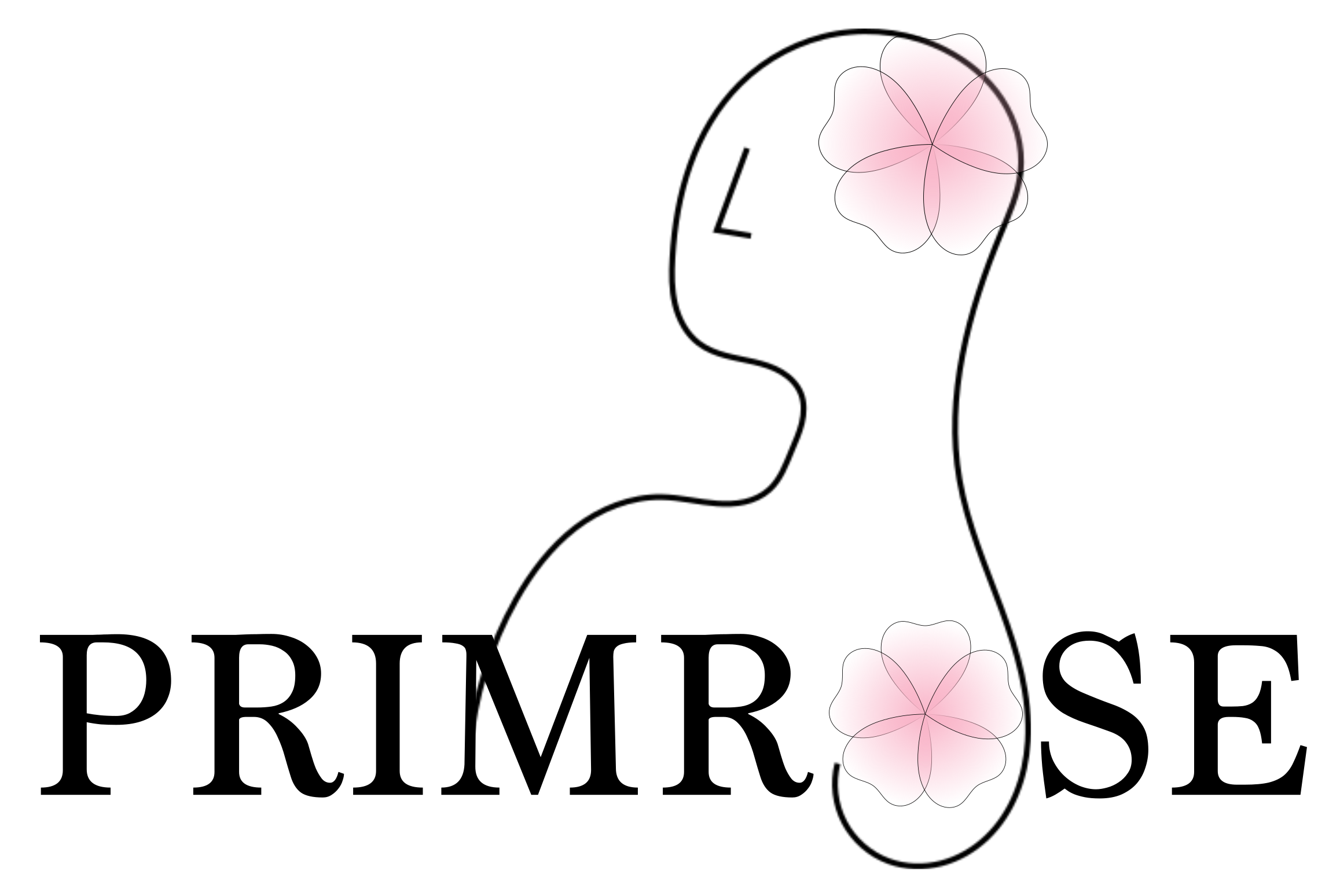
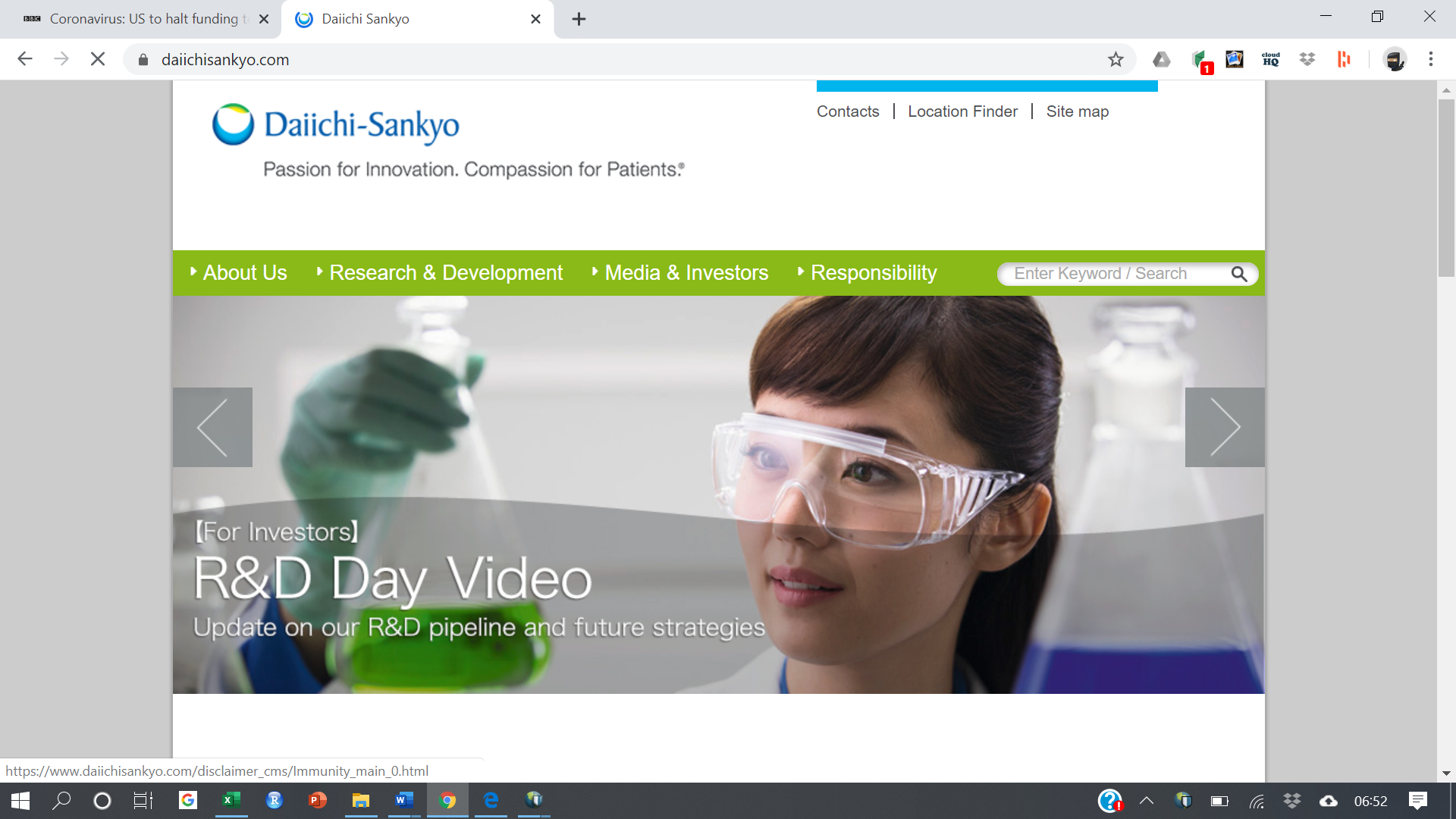
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**Protocol for PRIMROSE Audit**

