Clinical Trial Details (PDF Generation Date :- Mon, 03 Oct 2022 12:26:53 GMT)

CTRI Number	CTRI/2019/03/017918 [Registered on: 05/03/2019] - **Trial Registered Prospectively**
Last Modified On	07/09/2021
Post Graduate Thesis	No
Type of Trial	Observational
Type of Study	Prospective Observational Study
Study Design	Other
Public Title of Study	Liquid biopsy to replace tissue biopsy
Scientific Title of Study	Tissue biopsy Replacement with Unique Evaluation of circulating bio-markers for morphological evaluation and clinically relevant molecular typing of malignancies from BLOOD sample.

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Dr Dadasaheb Akolkar
Designation	Director Research and Innovations
Affiliation	Datar Cancer Genetics Limited
Address	First Floor, Department of Research and Innovations, Datar Cancer Genetics Limited, F-8, D Road, MIDC, Ambad, Nasik, Maharashtra 422010 Nashik MAHARASHTRA 422010 India
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Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	Dr Dadasaheb Akolkar
Designation	Director Research and Innovations
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Source of Monetary or Material Support

Source of Monetary or Material Support
> Canconnect Foundation, Flat No.12, Ameya Sankul, B Wing, Sharanpur Road, Nasik, Maharashtra 422 005
> Datar Cancer Genetics Limited, F-8, D Road, MIDC, Ambad, Nasik, Maharashtra 422 010

Primary Sponsor

Primary Sponsor Details	
Name	Datar Cancer Genetics Limited
Address	Datar Cancer Genetics Limited, F-8, D Road, MIDC, Ambad, Nasik, Maharashtra 422 010
Type of Sponsor	Other [Molecular Laboratory and Research Centre]

Details of Secondary Sponsor

Name	Address
Canconnect Foundation	Flat No.12, Ameya Sankul, B Wing, Sharanpur Road, Nasik, Maharashtra 422 005

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
Dr Dadasaheb Akolkar	Datar Cancer Genetics Limited	First Floor, Department of Research and Innovations, F-8, D Road, MIDC, Ambad, Nasik, Maharashtra 422010 Nashik MAHARASHTRA	7387705888 dadasaheb.akolkar@datarpgx.com

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Datar Cancer Genetics Limited Ethics Committee	Approved	19/02/2019	No
Datar Cancer Genetics Limited Ethics Committee	Approved	31/12/2020	No
Datar Cancer Genetics Limited Ethics Committee	Approved	21/08/2021	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Neoplasms

Intervention / Comparator Agent

Type	Name	Details

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	99.00 Year(s)
Gender	Both
Details	For Inclusion, an individual must meet all of the following criteria.

	Inability to meet all inclusion criteria for a cohort will lead to exclusion. 1. Adult males and females, aged 18 years and above, 2. Provision of Informed Consent, 3. Willing and able to participate in the study and provide blood sample, as well as other (e.g., tissue, CSF, AF, PF, BM) samples as per availability and feasibility. 4. No co-morbidities which could impair study participation or sample collection, 5. Female participants: neither pregnant, nor lactating 6. For Cohort A (Known Cancer Cases) (6a). Diagnosed with any malignancy as per current appropriate Standard of Care approach (e.g., HPE confirmed diagnosis of solid organ cancer) (6b). Therapy Naïve as well as Received prior anticancer treatments. 7. For Cohort B (Suspected Cases) (7a). No prior diagnosis of (any) cancer, (7b). Presenting with radiological or clinical symptoms suspected of localized solid organ cancer and posted to undergo tissue biopsy as part of standard diagnostic procedure. 8. For Cohort C (Known Benign Cases) (8a). No prior diagnosis of any cancer (8b). Confirmed diagnosis of benign (non-cancerous / non-malignant) conditions as per relevant Standard of Care diagnostic work-up.

