PROSSPER

PROgesterone as a **S**teroid **SP**aring agent against o**E**dema occurring with secondary b**R**ain cancers

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GLOSSARY OF ABREVIATIONS

AE	Adverse Event
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BBB	Blood Brain Barrier
BTB	Blood Tumour Barrier
CaCTUS	Cancer Clinical Trials Unit, Scotland
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSQ-C	Dexamethasone Symptom Questionnaire-Chronic
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC BN20	EORTC Brain Cancer Module 20
EORTC QLQ-C30	EORTC Quality of Life Questionnaire Core 30
ER	Oestrogen Receptors
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FLAIR	Fluid attenuated Inversion Recovery
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigator Brochure
ICH	International Council for Harmonisation
ICP	Intracranial Pressure
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
LC/MS/MS	Liquid chromatography tandem mass spectrometry
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
NANO	Neurologic Assessment in Neuro-Oncology
NCRI	National Cancer Research Institute
NIHR	National Institute for Health Research
NON IMP	Non Investigational Medicinal Product
NSCLC	Non-Small Cell Lung Cancer
PgR	Progesterone Receptor
PHS	Public Health Scotland
PPE	Patient and public engagement
PPI	Patient Public Involvement
PR	Progesterone Receptor
PROMs	Patient Reported Outcome Measures
QoL	Quality of Life
QA	Quality Assurance
RANO	Response Assessment in Neuro-Oncology
RANO-BM	The Response Assessment in Neuro-Oncology for Brain Metastases

REC	Research Ethics Committee
SAE	Serious Adverse Event
SCTRU	Scottish Clinical Trials Research Unit
SDV	Source Data Verification
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SRS	Stereotactic radiosurgery
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDS	Three times daily
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
VEGFR	Vascular endothelial growth factor
WOCBP	Woman of child bearing potential

TRIAL SUMMARY

Protocol ID:	PROSSPER
Protocol Title:	**PRO**gesterone as a **S**teroid **SP**aring agent against o**E**dema occurring with secondary b**R**ain cancers
Trial Description:	A dose finding/pharmacokinetic study of progesterone as a steroid sparing agent against oedema occurring during secondary brain cancer treatment
Development Phase:	Experimental medicine/early phase
Aim/Objective:	The overall objective is to provide (a) pharmacokinetic data to guide the dosing of micronised progesterone as a steroid-sparing agent for the treatment of patients with brain tumour oedema, (b) evidence of feasibility and (c) preliminary evidence of efficacy to underpin a subsequent definitive randomised controlled trial comparing micronised progesterone and placebo in addition to standard treatment with dexamethasone.
Study Design:	Stage 1: Single arm, pharmacokinetic/dose confirmation Stage 2: Randomised, double blind, controlled evaluation of micronised progesterone as a steroid sparing agent
Study IMP:	The IMP is micronised progesterone in Stage 1 and micronised progesterone/placebo in Stage 2.
Non IMP:	Although used in the trial, Dexamethasone is not the IMP and will be supplied from hospital stock.
Randomisation:	Randomisation will be 1:1, with stratification by clinical site (Leeds and Liverpool)
Patient Accrual:	Stage 1: 6 patients (Leeds); Stage 2: 36 patients (Leeds and Liverpool). Please note that patients in Stage 1 are excluded from participating in Stage 2. Both are separate subsets of patients and will have a separate consent form
Final Analysis:	The final analysis will be performed when all patients have completed treatment and have been followed up for one week (i.e., after 22 days)
Interim Analysis:	No interim analysis is planned
End of Study:	The end of the study is defined as the date where all patients have completed their assessments and all data has been cleaned, Quality Controlled and the database is locked for analysis.

Inclusion Criteria:

1) Patients ≥18 years' old
2) Capable of giving informed consent

3) ECOG performance status 0, 1 or 2
4) Clinical and/or radiological diagnosis of cerebral metastases with peri-tumoural oedema on CT/MRI in the last 14 days
5) Responding symptomatically to dexamethasone for control of brain tumour symptoms at a dose of ≥4mg-12mg for ≥48 hours
6) Ability to swallow oral medication

Exclusion Criteria:

1) Patients who are unable or unwilling to give informed consent
2) History of unexplained vaginal bleeding
3) Concurrent meningioma
4) On HRT medication
5) History of venous thromboembolic disease, myocardial infarction or stroke in last 12 months
6) History of cholestasis in the last 6 months
7) History of allergy to either progesterone or other ingredients of the trial drug including peanut allergy.
8) Pregnant or lactating (all female patients of child bearing age will undergo pregnancy testing prior to enrolment (Stage 1)/randomisation(Stage 2)
9) Clinically significant co-morbidities that in the opinion of the investigator would preclude study participation
10) Planned surgery, chemotherapy or radiotherapy within the study treatment period
11) Patients participating in Stage 1 will not be eligible for Stage 2

1. INTRODUCTION

1.1. Summary of research

Corticosteroids, and in particular dexamethasone, remain central to the management of patients with brain tumours, despite their frequent and often serious side-effects. Furthermore, there is increasing evidence that patients who remain on corticosteroids fare worse than those in whom steroids can be withdrawn and not simply because they have worse disease; possible explanations include a radio-protective effect, and impaired immune response. The need for an alternative to corticosteroids has become increasingly recognised, but to date no such alternative has been identified.

Progesterone is also a steroid, with neuroprotective and anti-inflammatory properties in pre-clinical models, but fewer side-effects in patients. Progesterone warrants, therefore, investigation as an alternative to corticosteroids for patients with brain tumour induced oedema. Unfortunately, pre-clinical models of brain tumours do not replicate the oedema seen in patients, so laboratory studies are of limited value. In addition, from the published literature the dose of progesterone to achieve optimal drug exposure in this setting is unclear.

This trial in patients with brain tumours and oedema will investigate the pharmacokinetics of differing doses of oral progesterone. We also hope to gain preliminary evidence as to whether the addition of progesterone allows greater reduction in the dose of dexamethasone for these patients. If successful, this trial will underpin a definitive trial studying the efficacy of progesterone as a dexamethasone sparing agent in patients with primary and metastatic brain tumours with oedema.

1.2. Background and rationale

According to Cancer Research UK, >12,000 people are diagnosed with primary central nervous system tumours in the UK each year. Metastatic, or secondary, brain tumours are more common with 27,000 people affected each year in the UK (1). Untreated, both primary and brain metastases often cause rapid neurological deterioration and death, usually within 12 – 18 months.

Some patients with primary brain tumours can be treated successfully by a combination of surgery and radiotherapy; others, however, especially those with glioblastoma, are either inoperable or invariably recur soon following local treatment and then are rapidly fatal. Similarly, only a minority of patients with brain metastases have disease that is operable or amenable to “targeted” radiotherapy. Although the blood brain barrier (BBB) is distinct from the blood tumour barrier (BTB), systemic therapy for patients with brain metastases appears less effective than at other sites. Brain tumours, both primary and metastases, remain therefore a major unmet need.

Brain tumours cause signs and symptoms due to their own growth and by provoking an inflammatory response that leads to the accumulation of oedema. The oedema can be considerable and adds to the mass effect contributing to symptoms including headache, vomiting and seizures. The oedema is due to increased “leakiness” of the cerebral microvasculature as a result of damage to the BBB and/or BTB.

Although pre-clinical models of brain tumours have furthered our understanding of their biology, little attention has been given to studying peri-tumoural oedema. We undertook a

systematic search and established that pre-clinical models of brain tumours rarely show evidence of peri-tumoural oedema and there is no single pre-clinical model that can be used to study alternative agents to dexamethasone (2). This emphasizes the importance of early clinical studies in patients with brain tumours.

1.3. Dexamethasone and brain oedema

Corticosteroids have been used empirically to treat patients with brain tumour oedema since the 1950s (3,4). Dexamethasone, due to its potent glucocorticoid effect and low mineralocorticoid activity, high brain penetration, and long half-life (5) is the corticosteroid of choice for patients with brain tumours as is reflected in consensus guidelines (6,7). There is, however, little evidence regarding optimal dosing. The single such randomised study was in patients with brain metastases undergoing radiotherapy; it suggested that lower doses of dexamethasone may be as effective as higher doses (8,9) but with fewer side effects.

The reduction in symptoms, which can often be seen within hours of administration of corticosteroids, appears to be mediated predominantly by a reduction in tumour capillary permeability and a reduction in cytokines, including the pro-inflammatory transcription factor nuclear factor kappa B and interleukins involved in inflammation (5,10). Corticosteroids bind to cytoplasmic receptors, leading to nuclear localization and DNA binding to glucocorticoid response elements, affecting transcriptional regulation and activating or repressing various signalling cascades (10). Tight junction components, including occludin, are upregulated within endothelial cells, contributing to decreased capillary permeability (11).

Although patients' symptoms can be relieved within hours of taking dexamethasone, changes in the volume of oedema seen in imaging studies can take days (12). In magnetic resonance imaging (MRI) studies 2–3 days after dexamethasone administration there is local reduction in extracellular water content and diffusion, suggesting reduced local tissue pressure may alleviate neurologic symptoms (13,14).