**A prospective multi-centre cohort study to assess the presentation, management and outcomes of patients with CNS disease secondary to breast cancer**

|  |  |
| --- | --- |
| **Sponsor:**  University of Liverpool  1st Floor Block C  Waterhouse Building  3 Brownlow Street  Liverpool  L69 3GL |  |

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**Protocol Approval**

I, the undersigned, hereby approve this clinical study protocol:

**Authorised by Chief Investigator:**

|  |  |
| --- | --- |
| **Signature:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | **Date:** \_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Carlo Palmieri  **Chief Investigator** |  |

I, the undersigned, hereby approve this clinical study protocol:

**Authorised on behalf of Sponsor:**

|  |  |
| --- | --- |
| **Signature:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | **Date:** \_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Alex Astor |  |
| Head of Research Support Office |  |
| **University of Liverpool**  **Sponsor** |  |

I, the undersigned, hereby approve this clinical study protocol:

**Authorised on behalf of the Lead Statistician:**

|  |  |
| --- | --- |
| **Signature:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | **Date:** \_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Richard Jackson |  |
| **Trial Statistician** |  |
| **CRUK Liverpool Clinical Trials Unit** |  |

**Authorised on behalf of Director of LCTC**

I, the undersigned, hereby approve this clinical study protocol:

|  |  |
| --- | --- |
| **Signature:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | **Date:** \_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Professor Carrol Gamble |  |
| **Director of Liverpool Clinical Trials Centre (Fixed-Term)** |  |
|  |  |

**General Information**

This section describes the PRIMROSE Audit. The audit is to be carried out by clinical staff members and which does not involve experimental treatment or placebo treatment.

This protocol defines the participant characteristics required for audit study entry. There is no schedule of participant recruitment, treatment and follow-up aspect to this audit. This is a single-arm prospective observational audit study involving routine data. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the audit, but sites entering patients for the first time are advised to contact the coordinating centre Liverpool Clinical Trial Centre to confirm they have the most up to date version. Clinical problems relating to this audit should be referred to the relevant Chief Investigator, Professor Carlo Palmieri, via the CTU.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

| **Contact Details: Institutions** | | |
| --- | --- | --- |
| **Sponsor:** | **Trial Management, Monitoring and Analysis:** | **Statistics:** | |
| University of Liverpool  1st Floor Block C  Waterhouse Building  3 Brownlow Street  Liverpool  L69 3GL  Email : sponsor@liverpool.ac.uk | Liverpool Clinical Trials Centre  University of Liverpool  1st Floor Block C  Waterhouse Building  3 Brownlow Street  Liverpool  L69 3GL  Email: primrose@liverpool.ac.uk | Liverpool Clinical Trials Centre  University of Liverpool  1st Floor Block C  Waterhouse Building  3 Brownlow Street  Liverpool  L69 3GL | |

| **Contact Details: Individuals** | | |
| --- | --- | --- |
| **Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:** | **Chief Investigator (CI):** | **Medical Expert who will Advise on Protocol Related Clinical Queries (in cases where the CI is unavailable to respond to urgent queries):** |
| Charlotte Rawcliffe  Liverpool Clinical Trials Centre  1st Floor Block C  Waterhouse Building  3 Brownlow Street  Liverpool  L69 3GL  E: charlotte.rawcliffe@liverpool.ac.uk | Professor Carlo Palmieri  Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine  University of Liverpool  Level 6  Duncan Building  Daulby Street  Liverpool  L69 3GA  Tel: 0151 706 3616  E: [c.palmieri@liv.ac.uk](mailto:c.palmieri@liv.ac.uk) | Professor Michael Jenkinson  The Walton Centre NHS Foundation Trust  Lower Lane  Fazakerley  Liverpool  L9 7LJ |