Exclusion Criteria

Exclusion Criteria	
Details	For Exclusion, an individual may meet any of the following criteria. Meeting even one exclusion criteria will lead to exclusion. 1. Age less than 18 years, 2. Inability to provide Informed Consent, 3. Co-morbidities or ongoing treatments which could impair study participation or sample collection 4. Current febrile illness 5. Acute exacerbation or flare of an inflammatory condition requiring escalation in medical therapy within 14 days prior to screening, 6. Blood transfusion within 14 days prior to screening, 7. CT / PET-CT within 14 days prior to screening, 8. Positive for HIV / HBV / HCV, 9. Failure to meet general or cohort-specific Inclusion Criteria.

Method of Generating Random Sequence	Not Applicable
Method of Concealment	Not Applicable
Blinding/Masking	Open Label

Primary Outcome

Outcome	Timepoints
To determine the performance characteristics of TruBlood in detecting cancers and establishing cancer diagnosis, and discerning cancers from benign cases and asymptomatic individuals.	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)

Secondary Outcome

Outcome	Timepoints
To determine the clinical utility of TrueBlood test for morphological / histopathological typing of malignancy.	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim)

	Day 360 (final)
To determine the clinical utility of TrueBlood test for molecular evaluation of malignancy,	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)
To determine the clinical utility of TrueBlood test for functional evaluation of malignancy,	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)
To determine the clinical utility of TrueBlood test for theranostic or therapeutically- relevant typing of malignancy,	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)
To determine the clinical utility of TrueBlood test for response or resistance profiling of malignancy towards anticancer agents,	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)
To determine the clinical utility of TrueBlood test for longitudinal monitoring of malignancies.	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)
To identify and determine the clinical utility and performance characteristics of other additional circulating tumor and tumor cell biomarkers for screening, detection, diagnostic, localization, theranostic or prognostic application in malignancies.	Evaluation Timepoints: Day 0 (baseline: sample collection) Day 180 (interim) Day 360 (final)

Target Sample Size	**Total Sample Size=**80000 **Sample Size from India=**80000 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	N/A
Date of First Enrollment (India)	06/03/2019
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**5 **Months=**0 **Days=**0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Open to Recruitment
Publication Details	Akolkar D et al. Circulating ensembles of tumor-associated cells: A redoubtable new systemic hallmark of cancer. Int J Cancer. 2020 Jun 15;146(12):3485-3494. doi: 10.1002/ijc.32815. Ranade A et al. Hallmark Circulating Tumor-Associated Cell Clusters Signify 230 Times Higher One-Year Cancer Risk. Cancer Prev Res (Phila). 2021 Jan;14(1):11-16. doi: 10.1158/1940-6207.CAPR-20-0322. Crook T et al. Clinical utility of circulating tumor-associated cells to predict and monitor chemo-response in solid tumors. Cancer Chemother Pharmacol. 2021 Feb;87(2):197-205. doi: 10.1007/s00280-020-04189-8. Gaya A et al. Evaluation of circulating tumor cell clusters for pan-cancer noninvasive diagnostic triaging. Cancer Cytopathol. 2021 Mar;129(3):226-238. doi: 10.1002/cncy.22366.
Brief Summary	

1 BACKGROUND AND INTRODUCTION

Cancer is one of the leading causes of deaths in India and over 630,000 people die of cancer each year. According to the most recent predictions by the International Agency for Research on Cancer GLOBOCAN project, India's cancer burden will nearly double in the next 20 years, from a million new cases in 2012 to more than 1·7 million by 2035. (Ferlay J et al., Mallath MK et al.)