1.3.1 Limitations of dexamethasone

Side effects of corticosteroids	
Endocrine	Hyperglycaemia
	Weight gain
	Cushingoid habitus
	Adrenal insufficiency (after discontinuation)
Cutaneous or Vascular	Acne
	Striae
	Purpura
	Delayed wound healing
	Peripheral oedema
Haematologic/Immunologic	Opportunistic infections (e.g. oropharyngeal candidiasis, *Pneumocystis jirovecii* pneumonia)
Neurologic/Psychiatric	Insomnia
	Mood lability
	Anxiety/depression
	Psychosis
	Increased appetite
	Hiccups

	Tremor
Gastrointestinal	Dyspepsia/gastritis
Musculoskeletal	Proximal myopathy
	Osteoporosis
	Arthralgias
	Avascular necrosis
	Decreased growth/height (paediatric patients)
Ocular	Visual blurring
	Cataract formation

Although frequently effective in controlling symptoms associated with raised intracranial pressure (ICP), dexamethasone causes cumulative dose-dependent short- and long-term side effects (15–17), especially in the significant proportion (~19%) of patients who take steroids from the time of diagnosis until death (18) as listed above (5). Patients dislike taking dexamethasone because of the adverse impact on their quality of life (QoL) (19).

Additionally, there is increasing evidence that patients with malignant gliomas who remain on corticosteroids fare worse than those in whom steroids can be withdrawn and not simply because they have worse disease (20–22). This has given new impetus to reducing the use of dexamethasone (23), but there are currently no recognized alternatives. Patients with brain tumours and their doctors are, therefore, faced with balancing the beneficial and adverse effects of dexamethasone. In a survey of the Brain Tumour Charity's Research Involvement Network 80% of respondents agreed or strongly agreed that "searching for an alternative to steroid use in brain tumours is important and would significantly decrease the burden on quality of life". This is similarly highlighted in the 2015 NCRI James Lind Alliance Priority Setting Partnerships for neuro-oncology as a question the patient community wants answered (24). Further support has come from the NCRI Brain Tumour Clinical Studies Group.

1.3.2 Dose of dexamethasone

The optimal dose of dexamethasone is not known (8). Clinicians generally initiate a high dose of dexamethasone (e.g. 16mg/day) that is reduced as symptoms improve over successive days (8). In some patients, dexamethasone can be stopped, usually following effective local treatment with surgery or radiotherapy, but many patients remain on long-term dexamethasone.

To date, most brain tumour studies have not looked at the effect of treatment interventions on the dose of dexamethasone a patient requires. However, a recent European study of anti-VEGF monoclonal antibody bevacizumab (Avastin™) plus radiotherapy and temozolomide in patients with newly diagnosed glioblastoma did report changes in dexamethasone dose (25). In patients taking dexamethasone, discontinuation (defined as being off dexamethasone for ≥ 5 days) occurred in two thirds of those on bevacizumab compared with less than half of those receiving placebo (66.3 and 47.1%, respectively).

The International Response Assessment in Neuro-Oncology (RANO) Working Group has published standardised endpoints for evaluating corticosteroid use in neuro-oncology clinical trials (5,26). "Responders" are defined as patients with a 50% reduction in total daily dexamethasone dose compared to a baseline dose of $\geq$4mg/day, or reduction in the total daily dose to $\leq$2mg. Responders must also have a stable or improved Neurological Assessment in Neuro-Oncology (NANO) score or Eastern Cooperative Oncology Group (ECOG) and an improved score on a relevant clinical outcome assessment tool.

1.4. Previous steroid-sparing studies

To date, there has been limited research into alternatives to dexamethasone to treat oedema associated with brain tumours. We sought relevant trials on the European Clinical Trials Register (clinicaltrialsregister.eu), the United States' National Library of Medicine Clinical Trials Register (ClinicalTrials.gov) and the ISRCTN Registry (isrctn.com) by searching for "brain edema" and "brain oedema".

Corticorelin, a synthetic targeted human corticotropin-releasing factor analogue, underwent a double-blinded, randomized, placebo-controlled 12-week trial in 200 patients with peri-tumoural oedema from malignant brain tumours. The primary endpoint (a 50% reduction in dexamethasone dose with no worsening in neurologic function) was not achieved, and corticorelin has not been pursued further in this setting. The authors note that the trial design was hampered by a lack of data on dexamethasone dose reduction (27).

Following small prior reports postulating an anti-inflammatory and anti-oedema effect, the frankincense extract *Boswellia serrata* was investigated in a pilot study of 12 patients with brain tumours (28). A small randomized study in 44 patients with brain tumour undergoing radiotherapy (29), showed a major (>75%) reduction in the volume of oedema assessed by MRI in a higher proportion of patients receiving *Boswellia serrata* than placebo (60% and 26%, respectively; $P = 0.023$). There was, however, no significant clinical benefit with no difference in health-related QoL, neurocognitive function or dexamethasone dose between treatment groups.

A small randomised controlled trial in patients with non-small cell lung cancer (NSCLC) and brain metastases of recombinant human endostatin, an angiogenesis inhibitor, found that its addition to whole brain radiotherapy significantly reduced cerebral oedema and improved short-term outcomes but not survival (30). An ongoing trial is evaluating anlotinib, an oral multi-targeted tyrosine kinase inhibitor with particular effect against Vascular endothelial growth factor2 (VEGFR2) and VEGFR3, in reducing perilesional oedema in patients with NSCLC prior to Stereotactic radiosurgery (SRS).

A retrospective study suggested that angiotensin-II inhibitors, which have putative anti-VEGF properties, may reduce the need for corticosteroids (31). A randomised, placebo-controlled study (ASTER Trial) recently reported no difference in steroid dosage required on the last day of radiotherapy or 1 month after completion of radiotherapy in glioma patients (32).

A trial of cobitolimod, an immunomodulator targeting the Toll-like receptor 9 present in immune cells, was launched in 2009 but never completed. Finally, there is a trial registered as still recruiting, looking at glyburide, which inhibits Adenosine Triphosphate (ATP)-sensitive potassium channels, also in patients undergoing radiosurgery for brain metastases.

No clinical trials are registered looking at progesterone in brain tumour oedema; a systematic search of the literature (33) (enclosed as additional material) confirms no human studies in this setting and only 2 pre-clinical studies.

1.5. Progesterone

Progesterone is an endogenous steroid involved in control of the menstrual cycle, pregnancy, and embryogenesis. It is also a metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids. In addition to being a natural

hormone, progesterone has been used therapeutically since 1934, largely to treat menstrual disorders. In 2011, the US Food and Drug Administration (FDA) approved the use of hydroxyprogesterone caproate during pregnancy to reduce the risk of recurrent preterm birth in women with a history of spontaneous preterm delivery.

1.5.1 Progesterone and synthetic progestins

Progesterone belongs to the progestogen group of steroid hormones and is predominantly produced by the ovaries in premenopausal women. It is also present at low levels in men, in whom it is converted to the “male” hormone testosterone.

It is important to differentiate between natural progesterone, progestogens and synthetic progestins (34). Any natural or synthetic substance that exerts progesterone-like activity through the activation of the progesterone receptor (PR) is deemed a progestogen. Progesterone is, however, the only naturally occurring progestogen and is also available clinically as oral micronised progesterone. The synthetic progestogens, specifically referred to as progestins, include medroxyprogesterone acetate, levonorgestrel and norethindrone acetate; they are structurally diverse and prescribed worldwide.

1.5.2 Progesterone and tumours

Progesterone has anti-proliferative and apoptotic effects in breast, endometrial, ovarian, colon and salivary gland tumours *in vitro* and *in vivo* (35). Progesterone also enhances the *in vitro* efficacy of temozolomide, which is standard of care chemotherapy for patients with glioblastoma during and after radiotherapy (35).

There is some limited evidence that menstrual/reproductive factors or exogenous hormone use may play a role in the development of glioma. The incidence of glioma in adults is lower in women, especially those who are premenopausal (36). Other studies have shown mixed results but some suggest an increased glioma risk with later menarche, and reduced risk with hormone replacement therapy and oral contraceptive use (37).

Natural progesterone and synthetic progestins have been used in routine clinical practice for decades, in contraceptives, as post-menopausal hormone replacement therapy and in preventing premature labour. Its use in treating cerebral oedema is investigational but clinical experience to date suggest this should be safe.

In a study investigating the effect of oral progesterone on suppressing labour contractions (38,39) at a dose of 800 or 1600 mg/day for 3 days then 600mg/day the only reported side effect was “mild drowsiness”. Oral progesterone 400mg nocte for 10 days has FDA approval for secondary amenorrhea and the safety profile was good with only 5% withdrawal due AEs, none of which were serious (40). Steroids, including progesterone, are also a risk factor for developing intra-hepatic cholestasis of pregnancy (41,42). Ovarian hormones affect lipid metabolism (43). Chronic administration of progesterone 300mg nocte was associated with increased levels of growth hormone and decreased levels of both luteinising hormone and thyroid-stimulating hormone, but not thyroxine (44); symptomatic endocrine sequelae have not been reported. Of note, the ongoing PEARL trial (CI, Palmieri) is assessing the biological effects of micronised progesterone in patients with premenopausal ER-positive (oestrogen receptors), PgR-positive (progesterone receptor) early breast cancer.

The apparently good tolerability of progesterone reflects, at least in part, the plasma concentrations achieved being similar to those seen in the luteal phase of the menstrual cycle or in pregnancy.