**Additional Contacts:**

The contact details for the audit oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1. **Glossary**

|  |  |
| --- | --- |
| ABN | Association of British Neurologists |
| BCTRCG | Breast Cancer Trainees Research Collaborative Group |
| BNSU | British Neurological Surveillance Unit |
| CI | Chief Investigator |
| CM | Cerebral Metastases |
| CNS | Central Nervous System |
| CSF | Cerebrospinal Fluid |
| CT | Computed Tomography |
| GCP | Good Clinical Practice |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| ISRCTN | International Standard Randomised Controlled Trials Number |
| LCTC | Liverpool Clinical Trials Centre |
| LM | Leptomeningeal Metastases |
| MBC | Metastatic Breast Cancer |
| MRI | Magnetic Resonance Imaging |
| NHS | National Health Service |
| PND | Paraneoplastic Neurological Disorders |
| QA | Quality Assurance |
| QC | Quality Control |
| REDCap | Research Electronic Data Capture |
| SRS | Stereotactic Radiosurgery |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |

1. **Protocol Overview**

|  |  |
| --- | --- |
| **Full Title** | PRIMROSE Audit: prospective multi-centre cohort study to assess the presentation, management and outcomes of patients with CNS disease secondary to breast cancer |
| **Acronym** | PRIMROSE Audit |
| **Phase** | Not applicable (Observational multi-centre cohort study) |
| **Target Population** | Breast cancer patients, male or female over 16 years old with CNS disease secondary to breast cancer in the UK. |
| **Sample size** | Uncapped (minimum N = 300) |
| **Inclusion Criteria** | 1. Male or female.  2. >16 years of age  3. Histologically and/or cytologically confirmed breast cancer with Central Nervous System (CNS) involvement as defined as having one or more of the following:  a. Metastases to the brain parenchyma  b. Metastases to the leptomeninges  c. Paraneoplastic Neurological Disorders |
| **Exclusion Criteria** | No formal exclusion criteria |
| **Number of sites** | Open to all NHS centres involved in care of patients with breast cancer |
| **Patient Study Duration** | Information will be collected from time of patient registration until death or end of study |
| **Study Duration** | 2 years |
| **Description of intervention** | None, anonymised collection of routine clinical data |
| **Objectives** | **Primary Objectives**   * To report the survival of patients diagnosed with CNS involvement secondary to breast cancer. * To describe the current practice in diagnosis, staging and management of CNS involvement secondary to breast cancer in relation to national and international guidelines, including the NICE guidelines for the management of brain metastases in adults (NICE Guidance 99, July 2018), European Association of Neuro-Oncology (NANO 2017)) and the National Comprehensive Cancer Network guidelines (Version 1.2018 Central Nervous System Cancers).   **Secondary Objectives**   * To define the number of new cases of CNS involvement secondary to breast cancer in the UK per year. * To evaluate the outcomes of patients treated for CNS involvement secondary to breast cancer in the UK. * To inform and help in the development of potential prospective studies and clinical trials. |

1. **Schematic of Study Design**

**Inclusion Criteria for patients to be entered into PRIMROSE Audit:**

1. Male or female

2. >16 years of age

3. Histologically and/or cytologically confirmed breast cancer with CNS involvement as define as:

a. Metastases to the brain parenchyma

b. Metastases to the leptomeninges

c. Paraneoplastic Neurological Disorders

**Patient Identification:**

New or existing patients (in contact with clinical services) with a clinical diagnosis of CNS involvement secondary to breast cancer identified by member of medical or nursing staff in inpatient or outpatient settings.

**Log on to REDCap database to:**

* Check for existing record using NHS number
* Assign new anonymised study ID
* Populate REDCap database using patient notes retrospectively or prospectively after routine clinical visits

Consent not required

**On REDCap:** NHS ID will only be available to be viewed by relevant clinical staff only to prevent double entry.

1. **Roles and Responsibilities**

**Sponsor**

The Sponsor is the University of Liverpool and is legally responsible for the study. They will formally delegate specific sponsoring roles to the Chief Investigator and Clinical Trials Unit.

**Chief Investigator**

Professor Carlo Palmieri is the Chief Investigator for the study and is responsible for overall design and conduct of the study in collaboration with other members of the study team.

**Principal Investigators**

In each participating centre a principal investigator – or a regional lead / breast cancer trainee – will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

**Clinical Trials Centre**

The Liverpool Clinical Trials Centre at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for study management activities including (but not limited to) study planning, budget administration, Audit Master File management, data management, statistical analysis and participating site coordination.

**Funder**

This study is funded by Daiichi Sankyo Europe GmBH.

**4.1 Oversight Committees**

The PRIMROSE Audit is subject to oversight from the following committees:

**Trial Management Group (TMG)**

A Trial Management Group (TMG) for this audit study will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the audit and will be responsible for the day-to-day running and management of the audit. The TMG will meet at least monthly at setup stage and then reduce to quarterly throughout the year unless more frequent meetings are required. Additionally, the group will work with research nurses and members of the Breast Cancer Clinical Trainees Research Collaborative Group to

* Build the clinical network to maximise recruitment opportunities
* Ensure consistent identification and registration of eligible patients to the study
* Increase the study’s exposure to trainees at all UK cancer and neurological units and centres.

**Trial Steering Committee (TSC)**

The Trial Steering Committee for this audit study will consist of an independent chairperson (i.e. the individual will not be involved in the development of the audit and the hospital they work will not open as a site), independent experts in the field of CNS involvement secondary to breast cancer, independent statistician, and non-independent members including the CI, TC and observers. The role of the TSC is to provide overall supervision for the progress of the audit data collection and provide advice through its independent Chairman. The decision for the continuation of the audit lies with the TSC and as such they will meet throughout the audit (at least annually).