First step in cancer management is establishing cancer diagnosis with histopathological typing of tumor tissue sample. Tissue sampling is achieved either through Fine Needle Aspiration Cytology (FNAC) or tissue biopsies or other specialized cytology procedures e.g. bronchoscopy, ultrasound-guided bronchoscopy, transthoracic needle biopsy, and thoracoscopy in lung cancer. The diagnostic yield of these procedures varies. In lung cancer the diagnostic yield varies between 58-97% among various tissue sampling procedures. (Ofiara LM et al.). These techniques are invasive and may not always feasible in all patients due to various factors like associated comorbidities or localization of tumor close to vital organs. Additionally, these techniques may be associated with complications due to their invasive nature. In tissue sampling procedures for lung cancer, various complications like pneumothorax, hypoxemia, hemorrhage etc. may occur. The rates of these complications vary with type of procedure used like major complication rates between 0.08 and 5% for fiberoptic bronchoscopy (Simpson FG et al) whereas rate of major complications like bleeding and pneumothorax may occur in 10% and up to 20% of cases, respectively with transthoracic needle aspirate. (Klein JS et al.)

In certain percentage, tissue sampling may be inadequate or may not representative leading to repetition of these invasive procedures. For example, in case of lung cancer up to 80% of patients receiving chemotherapy for advanced disease will have only a small biopsy and/or cytology samples available for diagnosis. (Kerr et al.). Also, with advances in molecular testing and targeted therapies, in addition to routine histopathological and immunohistochemical examination, molecular testing has become imperative in certain malignancies. The recent discovery of driver mutations and their association with greater responsiveness to specific targeted agents led to a paradigm shift in cancer treatment from conventional chemotherapy to biomarker-driven targeted therapy. This new era of personalized therapy brings an increasing demand for characterization of tumour genotypes and phenotypes. Tissue samples are routinely formalin fixed for further examination. The accuracy of molecular tests depends on sample quality as much as the molecular analyses themselves. The formaldehyde initiates DNA and RNA denaturation, formalin fixed tissue exhibit a high frequency of nonreproducible sequence alteration because of formalin cross-linking cytosine nucleotides on either strand, creating an artificial C-T or G-A mutation. (Srinivasan M et al.) All these fixation induced artefacts can finally impact the quality of molecular analysis and its results.

Tissue sampling also faces challenge of tumor heterogeneity. Intratumor heterogeneity and heterogeneity between tumors at different sites, can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples and may present major challenges to personalized-medicine and biomarker development. (Gerlinger M et al.). Due to invasive nature of these tissue sampling modalities, it is difficult to repeat them for longitudinal disease monitoring for therapy response evaluation, detection of molecular evidence of acquired resistance or tumor evolution. Tissue biopsy from cancer of internal organs including brain are invasive to various extent and may at times require multiple attempts to get representative tissue sample to arrive at a diagnosis which not only delays starting treatment but also necessitates the patient to undergo several invasive procedures along with its antecedent complication. In cases of recurrence, repeat invasive biopsy will have to be undertaken to establish whether it is recurrence or new malignancy. Primary Central Nervous System (CNS) malignancies including high grade gliomas pose a clinical challenge as MRI at times can be equivocal. Repeated brain biopsy especially of deep seated and eloquent structures to evaluate disease progression is both invasive and impractical given the cumulative surgical risk. All these limitations of invasive tissue sampling modalities urge us to find a non-invasive modality which can provide information about cancer diagnosis and molecular evaluation necessary to plan treatment protocols in cancer patients..

2 RATIONALE

Liquid biopsy involves the analysis of biomarkers like circulating tumor cells (CTCs), cell-free nucleic acids - circulating free DNA (cfDNA), exosomal messenger RNA (mRNA) and micro RNA (miRNA) in bodily fluids such as blood. The obtaining of specimens for liquid biopsy is easier and less invasive than tissue biopsy.

Current liquid biopsy approaches focus on CTC enumeration for disease prognostication and cfDNA analysis for cancer genotyping for selection of certain targeted therapies e.g. Osimertinib in EGFR T790M NSCLC.

There is no data available for utility or potential of liquid biopsy for morphological typing of malignancies.

