management of the study.

The University of Manchester’s insurance and indemnity will apply in the event of harm to the participants arising from the design of the study.

Participating sties will be liable for clinical negligence and other negligent harm to participants taking part in the study and covered by the duty of care owed to them by the sites concerned. For participating sites which are part of the NHS, the NHS indemnity scheme will also apply.

10.12 End of Study Notification

The end of study notification will be submitted in writing to the REC within 90 days of the date of termination of the study as defined in section 5.4.

In the event that the study is terminated early, the notification will be submitted to REC within 15 days.

10.13 Study Summary Report

The study team and Chief Investigator are responsible for compiling and submitting the final study report to the sponsor and REC within one year of study closure.

10.14 Publication Policy

The data arising from the study will belong to the sponsor, The Christie NHS Foundation Trust. The Operational Director for Research will act as the data custodian for this study.

The main study results will be published in a peer reviewed journal, on behalf of all collaborators.

Participants will be given the option to request a summary of the study results should they so wish.

The Publishing Party shall ensure that the contributions of the other relevant Parties, and Roche, are acknowledged in accordance with good academic practice. Prior to submission of publications or any other dissemination of the results, the Sponsor shall invite Roche to review the draft publication for factual accuracy in relation to the FMI services. The sponsor shall remove from the publication or presentation, any trade secret, propriety or Confidential Information disclosed by Roche to the Trust or belonging to Roche. Scientific information regarding effectiveness of IMP(s), their side effects or adverse events that may appear as a result of their use in the concerned indication shall never be considered confidential.

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Appendix 1. Summary of 2022 ESMO clinical practice guidelines for CUP[5]

CUP diagnosis should include:

- Thorough medical history and physical examination
- Basic blood counts including blood differential test.
- Biochemistry analyses including [alkaline phosphatase (ALP), lactate dehydrogenase (LDH), albumin]
- Intravenous contrast Computed tomography (CT) or magnetic resonance imaging (MRI) scans of neck, thorax, abdomen, and pelvis.
- Tumour Markers for:
    - All
        - Carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), Chromogranin A, cancer antigen 72-4 (CA72-4)
    - All males
        - Prostate-specific antigen (PSA), α-fetoprotein (AFP), human chorionic gonadotropin (β- hCG)
    - All females
        - Cancer antigen 15-3 (CA15-3), cancer antigen CA125 (CA125)
- Positron Emission Tomography (PET) Scan for:
    - Single-site or oligometastatic CUP
    - Head and neck-like CUP
- Mammography for:
    - All females
- Breast MRI for:
    - Females with axillary adenocarcinoma
- Brain MRI for:
    - Clinically suspected brain metastases
    - Putative lung primary
    - Single-site or oligometastatic CUP
- Gastroscopy or colonoscopy for:
    - Positive gastrointestinal primary
- Bronchoscopy for: Putative lung primary

Acceptable histology will include:

- Adenocarcinoma
- Poorly differentiated adenocarcinoma or carcinoma
- Squamous cell carcinoma

Histology and immunohistochemical profiles (per ESMO guidelines) that are not included above can be included but **MUST** be discussed with the Chief Investigator. Examples include non-epithelial cancer and neuroendocrine tumours.

If there is suspicion of a primary cancer, yet following the above examinations a primary cannot be found, treatment would be recommended based on known available site specific therapies for the proposed cancer type.

Where there is no strong suspicion of a primary site, but a specific subset of CUP can be identified, specific treatment would be recommended (see Table 1)

Patients for which no specific subset of CUP can be identified, including those with favourable or poor prognosis, can be considered for enrolment into the study.

Appendix 2: Serious Adverse Event Report Form

The Christie
Research and Innovation

Serious Adverse Event: EGG-CUP CFTSp213

Study and subject details	**For Project Team use only - SAE ID no:**
Date: ☐☐ / ☐☐ / ☐☐☐☐ Notification type: ☐ Initial ☐ FU1 ☐ FU2 ☐ FU3 ☐ Other	
Site ID	Participant no.
SAE details and concomitant treatment	
SAE category*	SAE start date/time
*Categories: 1) Fatal 2) Life threatening 3) Involved or prolonged hospitalisation 4) Disability or incapacity 5) Other (describe in SAE details)	
SAE medical term	
SAE details (provide a brief description of the event, grade and treatment given to treat SAE etc)	

Date or duration of treatment	Outcome+	+ Outcome categories:
		1) Resolved 2) Resolve with sequelae 3) Ongoing, no therapy 4) Ongoing, therapy 5) Death

Relevant diagnostic tests	
Concomitant treatment(s) (exclude those used to treat SAE) OR attach relevant CRF pages	Date(s) of administration
Relevant patient medical history OR attach CRF	

Please email the completed form to the-christie.egg-cup@nhs.net

Reporter details			
Reporter name	Reporter email	Reporter phone no.	Reporter fax no.

PI assessment of SAE causality and expectedness (to be completed by the local PI or appropriately qualified delegate only)			
Could the trial intervention(s) have reasonably caused the SAE?		☐ No ☐ Yes	If the two right-hand boxes are checked, event is an unexpected and related event and will be reported to REC.
If caused by the trial intervention(s), is the nature, severity, seriousness or outcome of the SAE consistent with the reference safety information? i.e. can it be expected from the intervention(s)?		☐ Yes ☐ No ☐ NA	
If there is more than one intervention, specify which is likely to have caused the SAE			
PI signature		Date	

CI assessment of SAE causality and expectedness (to be completed by the CI or appropriately qualified delegate only)			
Could the trial intervention(s) have reasonably caused the SAE?		☐ No ☐ Yes	If the two right-hand boxes are checked, event is an unexpected and related event and will be reported to REC.
If caused by the trial intervention(s), is the nature, severity, seriousness or outcome of the SAE consistent with the reference safety information? i.e. can it be expected from the intervention?		☐ Yes ☐ No ☐ NA	
If there is more than one intervention, specify which is likely to have caused the SAE			
CI signature		Date	

Notes for completion:

For initial notifications: Assessment by the CI is not required on the initial report and this and further details may be sent later. Please ensure that any patient-identifying information is redacted before providing medical history or other requested information.

Follow-up reports: Follow-up information should be sent as soon as possible after the initial report. Apart from trial / SAE identifiers and reporter contact details, there is no need to duplicate information previously sent. Please complete only those fields with the additional information.

It is not necessary to notify those SAEs indicated in the protocol as not requiring immediate reporting. Errors or corrections should be scored through with a single line and the correct entry clearly written with the corrector's initials and the date. Correction fluid or tape is not permitted.

Please store original copies in the Investigator Site File.

Please email the completed form to the-christie.egg-cup@nhs.net