**4.2 Protocol Contributors**

|  |  |  |
| --- | --- | --- |
| **Name** | **Affiliations** | **Contribution to protocol** |
| Professor Carlo Palmieri | University of Liverpool | Initiating the study, drafting the protocol and providing necessary guidance and review during development of the protocol. |
| Dr Vinton Cheng | Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust | Drafted the main protocol for grant submission |
| Dr Tim Robinson | University of Bristol | Drafted the main protocol for grant submission |
| Dr Amy Kwan | Dept. of Academic Oncology, Medical School University of Sheffield | Drafted the main protocol for grant submission |
| Dr Hayley McKenzie | Dept. of Medical Oncology, Southampton University Hospitals NHS Trust | Drafted the main protocol for grant submission |
| Dr Amanda Fitzpatrick | The Institute of Cancer Research, Chester Beatty Laboratories | Drafted the main protocol for grant submission |
| Dr Apostolos Konstantis | UCLH and Princess Alexandra Hospital | Drafted the main protocol for grant submission |
| Mr Ruichong Ma | Dept. of Neurosurgery, John Radcliffe Hospital | Drafted the main protocol for grant submission |
| Dr Pei Jing Teo | Dept. of Medical Oncology, Queen Elizabeth Hospital | Drafted the main protocol for grant submission |
| Lesley Stephen | Public and Patient Involvement Representative | Drafted the main protocol for grant submission |
| Miss Helen Scott | University of Liverpool, Liverpool Clinical Trial Centre | Reviewed drafts of the protocol in LCTC template |
| Mrs Andrea Newhouse | University of Liverpool, Liverpool Clinical Trial Centre | Drafted protocol in the LCTC template and produced final protocol version. |
| Dr Richard Jackson | University of Liverpool, Liverpool Clinical Trial Centre | Drafted and reviewed (Outcomes and Statistical Considerations) |

1. **Introduction**

**5.1 Background**

Breast cancer is the second most (after lung cancer) common primary tumour to metastasise to the brain (also known as Breast Cancer Brain Metastases or CNS involvement secondary to breast cancer) accounting for 17% of brain metastases1,2. Improvements in the systemic treatment of extracranial metastatic disease have resulted in patients surviving longer with their metastatic disease, which appears to be contributing to the increase in the incidence of cerebral metastases3.

Local treatment in the form of open surgical resection, stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT) have all been applied in isolation or combination in the treatment of cerebral metastases from breast cancer with the aim of improving local control, extending life and preventing further neurological manifestations such as leptomeningeal metastases and Paraneoplastic Disorders. A number of randomised controlled trials have been performed, but treatment guidelines in North America, Europe and the UK reflect deep uncertainty about which strategies serve patient needs best 4. There is also questionable relevance of many studies to BCBM patients as they are largely underrepresented in older randomised trials 5. These trials are usually underpowered for stratification by receptor type.

This study aims to improve the current knowledge/literature base following on from recent publications by implementing a nationwide data collection of routine clinical care in Breast Cancer Brain Metastases (BCBM). The audit will focus primarily on understanding more on cerebral metastases. However, secondary aims will also place emphasis on understanding the clinical presentation and manifestation of Leptomeningeal disorders and Paraneoplastic Disorders should they be diagnosed among BCBM patients.

**Cerebral Metastases**

Cerebral metastases is a growing problem among patients living with metastatic breast cancer, particularly for patients with triple negative and human epidermal growth factor receptor 2 (HER2)-positive disease 2, and is associated with significant morbidity and mortality. The median overall survival ranges from 3 months to 26 months 3. The most recent breast cancer-specific prognostic model, the Modified Breast-Graded Prognostic Assessment (GPA), confirmed that tumour receptor status, along with age, performance status and number of brain metastases, predicted overall survival 3.

Current National Comprehensive Cancer Network (NCCN) guidelines recommend brain Magnetic Resonance Imaging (MRI) screening for recurrent or stage IV breast cancer patient only if symptoms are present. Symptoms can present as headaches, vomiting, seizures or forms of neurological deficits 3. Systemic treatment is the treatment of choice following central nervous system progression in patients who have had prior local therapy. Relative to other cancers, little is known about the tumour microenvironment within the brain, a setting unique to all other metastatic sites. The nature of the systemic therapy will depend on the tumour subtype, preceding systemic treatment and the patient’s performance status 6. These therapies may include chemotherapy, HER2-directed therapy and endocrine therapy. However, therapeutic options for intracranial disease remain limited; therefore, novel therapeutic approaches need to be developed.

**Leptomeningeal Metastases (LM)**

Whilst most CNS metastases develop in the parenchyma, a minority may arise in the leptomeninges. The exact incidence of LM is difficult to estimate, however they are thought to comprise between 10 to 20% of CNS metastases7. Treatment of LM is highly variable between patients, depending on the clinical context and the presence of any co-morbidities. There is also considerable inter-institutional variation with regard to treatment, reflecting controversies that exist in the relative merits of different treatment modalities. Neurosurgery, in the context of LM, has a role in relieving non-communicating hydrocephalus and the insertion of a ventricular “Ommaya” reservoir to provide access for administering intrathecal chemotherapy 8. CNS-targeted radiotherapy is often given to treat sites of LM, often in combination with systemic anti-cancer drug therapy. Intrathecal chemotherapy usually takes the form of methotrexate, cytarabine or thiotepa 9,10. Clearance of malignant cells from the CSF following chemotherapy has been shown to be a good prognostic factor. However, survival remains poor, reaching a median of 15 weeks 11.

Thus, breast cancer leptomeningeal disease is an area of significant unmet need. Its relatively uncommon occurrence hinders the development of a standard approach to its management and the lack of a well annotated bank of tissue and cerebrospinal fluid hampers the development of relevant and meaningful research contributing to the need for this audit study in collecting such data.