1.5.3 Progesterone in the treatment of cerebral oedema

Data are accumulating from studies in brain injury where there is severe oedema, that progesterone has neuroprotective and anti-inflammatory properties (45,46). It may, therefore, have a role in the treatment of cerebral oedema caused by brain tumours.

Pre-clinical studies have demonstrated neuroprotective effects of progesterone in neurotrauma models, specifically reducing oedema by mechanisms similar to those of dexamethasone, including enhancing function of the BBB (47), reducing inflammatory cytokines e.g. prostaglandin E2, and reducing expression of factors promoting oedema e.g. vascular endothelial growth factor and matrix metalloproteases.

Although Phase I and II clinical trials of high-dose intravenous (i.v.) progesterone in neurotrauma patients were encouraging, two Phase III trials failed to confirm efficacy, although they did show high-dose progesterone was safe in both men and women (48–53); of note, dexamethasone was associated with worse outcomes (54). Subsequently, a review suggested that progesterone has an inverted U-shaped dose/efficacy curve, with reduced activity at both low and high doses (55). This review concluded that the high dose of progesterone contributed to failure of the Phase III neurotrauma trials. The authors proposed targeting lower mean plasma progesterone levels (50-100ng/ml) than in the Phase III trials (>300ng/ml), but maintained for longer periods (55). Other potential factors for the failure of drugs trialled to date in head injured patients include the heterogeneous nature of the injured brain and the insensitivity of the outcome measures used. In contrast, the oedema associated with brain tumours is much more homogenous.

Notwithstanding the limitations of pre-clinical models, the protective effect of progesterone in comparison to dexamethasone in a pre-clinical model of surgical injury has been confirmed (56). These authors subsequently reported in a rat orthotopic glioblastoma model that low dose progesterone was more effective than either a higher dose of progesterone or dexamethasone in prolonging overall survival and preserving neurologic function (57). Progesterone reduced VEGF levels, down-regulated matrix metalloproteinase-9 and aquaporin -4 production resulting in reduced BBB permeability (assessed indirectly by Evans Blue staining).

Neurotrauma is an acute condition, so progesterone administration in trials was intravenous (i.v.). Patients with brain tumours may be treated over many months, so progesterone would be best given orally. To improve its absorption, oral progesterone can be micronised; this is a process by which average particle diameter is reduced. Plasma levels can be further increased by taking with food (58). Additionally, some breakdown products of progesterone are also biologically active e.g. allopregnanolone, which acts on gamma-aminobutyric acid receptors in the brain to act as an anxiolytic agent (59) and improve sleep patterns (44). Extrapolation from lower dose oral progesterone pharmacokinetic data (58) suggests daily oral micronised progesterone at a dose of 600 – 1800mg, given as three divided doses, should achieve the target mean plasma progesterone levels 50 -100ng/ml. Due to differences between i.v. and oral dosing, we propose to target and match exposure expressed as the area under the curve (AUC) of the earlier studies.

1.5.4 Micronised progesterone for administration (Utrogestran)

Details of micronised progesterone are contained in the current version of the SmPC.
Of note, much of the information in the SmPC relates to the approved use of micronised progesterone in combination with oestrogen in post-menopausal women with an intact uterus at potential risk of endometrial cancer, as hormone replacement therapy.
Micronised progesterone is not taken with food in routine practice as this increases its boavailability. The recommended daily dose is 100 mg or 200 mg daily at bedtime.

With regard to potential drug interactions, drugs known to induce hepatic CYP450-3A4 such as anti-epileptic agents (phenytoin, carbamazepine) may increase the metabolism and elimination of progesterone; ketokonazole and other inhibitors of CYP450-3A4 may increase the bioavailability of progesterone.

The incidence of adverse drug reactions with oral micronised progesterone was calculated as 1.43/1,000 patient years', corresponding to approximately 1.5 spontaneously reported cases in every 1000 patients exposed. Clinical trial data comparing micronised progesterone in combination with conjugated oestrogen to conjugated oestogens alone or placebo suggest an excess of headache and breast tenderness in those taking micronised progesterone. Somnolence, fatigue or transient dizziness may occur 1 to 3 hours after intake of micronised progesterone and is reported to be associated with high doses of progesterone. Withdrawal vaginal bleeding may occur in women in in the week following discontinuation.

Micronised progesterone is absorbed by the digestive tract and in healthy volunteers plasma progesterone levels were maximum 2.2 +/- 1.4 hours following administration. Progesterone is highly (96%-99%) protein bound, primarily to serum albumin and transcortin. Progesterone is metabolised primarily by the liver predominantly 20 α hydroxy- Δ 4 α- prenolone and 5 α-dihydroprogesterone. The elimination half-life observed is 16.8 +/- 2.3 hours with urinary elimination accounting for 95% in the form of glycuroconjugated metabolites. The pharmacokinetics of micronized progesterone are reported as independent of dose. Individual pharmacokinetic characteristics were maintained over several months.

2. AIMS AND ENDPOINTS

The overall objective is to provide (a) pharmacokinetic data to guide the dosing of micronised progesterone as a steroid-sparing agent for the treatment of brain tumour oedema, (b) evidence of feasibility and (c) preliminary evidence of efficacy to underpin a subsequent definitive randomised controlled trial comparing micronised progesterone and placebo. Prior to a definitive randomised controlled trial several key issues need to be addressed:

- The pharmacokinetics of intermediate-dose oral micronised progesterone require further characterisation,
- The ability to achieve the target steady state plasma progesterone levels requires confirmation as does tolerability in this patient population
- Finally, subsequent trials will greatly benefit from piloting the patient reported outcome measures (PROMs) of QoL, the structured dexamethasone reduction protocol and a preliminary assessment of the efficacy of micronised progesterone as a dexamethasone sparing agent

This information could not be obtained from pre-clinical studies. Whilst well-characterised brain tumour models do exist, our systematic review (2) has shown that no suitable pre-clinical model exists to study peri-tumoural oedema. Furthermore, patients often experience symptomatic

relief within hours of receiving dexamethasone before radiological improvement becomes apparent, which could not be adequately addressed in pre-clinical models. Finally, our approach respects the principles of the 3Rs (Replacement, Reduction and Refinement) in pre-clinical research (60).

This is a two stage trial in patients with brain metastases and symptomatic cerebral oedema. Although we anticipate the study findings to be relevant to patients with primary brain tumours, and that such patients would be included in a future definitive efficacy study, we have excluded them from the current trial because (a) at initial diagnosis patients with high grade primary brain tumours will most likely need early surgical or other intervention and (b) clinical experience suggests that at relapse the dexamethasone dose they require is much more variable.

Stage 1:
Single arm, pharmacokinetic/dose confirmation

Stage 2:
Randomised, double blind, placebo controlled evaluation of micronised progesterone as a steroid sparing agent. Randomisation will be 1:1, with stratification by clinical site (Leeds and Liverpool).

Randomisation is proposed as there are insufficient historical data on which to base estimates of the "average" reduction in dexamethasone dose in this population over the study period nor of the variability in that dose. Statistical comparison of dexamethasone dosing in the control and micronised progesterone arms is not planned. The control arm will, however, act as a comparator when evaluating dexamethasone dosing in the progesterone arm. While this study is not powered to perform formal statistical analyses, we plan to carry out exploratory work to compare the (i) cumulative dexamethasone dose (ANOVA/t-test or Mann Whitney U if the data are not normal); (ii) final dexamethasone dose (ordered logistic regression) and (iii) time to reach final dose in each arm (Cox regression). The comparator arm will also aid statistical design of the planned, subsequent definitive efficacy trial. Patients in the control arm will receive placebo provided by the manufacturer. This number of patients was chosen empirically, but is similar to the size of a typical "expansion cohort" in Phase 1 oncology trials that seek to better characterise toxicity and inform the design of a future trial; the use of such cohorts appears to increase the likelihood of success in that future trial (60).

2.1. Aims

2.1.1 Primary

- Characterise the pharmacokinetics of oral intermediate dose micronised progesterone in comparison to that achieved by iv dosing in the literature (Stage 1) after a single dose of 200mg and 600mg of micronised progesterone and Stage 2 after repeated (TDS) administration at a dose to be determined. Establish the acceptability, tolerability and safety of a dose of micronised progesterone that achieves the target drug exposure (Stage 2)

2.1.2 Secondary

- Assess the feasibility of structured dexamethasone dose reduction in this population (Stage 2)
- Evaluate patient symptom burden and QoL (Stage 2)

- Make a preliminary assessment of the effectiveness of micronised progesterone by measuring the extent and duration of dexamethasone dose reduction in patients receiving micronised progesterone and a parallel placebo “control” group (Stage 2)

2.1.3 Tertiary

- Describe endocrine, liver function and lipid profiles of patients on micronised progesterone and/or placebo (Stage 2)
- Ensure no undesired CT/MRI changes in tumours (size, enhancement pattern) whilst on micronised progesterone/placebo (Stage 2)
- Establish the acceptability and feasibility of PROMs (Stage 2)
- Evaluate the acceptability of a subsequent randomised controlled trial (Stage 2)

2.2. Endpoints

2.2.1 Stage 1

2.2.1.1 Primary:

Pharmacokinetic profile (including Cmax, Cl and AUC) of micronised progesterone after single doses of 200mg and 600mg in >4 of 6 patients that allow estimation of serum progesterone exposure (AUC) that is 50 – 150% of that targeted in order to determine the dose in Stage 2..