A preliminary trial has suggested that a single blood test could one day be used to detect a variety of cancers. (Joshua D Cohen et al.) However, development of methods for noninvasive detection of cancer has still not been standardized. (Jillen Phallen et al.) Biopsy of tumour tissue and tumour

markers from tumour tissue and blood remains the gold standard for diagnosis and prognostication.

Analysis of cell free DNA and mRNA in the peripheral blood (Liquid Biopsy) has shown high degree of concordance both in terms of diagnosis and grading of tumour even in CNS malignancies. (Lee I et al.)

However liquid biopsy based on cfDNA is currently unable to identify underlying tissue of origin in a large number of cases due to the fact that most somatic alterations are not cancer type specific. (Cohen et al.)

Circulating tumor cells (CTCs) are the tumor cells which have detached from primary tumor site and have gained access to peripheral circulation. These may potentially lodge in distant organs giving rise to metastasis. Thus, CTCs are a pre-requisite for distant disease spread and thus are detectable before late stage/metastatic disease develops. Also, CTCs have additional advantage of expressing tissue-of-origin specific markers in their cytoplasm/nucleus/membrane giving rise to possibility of identification of primary tumor site. In certain cases, morphological classification into probable cancer type e.g. squamous vs adenocarcinoma may be feasible, giving better access to patient management in addition to the diagnosis. Thus, the evaluation of CTCs in cancer management, has potential to extend beyond prognostication. As technologies emerge to analyze CTCs at the molecular level, biological behavior of the tumour can be obtained in real time, with the promise of CTCs eventually acting as a ‘surrogate tumour biopsy’. (Mathew G Krebs et al.).

All in all, comprehensive blood based biomarkers based liquid biopsy has potential to replace tissue biopsy and to pave a way for non-invasive, accurate blood based diagnostic modality to improve patient care and quality of life.

Current study is undertaken to evaluate the feasibility of tissue biopsy replacement with unique evaluation of circulating bio-markers at Datar Cancer Genetics Limited for morphological evaluation and clinically relevant molecular typing of malignancies from blood sample.

3 STUDY OBJECTIVES

3.1 Primary Objective

To determine the performance characteristics of TruBlood in

- detecting cancers and establishing cancer diagnosis,
- discerning cancers from benign cases and asymptomatic individuals.

3.2 Secondary Objectives

To determine the clinical utility of TrueBlood test for

- morphological / histopathological typing of malignancy,
- molecular evaluation of malignancy,
- functional evaluation of malignancy,
- theranostic or therapeutically- relevant typing of malignancy,
- response or resistance profiling of malignancy towards anticancer agents,
- longitudinal monitoring of malignancies.

3.3 Exploratory Objectives

- To identify and determine the clinical utility and performance

characteristics of other additional circulating tumor and tumor cell biomarkers for screening, detection, diagnostic, localization, theranostic or prognostic application in malignancies.

4 OUTCOME MEASURES

4.1 Primary Outcome Measures

- Specificity for detection of malignancy
- Sensitivity for detection of malignancy
- Specificity for morphological / histopathological typing of malignancy
- Sensitivity for morphological / histopathological typing of malignancy

4.2 Secondary Outcome measures

- Specificity for functional evaluation of malignancy,
- Sensitivity for functional evaluation of malignancy,
- Specificity for theranostic or therapeutically- relevant typing of malignancy,

- Sensitivity for theranostic or therapeutically- relevant typing of malignancy,
- Specificity for response or resistance profiling of malignancy towards anticancer agents,
- Sensitivity for response or resistance profiling of malignancy towards anticancer agents,
- Specificity for longitudinal monitoring of malignancies.
- Sensitivity for longitudinal monitoring of malignancies.