**Paraneoplastic neurological disorders (PND)**

Paraneoplastic neurological disorders are defined as remote effects of malignancy, not due to the presence of metastatic spread to the nervous system. PND are rare, occurring in less than 1% of women with breast cancer 12,13. However, they are important because they frequently precede the diagnosis of the breast cancer primary and because they cause severe neurological disability. Current thinking is that they are caused by an autoimmune response to ‘onconeural’ antigens, aberrantly expressed antigens on tumours that are also present on CNS cells, although the precise immunopathogenic mechanisms are unknown 14. It is likely that there is an important cellular immune response, evidenced by the presence of lymphocytic infiltration and activated cytotoxic T lymphocytes in the CSF of affected patients.

PND may affect any part of the nervous system either focally (e.g. cerebellar degeneration) or diffusely (e.g. encephalomyelitis). Both the central and peripheral nervous system may be affected, with antigenic targets being either intracellular (both nuclear and cytoplasmic) or extracellular (receptors and ion channels). As a general rule, PND associated with antibodies against intracellular targets cause predominantly CNS disorders, while those associated with antibodies against extracellular antigens cause predominantly neuromuscular disorders. PND affecting the CNS are commonly associated with specific anti-neuronal antibodies, which are present in both serum and CSF. The most common PND associated with breast cancer are cerebellar degeneration, encephalomyelitis with rigidity and opsoclonus-myoclonus syndrome. The most common anti-neuronal antibody in breast cancer is anti-Yo 12. Most CNS syndromes respond poorly to immunomodulatory treatment although occasional improvement is seen when the underlying tumour is treated. In contrast, disorders affecting the neuromuscular junction e.g. Lambert-Eaton myasthenic syndrome (LEMS) do improve with treatments that remove the relevant antibodies directed against voltage-gated calcium channels 15,16. The prognosis for the majority of PND is poor, even if the tumour is detected and treated, and patients are forced to remain in a severely disabled state.

Currently, there is a lack of active research into PND in general as well as in breast cancer specifically, as well as no centralised resource of relevant biological material for research.

Logistically, The PRIMROSE Audit study anticipates using the trainee collaborative model 17 to establish an observational database collecting presentation, diagnosis, management and outcome data from patients with newly diagnosed CNS involvement secondary to breast cancer in the UK.

**5.2 Rationale**

There is an urgent need to better understand the outcomes and disease patterns after local therapy in the BCBM patient group in the context of current modern oncological treatment. Furthermore, an understanding of how local therapy influences quality of life and neurocognitive functioning in breast cancer patients is needed, particularly as patients may undergo a number of different local therapies over their disease course. Finally, it is recognised that there is inequitable access to specific types of local therapy nationwide. Mapping out the geographic variation in availability of these local therapies will help guide future policy and local clinical commissioning to improve breast cancer patient outcomes.

Basic and translational research to understand the pathophysiology of breast cancer involving the CNS remains limited by a lack of access to annotated clinical material. Such research is needed if preventative and novel treatment strategies are to be developed. Moreover, there is currently a lack of basic information regarding the incidence and management of cerebral metastasis in the UK, how it may vary and its impact on patient outcomes. Furthermore, clinical studies have been hampered by a lack of a central resource to aid feasibility work; as well as, when open, to identify possible eligible patients. Finally, any future advances in systemic therapy may ultimately be limited, in certain breast cancer subtypes, by the development and progression of intracranial disease.

Recent literature in the breast cancer brain metastasis has highlighted the need of the audit and related research. A recent literature review3 presented current updates on the presentation, prognosis and impact of treatments among breast cancer brain metastases patients. The review reported “significant heterogeneity of outcomes” within BCBM. A continuation of multidisciplinary approach where “as systemic disease treatment continues to improve, simultaneous improvement in BCBM management will be required”. This directly feeds into the aim of the development of a BCBM registry of understanding presentation and management practices. Another study investigating stage IV breast cancer using a publicly available cancer dataset in the world 18 consisting of 18 US based population cancer registries found that brain metastases had the worst survival compared to bone metastasis. By initiating this audit in the UK, we can conduct investigations pertinent to affected UK cohorts with breast cancer and brain metastases. Similarly, another cohort study used an electronic oncology registry to understand metastatic breast cancer 19. They were able to understand a rare diagnosis of LM and found that leptomeningeal carcinomatosis occurred in 21% of the study cohort overall (n = 25), but twice as frequently in women less than 40 years of age compared to women 40 or more years of age. They also found that difference in treatment did not affect survival, because compared with their older counterparts, younger women with leptomeningeal carcinomatosis tended to experience longer survival19.

The development of a central audit documenting the clinical journey of patients presenting with BCBM, LM and PND will contribute towards overcoming these limitations through the conduct of an audit.

**5.3 Primary Objectives**

* + - To report the survival of patients diagnosed with CNS involvement secondary to breast cancer.
    - To describe the current practice in diagnosis, staging and management of metastatic disease in the central nervous system in relation to national and international guidelines, including the NICE guidelines for the management of brain metastases in adults (NICE Guideline 99, published in July 2018), European Association of Neuro-Oncology (2017) and the NCCN guidelines (Version 1.2018 Central Nervous System Cancers).
  1. **Secondary Objectives**
     + To define the incidence of metastatic breast cancer involving the central nervous system in the UK.
     + To evaluate the outcomes of patients treated for breast cancer related central nervous system metastases in the UK.
     + To inform and help in the development of potential prospective studies and clinical trials.

**5.5 Risk and Benefits**

**5.5.1 Potential Risk**

This is an audit study and does not involve treatment arms, medical devices or products. All data collected forms part of the routine clinical care for all patients with CNS involvement secondary to breast cancer and hence there are no patient reported outcomes.