2.2.2 Stage 2

2.2.2.1 Primary:

- ≥13 of 18 patients able to tolerate micronised progesterone until the end of the 14-day treatment period at a dose predicted to achieve the target progesterone exposure.
- Trough progesterone concentrations within 50 – 150% of target

2.2.2.2 Secondary

- Compliance with the structured dexamethasone dose reduction guidelines at 75% of decision points in at least 13 of 18 patients in line with protocol guidelines and as clinically appropriate.
- Description of dexamethasone related symptoms and QOL.
- Percentage of patients achieving a ≥50% reduction in dexamethasone dose taken on Day 14
- Comparison (progesterone v placebo) of final dexamethasone dose on Day 14

2.2.2.3 Tertiary

- Confirmation that patients on micronised progesterone have no additional clinically significant changes in their endocrine, liver function or lipid profile.
- Description of changes on CT/MRI in patients on micronised progesterone compared to those on placebo
- Acceptability/feasibility of PROMs and future trial design, including randomisation, established through patient interviews.

3. RESEARCH PLAN

3.1. Trial design

3.1.1 Patient eligibility

Major eligibility criteria will be the same in Stages 1 and 2 (see below).

Although progestins may play a role in the development of such cancers, in the context of the poor prognosis of patients with brain metastases, this risk is not clinically relevant. Moreover,

progestins have been widely used with clinical activity and benefit in patients with hormone receptor positive metastatic breast cancer.
Patients with brain metastases not infrequently present with seizures and require anticonvulsant medication. The metabolism of dexamethasone, progesterone and many of the anticonvulsants are affected by CYP450 induction/inhibition; concurrent medication will, therefore, be recorded but will not preclude study entry.

3.1.2 Inclusion Criteria

1) Patients ≥18 years' old
2) Capable of giving informed consent
3) ECOG performance status 0, 1 or 2
4) Clinical and/or radiological diagnosis of cerebral metastases with peri-tumoural oedema on CT/MRI in the last 14 days
5) Responding symptomatically to dexamethasone for control of brain tumour symptoms at a dose of ≥4mg-12mg for ≥48 hours
6) Ability to swallow oral medication

3.1.3 Exclusion Criteria

1) Patients who are unable or unwilling to give informed consent.
2) History of unexplained vaginal bleeding
3) Concurrent meningioma
4) On HRT medication
5) History of venous thromboembolic disease, myocardial infarction or stroke in last 12 months
6) History of cholestasis in the last 6 months
7) History of allergy to either progesterone or other ingredients of the trial drug including peanut allergy.
8) Pregnant or lactating (all female patients of child bearing age will undergo pregnancy testing prior to enrolment (Stage 1)/randomisation(Stage 2)
9) Clinically significant co-morbidities that in the opinion of the investigator would preclude study participation
10) Planned surgery, chemotherapy or radiotherapy within the study treatment period
11) Patients who have participated in Stage 1 will not be eligible for Stage 2

3.1.4 Participation in concurrent clinical trials

Patients should not participate simultaneously in more than one IMP trial at a given time; participation in a non IMP e.g. observational research could be acceptable.

3.1.5 Stage 1: Single arm, pharmacokinetic/dose confirmation

Please refer to Stage 1: Schedule of activities (Appendix 4).

We will recruit 6 evaluable patients in Leeds from whom blood samples will be collected for progesterone pharmacokinetic profiles after receiving a single oral dose of IMP (micronised progesterone) 200mg on day 1 and then a single 600mg IMP dose 5-10 days later. The daily non IMP dexamethasone dose (8mg) will be the same on both sampling days, but can be adjusted as clinically indicated between the sampling days.

Patients will be identified through site-specific teams either as an outpatient or as an inpatient. Patients will be treated and blood collected at the NIHR Leeds Clinical Research Facility. Pharmacokinetic analyses will be undertaken at the University of Bradford.

No safety issues are anticipated but patients will undergo routine clinical observations; they will not undergo any additional study specific investigations. Any patient from whom paired pharmacokinetic analyses are not obtained will be replaced. The dates and timings of pharmacokinetic sampling are shown in the Stage 1: Schedule of activities (Appendix 4).

After paired samples for 6 patients have been collected, these will be shipped to the University of Bradford for pharmacokinetic analysis. Recruitment will be suspended until pharmacokinetic analysis has been conducted.

Following pharmacokinetic analysis, if the primary endpoint is achieved a micronised progesterone dose will be selected for Stage 2 (Stage 2: Schedule of activities Appendix 5). Should the Stage 1 primary endpoint not be met, we may recruit up to 6 further evaluable patients for progesterone pharmacokinetic profiles after receiving alternative single oral micronised progesterone doses.

3.1.6 Stage 2: Randomised, double-blind, placebo pharmacokinetic/dose confirmation

Please refer to Stage 2: Schedule of activities (Appendix 5).

Please note that patients in Stage 1 are excluded from participating in Stage 2. Both are separate subsets of patients and will have a separate consent form.

We will recruit 36 evaluable patients from Leeds and Liverpool over 18 months (1 patient/month at each site), who will receive oral micronised progesterone/placebo three times a day (t.d.s.) at an initial dose determined in Stage 1; patients who are not evaluable will be replaced. The on-study starting dose of non IMP dexamethasone will be 8mg/day, which will be modified as described in Section 11.

Patients will be treated and blood collected on the NIHR Leeds Clinical Research Facility and Clatterbridge Cancer Centre, Liverpool according to the Schedule of Events. Pharmacokinetic assays and analyses will be undertaken at the University of Bradford.

Please refer to Section 11 for detail on the non IMP dexamethasone and IMP micronised progesterone/placebo dose and administration.

3.2 Pharmacokinetic (PK) sampling and analysis

Pharmacokinetic analyses will be undertaken at the University of Bradford (Professor Loadman). Levels of progesterone, dexamethasone and their metabolites will be measured by using liquid chromatography-triple quadrupole mass spectrometry (LC/MS/MS) [37,45] according to agreed SOPs (standard operating procedures) and validated methodology.

Appropriate pharmacokinetic parameters will be derived and analysed by the laboratory.

3.2.1 Timing of PK samples

3.2.1.1 Stage 1

On Day 1, and another day between Days 5 and 10, blood samples (approximately 5 mL) for pharmacokinetic analysis will be collected into heparinised tubes (BD 367874 plasma tube, sodium heparin).
These samples will be collected at baseline (pre-dosing with progesterone); then t = 1, 2, 3, 4 and 6 hours (all +/- 15 minutes); then 10 and 24 (both +/- 2 hours) after administration of progesterone. The timing of each sample collection will be recorded.

3.2.1.2 Stage 2

On days 1, 8 and 14 a blood sample (approximately 5 mL) will be collected into a heparinised tube (BD 367874) before the dose of progesterone and dexamethasone. The timing of sample collection will be recorded.

3.2.2 Sample processing and storage

Immediately following blood collection, the vacutainer tubes should be gently inverted 10 times. Within 30 minutes of blood collection, the sample should be centrifuged to separate the plasma (as per local protocol).

For each blood sample, the plasma layer should be transferred in roughly equal amounts to 3 labelled polypropylene tubes prior to storage. Full processing details will be provided in the Laboratory Manual.

Plasma samples for PK analysis should be stored at -80°C until shipment; storage at -20°C is acceptable if -80°C is not available.

3.2.3 Pharmacokinetic analysis

Samples will be couriered to the Clinical Trials Pharmacology Laboratory at the University of Bradford by courier; transportation boxes and dry ice will be supplied by the courier service.

3.3 Clinical and radiological assessment

Clinical review will include ECOG score and NANO scale.

Changes in cerebral oedema on imaging can be variable, difficult to demonstrate/quantify and take days to be apparent. Hence, oedema of imaging is not a reliable primary end-point to study alternatives to dexamethasone. Similarly, the heterogenous MRI scanning protocols that exist across different hospitals preclude a standardised approach to patient imaging without repeating imaging at baseline. Nonetheless, we feel it is important to measure tumour size and oedema extent at baseline (diagnosis scan) and on Day 14, in order to evaluate for any changes in these parameters, akin to the suggested guidelines specified by the RANO-BM working group (61).

Although MRI is considered the “gold standard” we recognise that its use is not universal; we permit, therefore, the use of CT at baseline to diagnose brain metastasis. The same scanning modality must be used at baseline and on Day 14.

Where MRI is undertaken at baseline and on Day 14 it will include a minimum of axial T2-weighted (or Fluid attenuated Inversion Recovery (FLAIR)), axial T1-weighted and axial T1-weighted post-gadolinium sequences, all performed at a minimum of 5 mm slice thickness. If volumetric imaging then another plane can be acquired (coronal & sagittal) and axial reconstructions provided. This will permit tumour response assessment using the RANO-BM

criteria and will allow an assessment of the extent of oedema using the system specified by Carlson et al. (62).

In those participants for whom volumetric CT/MRI data are available at both imaging time points, volumetric measurements of tumour and oedema will be made using BrainLab software. This practice is supported by the RANO-BM group: "The RANO-BM group judges that the existing data are not yet strong enough to justify the universal requirement of volumetric response criteria in clinical trials of patients with brain metastases. Volumetric analyses in real-time adds cost and complexity and is not available at all centres. Yet, RANO-BM also believes that the assessment and reporting of volumetric response in clinical trials (in addition to the unidimensional RANO-BM criteria) will add to the knowledge base, either justify or negate the need for volumetric measurements in future trials, and encourage its inclusion as a secondary endpoint when feasible." (61)

All scans will be sent to Leeds for central review. Images will be sent via PACS transfer.