5 INVESTIGATIONAL PLAN

Study Type: Observational

Study Design: Prospective

Allocation: Non-randomised

Masking: Not applicable

EC Status: EC Approved

Study Start Date: March 06, 2019 (Started)

Study Status	Active (Open for Enrollment)
Estimated Primary Completion:	August 20, 2023
Estimated Study Completion:	August 20, 2024
Estimated Enrollment:	80,000
Number of Sites	HCG-Cancer Centres (Multiple, Pan-India) DCG, Nasik, India

6 Study Population

COHORT A: Known Cancer Cases: Adult males and females who are known cases of cancers, where the cancer has been diagnosed via appropriate standard of care approach (e.g., biopsy followed by HPE).

COHORT B: Suspected Cancer Cases: Adult males and females with symptoms suggestive of cancers and who have been posted for appropriate (standard of care) diagnostic work-up with biological sample.

COHORT C: Known Benign Cases: Adult males and females with no prior diagnosis of cancer and no present symptoms suggestive of cancer, and are HPE confirmed cases of benign conditions.

6.1 Inclusion Criteria

Inability to meet all inclusion criteria for a cohort will lead to exclusion.

1. Adult males and females, aged 18 years and above,

2. Provision of Informed Consent,

3. Willing and able to participate in the study and provide blood sample, as well as other (e.g., tissue, CSF, AF, PF, BM) samples as per availability and feasibility.

4. No co-morbidities which could impair study participation or sample collection,

5. Female participants: neither pregnant, nor lactating

6. For Cohort A (Known Cancer Cases)

a. Diagnosed with any malignancy as per current appropriate Standard of Care approach (e.g., HPE confirmed diagnosis of solid organ cancer)

b. Therapy Naïve as well as Received prior anticancer treatments.

7. For Cohort B (Suspected Cases)

a. No prior diagnosis of (any) cancer,

b. Presenting with radiological or clinical symptoms suspected of localized solid organ cancer and posted to undergo tissue biopsy as part of standard diagnostic procedure.

8. For Cohort C (Known Benign Cases)

a. No prior diagnosis of any cancer

b. Confirmed diagnosis of benign (non-cancerous / non-malignant) conditions as per relevant Standard of Care diagnostic work-up.

6.2 Exclusion Criteria

Meeting even one exclusion criteria will lead to exclusion.

1. Age less than 18 years,
2. Inability to provide Informed Consent,
3. Co-morbidities which could impair study participation or sample collection
4. Current febrile illness
5. Acute exacerbation or flare of an inflammatory condition requiring escalation in medical therapy within 14 days prior to screening,
6. Blood transfusion within 14 days prior to screening,
7. CT / PET-CT within 14 days prior to screening,
8. Positive for HIV / HBV / HCV,
9. Failure to meet general or cohort-specific Inclusion Criteria.

7 PARTICIPANT SAMPLES

7.1 Samples Collected from all Participants

- 15 mL peripheral blood

7.2 Samples Collected as per Feasibility and Availability

- Cerebrospinal, ascitic or pleural fluids
- Tissue samples
- Other biological samples

7.3 Sample Collection

- Study participants will undergo blood draw at baseline of 15 ml as per appended sample collection protocol.
- Study participants (cancer cases) who are assigned to systemic anticancer treatments will undergo collection of additional (longitudinal) blood samples (15 mL) during course of further treatment, prior to each treatment cycle,
- Study participants (cancer cases) who are on active systemic anticancer treatments will undergo collection of additional (longitudinal) blood samples (15 mL) prior to each treatment evaluation

visit (e.g., radiological imaging or clinical evaluation), with a minimum gap of 1 month between each consecutive blood draw,

- Study participants (cancer cases) who have been posted for surgery or radiation, will undergo 15 mL blood sample collection prior to and after the surgery / radiation.

- In study participants (suspected cases) who have been posted for an invasive biopsy, an aliquot of the tissue may be collected and sent to the Sponsor where feasible and after obtaining consent of the patient.