There is no additional risk for the patient above that of routine care.

**5.5.2 Potential Benefits**

The audit will function as an anonymised research database enabling research in rare, under-investigated late stage cancer diagnosis. Meeting the objectives outlined in sub-section 5.3 and 5.4 would mean contributing further to the understanding of BCBM. Benefits include review of incidence/outcomes of the disease, review of current practice in terms of diagnosis/treatment and may help guide best practice guidelines for diagnosis, care and treatment of CNS involvement secondary to breast cancer in the future

Such research demonstrates the benefits of building a database to conduct an audit to understand more about CNS involvement secondary to breast cancer care.

1. **Study Design**

This is a prospective observational multicentre audit. Patients with histological confirmed locally advanced breast cancer and who meet the entry criteria will be registered, and data will be collected for these patients (informed consent is not required).

**6.1 Study Setting**

**6.1.1 Selection of Participating Sites**

All oncological and neurosurgical centres in the UK treating breast cancer or CNS involvement will be eligible to participate in the audit study.

Logistically, we anticipate the majority of cases will be identified by surgeons, oncologists or neurologists either sitting within breast and neuro-oncology multidisciplinary team meetings or via cases seen in the outpatient or ward setting. Relevant trainees from across the UK will be invited to participate in the study through the National Research Collaborative network, recently established Breast Cancer Trainee Collaborative model17 and other relevant professional bodies. We plan to engage with the Society of British Neurological Surgeons (SBNS), the joint Liverpool Manchester North West Surgical Trials Centre (Director Professor Nigel Bundred), one of five national Surgical Clinical Trials Units, trainee networks and, once all ethics have been received, we will also approach individual neurological centres.

The study intends to collaborate with the British Neurological Surveillance Unit (BNSU) to use their well-established network to identify relevant cases presenting to neurologist, in particular suspected cases of PND. It is accepted that diagnosing PND can be problematic. Where a diagnosis of PND is probable or possible, these patients may still be recruited but will be recorded as probable or possible cases of PND within the database.

Details of reviewing the sites and the formal greenlighting processes will be kept with TMG.

**Local Approval:** At participating sites, the appointed audit PIs will be responsible for applying for local approval at Trust level. Once local approval is obtained, it will be the responsibility of the PI to inform the clinical team of the audit and start data collection for the audit.

**6.1.2 Selection of Principal Investigators**

The audit intends to engage with the British Neurosurgical Trainees Research Collaborative (BNTRC) to appoint a trainee PI within each neurosurgery centre and the model for this has already been successfully established for trauma ([RESCUE-ASDH](http://www.rescueasdh.org/)) and hydrocephalus ([BASICS](http://www.basicsstudy.org.uk/summary.html)) randomised controlled trials.

All principal investigators will be required to demonstrate relevant experience and commitment during early phase feasibility assessment. All investigators must have the particular medical expertise necessary to conduct the study in accordance to the protocol. Written agreement to conduct research as such will be obtained prior to site initiation.

Hence the principal investigator at each site can constitute:

* Consultant level clinicians
* Trainee level clinicians
* Nursing (e.g. senior research nurses), physiotherapists or radiographers (all with proven experience)

A suitable co-investigator should be identified at each site to deputise in case of PI absence.

1. **Eligibility Criteria**
   1. **Inclusion Criteria**
      * Male or female.
      * >16 years of age
      * Histologically and/or cytologically confirmed breast cancer with CNS involvement, as defined as having one or more of the following:
        1. Metastases to the brain parenchyma
        2. Metastases to the leptomeninges
        3. Paraneoplastic Neurological Disorders

New or existing patients with a clinical diagnosis of CNS secondary to breast cancer (i.e. an active patient) are eligible to be registered on the study.

* 1. **Exclusion Criteria**

There is no formal exclusion criteria.

1. **Outcomes**
2. 1. **Primary Outcomes**

|  |  |
| --- | --- |
| **Outcome** | **Outcome measures** |
| 1. To report the survival of patients diagnosed with CNS involvement secondary to breast cancer. | Time from diagnosis of secondary breast cancer to time of death of any cause. |
| 1. To describe the current practice in diagnosis, staging and management of metastatic disease in the central nervous system in relation to national and international guidelines, including the NICE guidelines for the management of brain metastases in adults (NG99, July 2018), EANO (2017) and the NCCN guidelines (Version 1.2018 Central Nervous System Cancers). | Description of patient management including   1. Diagnosis 2. Staging 3. Therapy/treatment 4. Patient outcomes |

* 1. **Secondary Outcomes**

|  |  |
| --- | --- |
| **Outcome** | **Outcome measures** |
| 1. To define the incidence of CNS involvement secondary to breast cancer in the UK. | The number of patients with CNS involvement secondary to breast cancer registered per year. |
| 1. To evaluate the outcomes of patients treated for CNS involvement secondary to breast cancer in the UK | The time to progression following surgery, radiotherapy or systemic therapy given as treatment for CNS involvement.  The site of progression (cranial or extracranial) will be recorded.  Time from diagnosis of CNS disease secondary to breast cancer to time of death. |
| 1. To inform and help in the development of potential prospective studies and clinical trials. | All the information gathered during the audit will be used to understand the possible gaps in knowledge and therefore possible clinical trials. While data relating to number of patients and outcomes will help with trial design. |

1. **Participant Timelines and Assessments**

**9.1 Participant Identification, Screening and Registration of Patients**

Patients will be identified by the clinical team caring for the patient approaching the patient after reviewing eligibility and for enrolment onto the study. At participating sites, clinical staff will be made aware of the inclusion criteria for this audit. They will be responsible for ensuring that the patient is eligible to be included in the audit. New or existing patients with a clinical diagnosis of CNS secondary to breast cancer (i.e. an active patient) are eligible to be registered on the study.