3.4 Patient reported outcome measures (PROMS)

Patients in Stage 2 will report their QoL using PROMS and have their symptom burden assessed using mixed quantitative and qualitative methodologies.

3.4.1 Validated questionnaires

In concordance with the RANO recommendations (5) we will use a combination of patient reported outcome measures. The Dexamethasone Symptom Questionnaire-Chronic (DSQ-C) [2,3] will be used to assess side-effects related to dexamethasone use, the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [1] and Brain Cancer Module (EORTC BN20) [40] to assess generic and disease-specific QoL, respectively. Single items to assess micronised progesterone related side-effects, and side-effects that might result from drug interactions (e.g., with antiepileptic drugs), will be added from the EORTC item bank library (e.g. "have you had pain in your stomach area?", "'have you had a rash?"). These PROMs are widely used, have good psychometric properties and are validated in the relevant patient population. Completion is facilitated by use of the same scale (ranging from 1: 'not at all' to 4: 'very much') and the same recall period (past week). If necessary, patients can be assisted by a researcher or their caregiver in completing the questionnaires. Completion should take less than 15 minutes.

3.4.2 Side-effect diary

Participants will be asked to keep a structured daily side-effect diary. This will include noting the presence (yes/no) and severity (scale 1-10) of side-effects corresponding to the questionnaire items relating to dexamethasone and micronised progesterone use and meal times.

There will also be free text space for any additional side-effects.

3.4.3 Semi-structured patient interviews

A semi-structured qualitative interview [14], will be performed between Day 15-21 over approximately 60 minutes either in person, or by phone. Topics will include patients' views on their QoL and symptom/side-effect burden, the PROMs used to assess this, and their experience of participation in the trial. Patients will also be asked their opinion on future trial design, acceptability of outcome measures, and randomisation. Approximately 15 patients will be approached to participate in the patient interview.

3.5 Patient pathway and schedule of visits

Please refer to Appendix 3-5 for a breakdown of the patient pathway (Appendix No.3) and Appendix No.4 and No.5 for the Schedule of Visits (Stage 1 and 2), respectively.

3.6 Internal dissemination

3.6.1 Clinical staff

Before, and during, the trial we will raise awareness of the trial with oncologists and neurosurgeons in the Leeds and Liverpool Cancer Centres including seminar presentations to medical, nursing, pharmacy and support staff about brain metastases, their treatment and the challenges of using dexamethasone. We will describe the trial, key eligibility criteria and how to contact the research team. Details of the trial will be made available through secure portals at each trial site.

After the trial completes, results will be reported at local clinical and educational meetings to clinical, research and support staff.

3.6.2 Patients and carers

A patient and public engagement (PPE) representative will lead on the production of information for patients and the public. We will offer to engage with and discuss the treatment of brain tumours, including the role of clinical trials.

Patients and their carers will see the Patient Information Sheet and speak to their oncologist(s) and research nurse(s). They will also be directed to other sources of information e.g. Cancer Research UK and Macmillan websites to ensure they have the information to make informed decisions about their care and to engage the research team with confidence. We will enquire (and record) whether patients and their carers wish to be informed, in an appropriate way and time, of the trial findings.

3.7 External dissemination

During the trial we will use posters/oral presentations at scientific meetings and in journals, as well as social media, to raise awareness amongst clinicians and researchers of the challenges in managing these patients and the role of the current clinical trial.

3.7.1 Clinical and scientific researchers

When the trial findings become available they will be submitted for publication in a high impact, open access scientific journal. We will also submit abstracts to national and international cancer meetings, both general (e.g. Annual NCRI Conference, American Society of Clinical Oncology, European Society of Medical Oncology) and with a specific focus on neuro-oncology (e.g. European Association of Neuro-Oncology, European Association of Neurological Societies, American Association of Neurological Surgeons, British Neuro-Oncology Society).

3.7.2 Patients and public

Increasingly, patient groups attend clinical and scientific meetings so will have access to the trial results, and participate in discussion, through those meetings.

In addition, material will be generated created for use in press releases, blog posts, public magazine articles, social media and other media forms. Presentations that include key patient messages will be planned with key professional groups and organisations and local health systems. The production of any health information by patients and the public will be subject to the rigorous Department of Health Information Standard process to reduce risk.

3.8 Impact

If the current trial is successful we would apply for funding to conduct a definitive Phase II/III double blind, randomised controlled trial of micronised progesterone vs placebo in patients with primary or metastatic brain tumours and symptomatic peri-tumoural oedema that could transform the experience and QoL of patients with brain tumours.

With >12,000 people/year diagnosed with primary central nervous system tumours and >27,000/year affected by metastatic/secondary brain tumours, the overwhelming majority being on dexamethasone, each year up to 40,000 patients in the UK will benefit from micronised progesterone if shown to be an effective dexamethasone-sparing agent. Those who would benefit most are the significant proportion (~19%) of patients who take steroids from the time of diagnosis until death. Because the morbidity and mortality of many primary brain tumours and most with metastatic/secondary is so high, the benefits of reducing dexamethasone related side effects would be disproportionately high.

In addition, the structured dexamethasone dose reduction protocol may also enhance dexamethasone dosing in patients in the control arm. If so, its adoption in the Phase 3 trial has the potential for it to become standard practice and benefit patients with primary and secondary brain tumours in whom there may be scope to use dexamethasone more efficiently.

Finally, through publications and presentations described above and wider dissemination, this study has the potential for more far-reaching and clinically important impact improving outcomes for patients with metastatic brain cancers. The proposed trial will also raise awareness of brain cancer and brain cancer research.

4. PROJECT TIMETABLE

4.1 Trial set up: 8 Months

Secure release of funding; appoint project team; develop protocol; establish Trial Steering Committee (TSC) and Data Monitoring Committee (DMC); IMP preparation (packaging/labelling at distributor and distribution to sites); initiate contractual arrangements between participating institutions/departments; protocol sign off; parameters for monitoring agreed and schedule for meetings confirmed; commence centre set-up and application via IRAS (Integrated Research Application System) for Multi-centre Research Ethics Committee approval and sign off for individual sites; apply for MHRA approval; regular Trial Management Group (TMG) meetings and project oversight; training of site research teams.

4.2 Recruitment

4.2.1 Stage 1 and pharmacokinetic analysis: 6 months

Recruit 6 evaluable patients over a 3-month period; pharmacokinetic data analysis to establish dose for Stage 2.

Pharmacovigilance; data collection; TMG meetings; monitoring accrual progress, identification of problems and intervention as needed.

Central data quality monitoring and site visits as scheduled; independent oversight DMC meeting.

4.2.2 Stage 2: 18 months

Initiate 2nd centre for Stage 2; recruit 36 evaluable patients across both sites over 18 months. Commencement of data collection; pharmacovigilance; TMG meetings; monitoring accrual, identification of problems and intervention as needed; central data quality monitoring and site visits as scheduled; independent oversight, DMC meeting.

4.3 Data Collect & Validation Phase: 3 months

Pharmacokinetic analysis of Stage 2 patients.

Regular TMG meetings; independent oversight, DMC meetings; final data collection and data cleaning; database lock; final analysis.

4.4 Trial Close Down Phase: 1 month

Preparation of study report; upload results to EudraCT (or equivalent post Brexit); end of trial notification; preparing study files for archiving.

Preparation of abstract and manuscript for presentation at national/international meetings and journal submission.

5. PROJECT MANAGEMENT

5.1 Trial Management Group (TMG)

The trial will be managed by a TMG comprising key staff members at SCTRU, together with selected investigators and a PPI representative that will meet monthly throughout the set-up and duration of the study.

5.2 Trial Steering Committee (TSC)

A TSC will be established to provide overall supervision of the trial as per NIHR criteria. The TSC consists of the CI, an independent chairperson, an independent clinician, one independent public members, an independent statistician and observer members of the TMG. The committee will meet prior to the start of the study and convene regularly throughout the duration of the trial.

5.3 Data Monitoring Committee (DMC)

An independent DMC will undertake independent review and will monitor efficacy and safety endpoints. It will comprise an independent chairperson, clinician and statistician and will meet prior to the start of the study and convene 6-monthly throughout the duration of the trial.

6. ETHICS AND REGULATORY APPROVALS

The trial will be submitted to a research ethics committee, the MHRA and HRA for approval during the set up phase of the trial.

7. PATIENT AND PUBLIC INVOLVEMENT

Two surveys through the Brain Tumour Charity Research Involvement Network conducted during the initial concept stage of the trial confirmed support from patients and carers in finding an alternative to dexamethasone. The Marie Curie Research Voices Group was approached

and respondents, who read the proposal with interest, expressed the belief that this is an important study. Likewise, the 2015 NCRI James Lind Alliance Priority Setting Partnerships for neuro-oncology identified dexamethasone use as a question the patient community wants answered (24). Further support to look for an alternative to dexamethasone has come from the NCRI Brain Tumour Clinical Studies Group.