- In Study Participants (cancer cases or benign cases or suspected cases) who have been posted for a surgery, an aliquot of the resected / excised tumor tissue may be collected and sent to the Sponsor where feasible and after obtaining consent of the patient.

- In Study Participants (cancer cases or benign cases or suspected cases) who have been posted for collection of cerebrospinal / ascitic / pleural fluid or bone marrow, an aliquot of the sample may be collected and sent to the Sponsor where feasible and after obtaining consent of the patient.

8 STUDY EVALUATIONS AND MEASUREMENTS

8.1 Screening Evaluations and Measurements

Information that will be abstracted from the medical chart (paper or electronic).

- Patient Code / UHID
- Age
- Gender
- Ethnicity
- Personal medical history
- Family History of cancer
- Symptoms

8.2 Study Assessments

- After eligibility determination, detailed information sharing about the nature of study and answering all concerns and queries of study participants, study enrollment will be done and written informed consent will be obtained.

- SoC investigations will not be conducted as part of TrueBlood study but as part of routine management, and hence Sponsor or others working on sponsor's behalf will not be liable for any financial or legal implications arising out of these SoC investigations.

- Study participant will not undergo any additional procedure exclusively for TrueBlood project except for 15 ml blood sample collection which is not associated with significant health hazard.

- Tissue or other biological samples will be provided to

Sponsor only when patient is undergoing tissue sampling for SoC management and providing additional tissue sample to TrueBlood project does not impose any significant additional risk to study participant.

- The clinical records and results of SoC investigations like HPE, IHC and molecular analysis reports along with relevant clinical data will be collected as a part of TrueBlood project.

9 STUDY CONDUCT

9.1 STEP 1 (Recruitment and Consent):

Individuals fulfilling eligibility criteria are recruited after providing detailed information about study protocol, its utility and limitations. Participant enters study only after providing written informed consent.

9.2 STEP 2 (Sample Collection):

After consent, participants submit blood sample as proposed in study assessment, before starting treatment. Whenever feasible other biological samples like tissue will be provided.

9.3 STEP 3 (Sample Processing):

Samples will be processed at DCGL as per protocol.

9.4 STEP 4 (Data Evaluation):

The data from study analytes will be evaluated to determine various performance characteristics measures of TruBlood.

9.5 Safety Evaluation

As this is an observational trial and involves only peripheral blood draw as an additional study related procedure, there are no study related adverse events anticipated.

9.6 Data Management

Data confidentiality will be strictly maintained and only patient deidentified data will be utilized for analysis and publication. Protection of patient health information will be compliant with HIPAA guidelines. Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. No identifiable data will be used for future study without first obtaining IEC approval. The data used for publication will be deidentified. The data will be retained for minimum three years. Sponsor will have access to deidentified patient's medical history as well as diagnostically relevant information such as (but not limited to) clinical and diagnostic details of the participant in a pre-approved electronic or hard-copy format. Sponsor will retain ownership of all TruBlood findings. The data will be categorized into appropriate sections, analyzed by the Sponsor and will be published.

10 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be carried out according to the Declaration of Helsinki, ICMR, GCP AND the ICH GCP Guidelines. The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (EC) for approval. The PI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. The participation in the study is entirely voluntary and after providing appropriate consent. There is no active ongoing intervention involved in current study as it involves only single point peripheral blood draw and tissue sample collection only when feasible. No intervention except peripheral blood draw of 15 mL will conducted exclusively for TrueBlood. All such SoC investigations are not being conducted as part of TrueBlood study but as part of routine management, and hence DCGL or others working on sponsor's behalf will not be liable for any financial or legal implications arising out of these SoC investigations. There will be no financial implications for the study participation nor will there be any incentives.

Consent forms will be approved by EC and the participant will be asked to read and review the

document. The investigator will explain the study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

No incentives will be given to participant or relative. No reimbursement for travel, parking or meals will be paid. No compensation for time, effort or inconvenience will be paid. No gifts or tokens of appreciation will be given..