To register an eligible patient, the relevant clinical staff member will conduct the following steps (Patient consent is not required.):

* Log onto REDCap
* Check for existing entries for the patient (using NHS number)
* If patient has not already been registered, create a new study ID

Once the patient has been registered, the clinical staff member will populate the REDCap database retrospectively using patient notes and record further data onto REDCap from the patient notes for 12 - 18 months as and when the relevant data becomes available. No screening logs are required for this audit. Data can be retrospectively filled in onto REDCap for patients who have already known to the clinical services and have a diagnosis (also known as active patients). Data can be prospectively filled in on to REDCap for active patients they routinely visit the clinical care services and for new patients who have been newly diagnosed with CNS involvement secondary to breast cancer.

A Delegation of Duties Log will be prepared for each site. This log will name the Principal Investigator, sub-investigator(s), study coordinator(s), and all other clinical staff conducting activities for the audit. New or replacement staff will be added and signed off as appropriate.

**9.2 Informed Consent**

This study involves only limited data collection from the routine health record by clinical staff in direct care of the patient. The patient will not be identifiable from the data entered into the audit database. Informed consent does not need to be sought from the patient. Patient Information Sheets and/or Consent forms are not required for this study.

**9.3 Eligibility Assessment and Confirmation**

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log. Eligibility criteria are described in Section 7. Eligibility confirmation must be documented in the patient’s medical notes. No assessments additional to the patient’s standard care are required to confirm eligibility for this audit.

**9.4 Schedule for Assessments and Follow-up**

The frequency of follow-up or follow-up duration cannot be pre-determined or pre-planned. Follow-ups may take the form of face to face visit or telephone appointment. In either case, follow-up will be part of the routine assessment and care.

|  |  |  |  |
| --- | --- | --- | --- |
| **DATA COLLECTION** | Baseline  (Day 1) | Every routine clinic visit | Final visit |
| Demographic Information | X |  |  |
| Disease history and characteristics | X |  |  |
| Prior Cancer Treatment | X |  |  |
| Current anti-Cancer Treatment and Concomitant medications | X | X |  |
| Progression details |  | X |  |
| Outcome (Death, lost to follow up) |  |  | X |

**9.5 End of Audit**

The end of the audit is defined as the date on which data for all participants is frozen and data entry privileges are withdrawn from the audit database. The audit may be closed prematurely by the Trial Steering Committee (TSC).

Site and study closure activities will be centrally coordinated and conducted in accordance with CTU processes regardless of whether the closes as planned or prematurely. This includes activities such as:

1. Checking that all site data entered onto the study database, discrepancies raised, and satisfactory responses received
2. Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

**10. Safety Reporting**

The safety events cannot be attributed to this study as this is an audit study with no out-of-routine procedures, trials, interventions, devices etc. Therefore, assessment of “causality” – relationship of the safety event to the audit study is not required. Safety event recording is not necessary for this study.

**10.1 Reporting of Pregnancy**

Pregnancy women will not be excluded from this study. The audit will have no arms or factors to affect the pregnancy of the patient. All pregnancies will be followed up to outcome. A pregnancy report form will be filled out if a participant is pregnant or becomes pregnant.

**10.2 Notification of Deaths**

If the research team become aware of the death of a participant this should be notified to the LCTC using the appropriate CRF within 24 hours of becoming aware.

**10.3 Contact details and Out-of-hours Medical Cover**

This audit is low risk as it involves routine care and no non-standard care. Emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for participants in this observational study. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

**11. Statistical Considerations**

**11.1 Introduction**

Details are included on the statistical principles underlying the audit design and an overview of the statistical methodology applies. Full details of all analyses performed will be included in a separate Statistical Analysis Plan.

**11.2 Sample Size and Recruitment**

As an audit study, no formal sample size is set based on study hypothesis. A target for the audit is to obtain 300 patients and given the poor prognosis of the target population it is a reasonable target that 100 events will be observed. The primary endpoint of the study is to measure the overall survival of the patient group and what clinical/demographic factors are prognostic. Assuming 100 events, a log hazard ratio to evaluate differences due to any known prognostic factors will have a conservative estimated standard error of 0.25 meaning that a 95% confidence outside of the range 0.60 – 1.65 would be determined significant at the 5% level.

**11.3 Endpoints**

**11.3.1 Primary Endpoint**

* Overall survival measured as the time from diagnosis until death by any cause.
* Description of patient management including
  + Diagnosis
  + Staging
  + Prescribes therapy/treatment
  + Patient Outcome

**11.3.2 Secondary Endpoints**

* Incidence of CNS involvement secondary to breast cancer, measures as the number of cases observed per month.

**11.4 Analysis Methods**

**11.4.1 Patient Groups**

Analysis will be performed on all patients included in the audit unless there are sound and justifiable rational for their removal.

**11.4.2 Missing Data**

Analyses are planned on a complete case database. However, if greater than 10% data on a key outcome/prognostic covariate are observed then multiple imputation using chained equations will be employed.

**11.4.3 Levels of significance**

All analyses will be reported alongside 95% confidence intervals and the nominal p<0.05 used to determine statistical significance.

**11.4.4 Analysis of the Primary Endpoints**

The primary endpoint is overall survival measures as the time from diagnosis to death by any cause. Survival estimates will be obtained using Kaplan Meier estimates and the effect of key clinical/demographic data explored using multivariable cox proportional hazards techniques.

Descriptive analysis will be conducted to describe current patient management.

**Data Management and Audit Monitoring**

The responsibilities for Data Management and monitoring are delegated to the LCTC. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

**12.1 Source documents**

Data from eligible patients will be sourced from patient notes as the patient will have their usual treatment, their usual assessments which will, as per standard practice, be documented in the patient notes.