Peter Buckle is the PPI representative for the trial and as a co-applicant has been involved with the study design of the trial and writing the lay summary. He will be a member of the TMG and will help with writing the protocol and patient information sheet. He will be involved in writing up of the trial and help develop the dissemination plan.

8. PROJECT/RESEARCH EXPERTISE

Prof Chris Twelves: A clinician, with a first degree in Pharmacology and Experimental Medicine. He is Professor of Clinical Cancer Pharmacology and Oncology and Honorary Consultant Medical Oncologist specialising in the treatment of people with breast cancer and Director of the NIHR Leeds Clinical Research Facility. Over 25 years' experience as a Principal/Chief investigator for oncology experimental medicine trials. With the co-CI, he will have overall responsibility for the design and delivery of the trial, interpretation of the data and subsequent dissemination.

Mr Paul Chumas: Over 20 years as a consultant neurosurgeon treating adults and children with brain tumours and witnessing the side-effects of corticosteroids. The literature search, choice of potential agent, systematic reviews (on pre-clinical models of brain tumour oedema and progesterone and brain oedema) have been largely led by neurosurgery. With the lead applicant, he will have overall responsibility for the design and delivery of the trial, interpretation of the data, subsequent dissemination and planning of a definitive trial.

Prof Paul Loadman: Heads the drug metabolism team at the Institute of Cancer Therapeutics at the University of Bradford and has over 25 years' experience in the bioanalysis of small molecule drugs using LC/MS/MS. He is actively involved in the design, analysis and reporting of a range of small molecule pharmacokinetic studies in both the pre-clinical and clinical setting.

Prof Michael Jenkinson: An experienced clinical trial researcher and Professor of Neurosurgery. CI on the HTA funded ROAM trial (12/173/14), was co-CI of the completed HTA funded BASICS shunt trial (10/104/30).

Dr Florien Boele: Associate Professor of Medical Psychology with over ten years' experience of quality of life research in the brain tumour patient population. Her research includes RCTs (4 completed, 2 in setup) with quality of life outcomes, e.g., investigating modafinil vs placebo for reducing fatigue. She has contributed to trial design, provides expertise on patient-reported outcomes, and leads the qualitative work.

Dr Vinton Cheng: An NIHR Academic Clinical Lecturer and Honorary Specialty Registrar in Medical Oncology. He completed a DPhil at the University of Oxford investigating imaging biomarkers for brain metastases using pre-clinical MRI and his current research focus is on the role of the neuro-inflammatory response to breast tumours in facilitating metastatic spread to the brain. A member of the NCRI Screening, Prevention and Early Diagnosis Advisory Group and co-leads a national trainee-led collaborative project in breast cancer brain metastasis management.

Mr Peter Buckle: The PPI representative for the trial. Peter has been an active PPI representative on many other trials.

Dr Robert Murray: A Consultant Endocrinologist and is a collaborator to this study and has decided on the relevant endocrine tests as part of the safety profile for progesterone.

Dr Stuart Currie: An academic Consultant Neuroradiologist who is actively involved in neuro-oncology clinical trials and wrote the section on imaging for this trial and will undertake the reporting of all the MRI scans.

Dr Moritz Schramm: A Specialty Registrar in Neurosurgery. He has a track record of combining clinical and academic work having obtained an MB/PhD from the University of Cambridge and having completed an Academic Foundation Programme. As well as managing patients with brain tumours and metastases, he is an early-career scientist who has published peer-reviewed publications in cognitive and behavioural neurosciences as well as topics in adult and paediatric neurosurgery.

Prof Susan Short: An academic neuro-oncologist who is involved in many on-going clinical trials and who has been involved in the development of this trial. She will be integral to the interpretation of the results and the design of any future Phase III study which plans to include glioma patients.

Prof Carlo Palmieri: Professor of translational oncology and medical oncologist specialising in breast cancer. Has experience leading translational breast cancer studies including a study with micro-ionized progesterone and is Chief Investigator of a number of studies in set up in the area of breast cancer brain metastasis and sits on the Breast International group brain metastasis working group. He has provided input into the protocol, will help run the study and recruit patients.

The SCTRU is part of Cancer Clinical Trials Unit Scotland, a UKCRC Registered CTU. It has all the research, statistical, regulatory and administrative expertise necessary to develop and complete a trial. Key staff are: Eve Chisholm (Principal Trial Manager); Michelle Welsh (Senior Trial Coordinator); Jade Carruthers (Statistician); (Senior Trial Monitor).

9. SUCCESS CRITERIA AND BARRIERS TO PROPOSED WORK

9.1 Success criteria

The PROSSPER trial will have been successful if it generates results that underpin a subsequent definitive Phase 3 efficacy trial by

- Defining the oral dose of micronised progesterone required to reach target serum levels
- Confirming the acceptability, tolerability and safety of micronised progesterone, at the selected dose, in this patient population
- Verifying the acceptability and utility of the dexamethasone dose reduction protocol
- Collecting QoL data and PROMs relevant to the symptoms of raised intracranial pressure and dexamethasone side effects
- Demonstrating possible efficacy of micronised progesterone in reducing the dose of dexamethasone needed to control symptoms of cerebral oedema
- Establishing that a Phase 3 trial would be feasible and acceptable to patients.

9.2 Barriers and mitigation

9.2.1 Stage 1 fails to achieve the target progesterone exposure and identify a dose for Stage 2

We have the option to recruit a further 6 patients to Stage 1. If at that point a Stage 2 dose has not been identified, we will discuss with NIHR whether we should recruit additional patients to Stage 1 and modify Stage 2 accordingly, or whether the trial should end.

9.2.2 Stage 2 recruitment is less than anticipated

We have looked at the number of potentially eligible patients and our recruitment plan is conservative. In the event of recruitment slowing we will engage with colleagues, in particular those in the lung cancer and melanoma team; Prof Twelves is a senior member of the breast team. In the event of a further "surge" in COVID-19 cases, mandating suspension of recruitment and redeployment of trial staff, we will record all such instances and seek recompense from the NHS or other bodies for whom they are temporarily working. Patients discontinuing for reasons other than progesterone toxicity will be replaced.

9.2.3 The planned Stage 2 dose of micronised progesterone is not tolerable

This is unlikely to be an issue given that progesterone at the doses we anticipate using is well tolerated in other populations. In the event of patients withdrawing due to the toxicity of micronised progesterone they will be replaced, unless this occurs in >20% of patients in which case the combination of progesterone and dexamethasone will be considered unacceptably toxic.

9.2.4 COVID contingencies

Although the development of brain metastases and their management constitutes a medical emergency, the treatment of which would likely not be affected by national guidelines, we recognise that delivery of the trial may be affected by government guidelines and/or NIHR prioritisation of UPH COVID trials. In that event we would discuss mitigation with NIHR.

COVID (and other) vaccinations will be recorded as concomitant medication.

10. WITHDRAWAL OF SUBJECTS

Patients may withdraw from the study at any point, including after giving consent to the trial but before starting treatment; no further data collection will take place.

Patients may discontinue the study for reasons including toxicity, non-compliance, withdrawal of consent or if the investigator judges' continuation not to be in the patient's best interest. Any patient who does not start IMP, will be replaced.

In Stage 1, patients from whom two full pharmacokinetic profiles cannot be obtained will also be replaced

In Stage 2, patients withdrawing due to the toxicity of micronised progesterone will be replaced. The patients replaced will, however, remain evaluable for assessment of tolerability and if such withdrawals occur in >20% of patients the combination of progesterone and dexamethasone will be considered unacceptably toxic.

If at any point throughout the trial, a patient becomes unable to swallow, they should be withdrawn.

Any patients who permanently discontinue IMP should receive the non IMP dexamethasone and other standard of care treatments.

11. TREATMENTS

11.1 Patient pathway and Schedule of visits

Please refer to Appendices 3 - 5 for a breakdown of the patient pathway and Schedule of Visits (Stage 1 and 2).

11.2 Dexamethasone (standard care – non IMP)

Dexamethasone is also prescribed to patients in the PROSSPER trial but is the non IMP and will be supplied from hospital stock.

Dexamethasone will be prescribed as standard of care taken orally in the morning within 30 minutes of finishing breakfast.

At time of randomisation, patients must have been on 4mg-12mg of dexamethasone for at ≥48 hours.

Stage 1: Day 1 – 10 (Please refer to Appendix No.6 - Doses Stage 1)
Pharmacokinetic sampling days are Day 1 and one other day between Days 5 and 10. This day will be decided by the clinical team and patient

On Day 1, patients will take 8mg dexamethasone in the morning.

On Days 2-10, patients will take dexamethasone in the morning as clinically indicated, except on the second pharmacokinetic sampling day when the dose of dexamethasone will be 8mg.

Stage 2: Day 1 – 22 (Please refer to Appendix No.7 - Doses Stage 2)
On Day 1, patients will take 8mg dexamethasone in the morning.

From Day 3-14, if clinically appropriate, the dexamethasone dose will be reduced by 2mg/day on alternate days (see Appendix 6 [Drug Table Stage 1] and Appendix 7 [Drug Table Stage 2]) and can be discontinued if indicated.

Should symptoms of raised intracranial pressure recur, the dose of dexamethasone will be increased by 4mg (i.e. to 2mg above the dose at which the patient's symptoms had been controlled).