**12.2 Data collection method**

Anonymous data will be entered into the REDCap database. Breast cancer trainees, oncologists, neurologists and research nurses at the participating sites will have access to the database and will be appropriately informed on the study and the eligibility criteria.

Data are to be entered into REDCap by members of the research team at site. Training will be provided prior to any data entry.

**12.3 Monitoring**

Access to REDCap will be tested at each participating site during the site greenlight process. Centrally, the TMG will remotely check data collection to help maintain data quality however this will not hinder clinical practice and staff will only be emailed if core data for registered patients is missing. Site monitoring will only be triggered if the Chief Investigator and TMG deem it necessary.

* 1. **Risk Assessment**

A detailed Risk Assessment will be developed and agreed by the study Coordinator, Chief Investigator, Sponsor, Statistician and LCTC Operational Director.

In conducting this risk assessment, the contributors will consider potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is categorised into three groups:

* CTIMP Type A = Comparable to the risk of standard medical care.
* CTIMP Type B = Somewhat higher than the risk of standard medical care.
* CTIMP Type C = Markedly higher than the risk of standard medical care.

The risk assessment resulted in this audit being categorised as a CTIMP Type A.

**12.5 Confidentiality**

This audit will not be collecting personal or identifiable data (e.g. participant names, date of birth etc). NHS numbers will be entered by clinical staff involved in the care of the patient to check for prior entries or duplicate records. The REDCap database will be designed such that NHS ID will be viewable by clinical staff (who already have access to this information as part of their usual clinical role) and will not be viewable by any members of the TMG or TSC. At all times, data will be handled confidentially and securely.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool, LCTC is registered as a Data Controller with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the Sponsor and The University of Liverpool’s Data Protection Officer and appropriate processes followed.

**12.6 Quality Assurance and Control**

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur as part of quality assurance:

* + The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
  + The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the specific training.
  + A greenlight checklist will verify all approvals are in place prior to audit study initiation at LCTC and the individual centre.
  + Data quality checks and monitoring procedures will be undertaken in line with the Data Management Plan. The study coordinator and senior study members will be involved in Quality Assurance and will have access to REDCap data. The purposes of this will include, but are not limited to:
    - * assessing compliance with the study protocol;
      * working with QA and QC standards are being met;
      * discussing any emerging problems that may have been identified prior to the visit;
      * checking CRF and query completion practices.

To ensure recruitment rates, data entry etc. are tracked, and that the importance and need for data collection is consistently recognised an internal risk assessment and monitoring plan will be done as part of the green light process and thereafter reviewed annually.

This will be overseen by the TMG and TSC.

**12.7 Records Retention**

The retention period for the PRIMROSE audit data and information is 25 years from the official End of audit date.

The aim of the study is to build an Audit to aid in further research, to inform current practice and to evaluate outcomes. Hence, in the long terms, the records in this Audit will function as a research database which can be accessed for future research. While the current audit plans to run for two years, the data will be retained on REDCap securely and continually added to should research benefit from such data. There is currently no cap on the number of patients that can be included in the Audit.

The PI at each investigational site must make arrangements to store the essential documents (as defined by ICH GCP guidelines) including the Investigator Site File and the applicable participant medical records, for the full length of the study’s retention period and will arrange for destruction at the end of this period as instructed by the LCTC.

The PI is also responsible for archiving all relevant source documents so that the data can be compared against source data after completion of the audit study (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the audit study will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties.

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

**Regulatory and Ethical Considerations**

**13.1 Statement of Compliance**

The procedures detailed within this protocol are compliant with the Health Research Authority guidance for audit projects. Where projects meet the criteria for audit, evidence of local trust approval for participation is required prior to any data collection. This is in line with [HRA guidance](https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/) (Source: <https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/>).

Local audit approvals will need to be obtained, with a supervising named consultant, if the unit lead is a trainee. This approval will be collected by the TMG.

**13.2 Ethical Considerations**

The PRIMROSE audit does not require REC review as it is an audit, and not a research project. This has been confirmed using the HRA decision tools and as advised on the tools, we have sought further guidance from an HRA Approvals Specialist. Documents confirming the outcome of these are available on request.

**13.3 Approvals**

The audit will abide by the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible.

**13.4 Protocol Deviation and Serious Breaches**

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, are handled based on their nature and severity.

**13.4.1 Non-Serious breaches**

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to study oversight committees.

**13.4.2 Serious breaches**

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the study participants, or the scientific value of the study”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the study become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the TMG and/or TSC in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the audit study. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’.

Breaches confirmed as ‘serious’ will be notified to the TMG and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG or TSC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to oversight committees.

**Indemnity**

The University of Liverpool holds insurance against claims from participants for harm caused by their participation in this audit. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital’s duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

**Publication and Dissemination**

* 1. **Publication Policy**

The results of the audit from different participating sites will be analysed together and published in the name of the audit as soon as possible, on behalf of all collaborators, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The manuscript will be prepared by a writing group, appointed from amongst the TMG. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals will be respected. The members of the TSC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

Any publications arising from this research will be reviewed appropriately prior to publication.

* 1. **Authorship**

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the PRIMROSE Consortium which will also be named at the manuscript head.

* 1. **Dissemination to Key Stakeholders**

On completion of the research, a Final Report will be prepared and submitted to Daiichi Sankyo Europe GmBH in accordance with the stipulated guidance in the grant letter. Any results resulting from this audit will be published regardless of the magnitude or direction of effect.

* 1. **Data Sharing**

At the end of this audit study, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by an internal committee at the CTU and discussed with the Chief Investigator in accordance with the CTU policy on data sharing. As this is an Audit intended to function as a databank, the appropriate ethical processes will be followed should external researchers request use of the data.

**Chronology of Protocol Amendments**

**Version 1.0 (02/Jul/2020)**

Original Approved Version

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