Once the dose has been re-escalated, and after Day 14, subsequent dose adjustments will be at the clinician's discretion.

11.3 Micronised progesterone/placebo (IMP)

Micronised progesterone/placebo is the trial IMP and will be provided by the manufacturer as 200mg capsules. Progesterone/placebo should be taken orally within 30 minutes of finishing a meal.

Stage 1: Day 1-10 (Please refer to Appendix No.6 - Doses Stage 1)

On Day 1, patients will take 200mg micronized progesterone in the morning after breakfast (08.00 - 10.00).

A further dose of 600mg of micronized progesterone will be taken on another day between Days 5-10. This day will be decided by the clinical team and patient.

Stage 2: Day 1-22 (Please refer to Appendix No.7 - Doses Stage 2)
The Stage 2, Day 1 starting dose of micronized progesterone/placebo will be determined by the pharmacokinetic results of Stage 1.

In Stage 2, patients will also take progesterone/placebo at 08.00 - 10.00 (breakfast),12.00 – 14.00 (lunch) and 17.00 – 19.00 (dinner). Patients will record the time each meal is completed and micronised progesterone (or placebo in Stage 2) taken.

Patients will continue on this dose to Day 14 unless they do not tolerate this initial micronised progesterone/placebo dose due to side-effects. In that case, the dose of micronized progesterone/placebo will be reduced by 200mg; if that reduced dose is not tolerated, it will be reduced by a further 200mg. If the second reduced dose is not tolerable, the patient will be withdrawn from the study. For example, if the initial dose of micronized progesterone/placebo was 600mg t.d.s (three times a day) i.e. 1800 mg/day, the first dose reduction would be 400mg t.d.s, i.e. 1200mg/day in total and further dose reduction would be 200mg t.d.s. i.e. 600mg/day in total.

See Appendix 6 [Drug Table Stage 1] and Appendix 7 [Drug Table Stage 2]) for Drug tables.

Day 15-22 involves trials procedures but not micronized progesterone/placebo.

11.4 Missed or vomited doses

If a patient vomits within an hour of taking a dose, the Research Team should email the PROSSPER team (phs.prossper@phs.scot) to seek advice. The PROSSPER team may advise that an additional dose (IMP or Dexamethasone) should be taken. If a patient misses a dose, an additional dose (IMP or Dexamethasone) should be taken late unless omission not noticed until next administration of that drug.

11.5 Concomitant Therapy

Patients should receive concomitant medications as clinically indicated. These will be recorded in the CRF. Patients requiring to start hormone replacement therapy or coumarin anticoagulants should be withdrawn from the study.

11.6 IMP storage and accountability

More detail on IMP (micronized progesterone/placebo) storage and accountability are contained in the PROSSPER Pharmacy Manual.

11.6.1 Storage

All IMP must be kept in a secure place under appropriate storage conditions 15^{o}C - 25^{o}C. A description of the appropriate storage and shipment conditions for the study IMP are specified on the IMP labels. IMP must be kept out of the reach and sight of children.

11.6.2 Accountability and IMP compliance

The investigator or a delegated individual (e.g. pharmacist) must ensure that the IMP is stored and dispensed in accordance with hospital standard operating procedures and applicable regulatory requirements.

The medication provided for this study is for use only as directed in the protocol. Patients must be asked to bring all their trial medication (including any unused) every time they attend the clinic for the purposes of treatment compliance assessment and drug accountability.

Drug distribution and accountability logs will be provided to the site in a pharmacy pack. It is the investigator's responsibility to establish a system for handling the IMP to ensure that:

- Deliveries of IMP are correctly received by a responsible person (e.g., pharmacist or suitable pharmacy designee) and are handled and stored correctly and safely
- IMP are dispensed only in accordance with the protocol
- Participants return any unused IMP to the PI/Research nurse at the end of the trial
- A dispensing record (which will include the identification of the participant to whom the IMP was dispensed, the date of dispensing, the quantity of IMP dispensed, the date and quantity of any unused IMP returned to the pharmacy, delays and reasons for delays) is accurately maintained. Any discrepancies must be accounted for on the appropriate form.

In the case that any IMP is damaged, please contact SCTRU for reconciliation and replacement.

At the termination of the study or at the request of the sponsor, all unused drugs will be accounted for and destroyed locally at the study sites. Certificates of delivery and destruction or return must be signed and copies retained in the Investigator Site File.

11.7 IMP Supplies and Labelling

More detail on IMP Supplies and Labelling are contained in the PROSSPER Pharmacy Manual.

11.7.1 Supply

The IMP (micronised progesterone/placebo) is supplied free of charge by Besins Healthcare (UK) in capsules contained in blister packs. Besins Healthcare (UK) Ltd will supply both progesterone and placebo (placebo will be coated with sunflower oil so will taste and look the same as progesterone).

11.7.2 Labelling

All IMP supplied by Besins Healthcare (UK) Ltd will be re-packaged and labelled according to Annex 13 of the 'Good Manufacturing Practice'. The drugs will be re-packaged, labelled, QP released and distributed by Mawdsleys to sites.

11.8 Assessment of efficacy

No formal comparison of efficacy will be made.

12. PHARMACOVIGILANCE

12.1 Definitions

Adverse Event (AE): An adverse event is any untoward medical occurrence in a patient which does not necessarily have a causal relationship with the IMP or procedures. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with a treatment or procedure, whether or not considered related.

Adverse Reaction (AR): All noxious and unintended responses related to a IMP or procedure should be considered adverse drug reactions.

Serious Adverse Event (SAE): Any untoward medical occurrence in a patient 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
f) Is otherwise considered to be medically significant by the investigator

The term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisations planned prior to enrolment in the trial, scheduled by the trial protocol, or for social reasons, will not be considered as SAEs unless the hospitalisation has to be prolonged as a result of the AE. Treatment in an emergency room of less than 24 hours or on an out-patient basis that does not meet any other serious criteria should not be considered as an SAE.

Suspected Unexpected Serious Adverse Reaction (SUSAR): A suspected unexpected serious adverse reaction is an adverse reaction that is classified as serious and it is thought to be caused by a IMP or procedure. Expected events are detailed within the Summary of Product Characteristics (SmPC). The nature, severity or outcome of this adverse reaction must not be consistent with SmPC for the treatment for it to be reported as a SUSAR.

12.2 Recording and reporting of Adverse Events

All Adverse Events will be recorded in the Case Report Form and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5. The Investigator, or delegated co-investigators, will assess each event for relatedness. Any AE considered related becomes an AR.

All adverse events that occur after the signing of written informed consent and within 30 days after the final IMP will be recorded on the appropriate eCRF page. In addition, any events occurring more than 30 days after final IMP that are deemed to be related to the IMP should be notified to PHS by emailing phs.sctru@phs.scot.

12.3 Recording and reporting of Serious Adverse Events

All serious adverse events that occur after the signing of written informed consent and within 30 days after the final IMP will be recorded on the SAE report form on the trial eCRF. The CTCAE grading will also be captured. The Investigator, or delegated co-investigators, will assess each event for relatedness. Any SAE considered related becomes a SAR.
In addition, any events occurring more than 30 days after final IMP that are deemed to be related to the IMP should be notified to PHS by emailing phs.sctru@phs.scot.

The SAE case report form must be completed on the Trial eCRF and signed by the Principal Investigator, or delegated co-investigator of the centre involved, within 24 hours of the site team becoming aware of the event.

All initial SAE reports should contain the following minimum information:

- Reporter information
- At least one subject identifier (trial number/patient initials)
- Event term
- Assessment of relatedness
- Suspect drug or procedure
- Serious criteria

Sites must email phs.sctru@phs.scot to notify PHS that an SAE has been reported.

All SAEs will be forwarded to the CI by PHS for assessment of relatedness, and expectedness against the SmPC. Any SAE that is deemed to be both related and unexpected (i.e. a SUSAR) will be notified to the appropriate Competent Authorities and Research Ethics Committee within 7 days of becoming aware of the event for fatal or life threatening events and 15 days for all other serious events. An SAE will be treated as related if either the PI, CI or both consider it to be related.

Please refer to PROSSPER instruction manual for sites for reporting instructions.

12.4 Development Safety Update Report

A developmental safety update report will be submitted to the appropriate Competent Authorities and Research Ethics Committee, once a year for the duration of the trial. The time frame for the report starts with the date of first authorisation by a competent authority in an EU member state and the report should be submitted within 60 days of the anniversary of first authorisation.

12.5 Pregnancies

For female patients, pregnancy should be reported to PHS within 24 hours of becoming aware by completing the pregnancy case report form on the electronic data capture system. In this event, the patient should be withdrawn from the study and replaced. An email should also be sent to phs.sctru@phs.scot to notify PHS that a pregnancy has occurred.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary abortion, details of birth and presence or absence of any birth defects, congenital abnormalities or maternal or newborn complications. Any birth defects or congenital abnormalities must be reported as SAEs.

13 UNBLINDING

In Stage 2, the decision to unblind a single case should be made when knowledge of an individual's allocated treatment is required:

- to enable treatment of severe adverse event/s, or
- in the event of an overdose
- to enable reporting of a SUSAR
- patient request (patient would be removed from the trial should this request be granted)

13.1 Unblinding during working hours approval and responsible person

Requests for unblinding of individuals should be made via the Prossper team based in Scottish Clinical Trials Research Unit (SCTRU). Agreement of the Chief Investigator (CI) or a delegate will then be sought. However, in circumstances where there is insufficient time to make this request or for agreement to be sought, the treating clinician should make the decision to unblind immediately. The unblinding procedure can be completed by the SCTRU Quality Assurance (QA) Team.

13.2 Unblinding during out of hours approval and responsible person

During out of hours, and should it not be possible to contact the CI or delegate, the treating clinician should make the decision to unblind immediately if it will influence the patient's immediate management. All instances of unblinding should be recorded and reported in writing to SCTRU Prossper team by the local investigator.

The unblinding procedure can be completed by the local investigator or the on-call pharmacistat the site where the patient was randomised. .

13.3 Unblinding for data safety reporting approval and responsible person

Requests for unblinding of individuals should be made via the Prossper team based in SCTRU. Agreement of the CI or delegate will then be sought. The unblinding procedure can be completed by the SCTRU QA Team. The Principal Investigator will assess every Serious Adverse Event (SAE) reported against the Investigational Medicinal Product (IMP) as will CI and if this results in a Suspected Unexpected Serious Adverse Reaction (SUSAR) assessment then unblinding will be performed.

13.4 Unblinding procedure and documentation

Unblinding will be done via the Interactive Voice Technology (IVR). This is a telephone or web-based application.

All instances of unblinding should be recorded and reported in writing to SCTRU Prossper team by the local investigator, including the identity of all recipients of the unblinding information.

Details of how a patient can be unblinded will be included in the site file and in the patient's medical records. This will also be covered in the site initiation visit.

Allocation should not routinely be revealed to Prossper personnel, the CI, or members of the research team at the site.

At the end of the study, participants (or their GPs) may request to be unblinded in order to inform ongoing treatment decisions. In such cases, the CI will have a telephone conversation with the participant or GP, to include discussion of the methodological and scientific advantages of maintaining the blind until the data is analysed. If the CI is not available to have this conversation, it will be made by another senior member of the trial team. Following this conversation, if the participant or GP still wishes to be unblinded, a request to SCTRU Prossper team to permit unblinding will be made. If the SCTRU Prossper team agrees, the unblinding will be done by the SCTRU QA Team, such that the CI, trial office team and site research team can remain blind to treatment allocation.

14 DATA MANAGEMENT

All data will be handled, computerised and stored in accordance with the Data Protection legislation and Public Health Scotland Confidentiality Guidelines.

14.3 Data Collection

Data generated will be entered by site staff onto a Trial specific eCRF. SCTRU will be responsible for checking the data, and validating it. All source data should be recorded within patient files.

The data collected will include:

- initial clinical details at randomisation
- drug administration (progesterone/placebo and dexamethasone) including concomitant medications
- adverse events
- blood tests (see Appendices 4 & 5) including endocrine studies
- ongoing clinical details during study period
- patient questionnaires

14.4 Record Keeping and Archiving

PHS will store study documentation until the end of patient follow up. The documentation will then be archivedfor 5 years after the end of trial notification has been submitted. .

15 STATISTICS

15.3 Sample Size

In the absence of data necessary to make an informed power calculation for the secondary efficacy endpoint, this sample size for this study was arrived at empirically but is supported by clinical experience and/or simulated data, as outlined below.

In a group of 36 patients randomised 1:1 between intervention and control we would have 90% power to demonstrate an effect size of -1.00 between the two groups, and 80% power to demonstrate a difference of -0.85. In the context of the endpoint being final dexamethasone dose on Day 14, scenarios that would result in this effect size or greater are clinically reasonable (see below).

Final Dexamethasone dose	
+ placebo	+ progesterone

Mean	SD	Mean	SD	SD (pooled)	Effect size	N (per arm)	N (total)
4	2	2	2	2	-1.0	18	36
4	1	2	1	1	-2.0	6	12
2	1	1	1	1	-1.0	18	36

To further illustrate the potential effect sizes that we would be able to identify, and to assess the power that n=36 would provide for the *cumulative* dose of dexamethasone across the study period, simulated data have been generated, based on assumptions drawn from clinical experience. In these data the mean effect size (1000 simulations) for the final and cumulative dexamethasone doses was -0.88 and -1.04 respectively. The power that we have to detect effect sizes of this magnitude with n=18 (per arm) is 83.05% and 92.13% respectively.

A one sided t-test was used to calculate the sample size as we are testing specifically for reduction rather than a difference. The one sided t-test is exploratory and the primary outcome is safety.

15.4 Randomisation and Stratification

After ensuring that the patients meet **all** eligibility criteria and has consented to participate in the study, sites will randomise the patient following the instructions described in the PROSSPER work instructions for sites. Once a patient has been randomised, a patient study number will be issued and this should be used in all correspondence.

Stage 2 of the PROSSPER trial will be randomised into two treatment groups: Progesterone arm or placebo arm. Randomisation will be a 1:1 allocation; 18 patients in each group stratified by clinical site (Leeds and Liverpool).

15.5 Analysis Plan

The final analysis will be performed on the evaluable population (that is, patients who successfully completed the 14-day treatment period and were not subsequently found to be ineligible); no interim analysis is planned. Unless otherwise stated, 80% confidence intervals will be used; 1-sided p-values calculated and α=0.05 as a threshold for significance. Substantial missing data (i.e., missing in >10% patients) will be highlighted in statistical study reports but not imputed. A full statistical analysis plan will be developed prior to any analyses being performed.

14.4 Final analysis

The final analyses will be performed once the end of study has been declared. They will address each endpoint explicitly with evidence, including:

- Stage 1, primary endpoint (Section 2.2.1.1 Primary:) – to be assessed at end of Stage 1
    - Percentage of target exposure for each patient will be calculated and presented. Subsequent counts of number of patients to achieve 50-150% of target exposure will be presented.
- Stage 2, primary endpoint (Section 2.2.2.1 Primary:) – to be assessed at end of Stage 2
    - Number of patients tolerating progesterone until the end of the 14-day treatment period will be calculated and presented. Note that at least 13/18 patients should

be identified as tolerating progesterone (i.e., ensuring that >50% patients, using 80% CI, tolerate the treatment).

- Stage 2, secondary endpoint (Section 2.2.2.2 Secondary) – to be assessed at end of Stage 2
    - Compliance data will be presented and the number of patients complying with protocol guidelines on dose reduction will be calculated and presented. Note that at least 13/18 patients should be identified as complying with the dose reduction guidelines, to demonstrate compliance (i.e., ensuring that >50% patients, using 80% CI, comply).
    - Dexamethasone related side-effects will be coded according to the CTCAE toxicity criteria. These data will be presented in several ways, including worst value over the trial period for each patient and tabulation of all side-effectsgraded ≥ grade 1 in at least 10% of patients.
    - Presentation/analysis of QoL (DSQ-C, EORTC QLQ-30 & BN20) data.
    - Calculation of percentage reduction in dexamethasone at Day 14.
    - Comparison of final dexamethasone dose in the progesterone and placebo arms (e.g., by ordered logistic regression).
    - Comparison of cumulative dexamethasone dose in the progesterone and placebo arms (e.g. by ANOVA/t-test or Mann Whitney U if normality assumptions are violated).
    - Comparison of time to reach final dose in each arm in the progesterone and placebo arms (e.g., Cox regression).
- Stage 2, tertiary endpoint (Section 2.2.2.3 Tertiary) – to be assessed at end of Stage 2
    - Presentation of relevant lab results to assess endocrine, liver function and lipid profiles in patients on progesterone.
    - Comparison (progesterone v placebo) of CT/MRI data (including tumour size, enhancement pattern etc)

Acceptability of (future) trial design, randomisation, and outcome measures including PROMs. Any deviations from the original statistical plan will be discussed with the DMC and fully described and justified in statistical study reports.

14.5 End of Study

The end of the study is defined as the date where all patients have completed their assessments and all data has been cleaned, Quality Controlled and the database is locked for analysis.

15 ACCESS TO SOURCE DATA/ DOCUMENTS

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the Sponsor, SCTRU or the Coordinating Centre, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorised individuals.

Before a site is initiated, an agreement will be signed detailing where the source data will be recorded.

16 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control will be maintained through adherence to good clinical practice (GCP) and the coordinating centre's standard operating procedures (SOP)s. The coordinating centre will monitor that CRFs are being entered remotely in a timely manner and will evaluate entered CRFs for compliance with the protocol, inconsistencies and missing data.

16.1 Monitoring Visits

We have allowed for site visits in the UK to enable monitoring by SCTRU to check patient consent forms, confirm compliance with the protocol, check the management and accountability of the trial drug, ensure adequate maintenance of trial documentation, including participants' medical records, and complete source data verification (SDV) on the patient data as defined in the Data Monitoring Plan. Higher levels of monitoring will be performed, if requested, by the Data Monitoring Committee (DMC), or if the investigators, the Trial Management group or Trial Steering Committee identify particular safety issues**.**

Participating centres may be monitored by SCTRU to confirm compliance with the protocol and complete source data verification (SDV).

In the event that the COVID-19 pandemic precludes on site visits, these will be delivered remotely in discussion with the sites.

17 ETHICAL CONSIDERATIONS

Ethical approval by a Research Ethics Committee will be needed before the trial can be started. The trial will be carried out according to guidelines of good clinical practice (GCP) as defined by paragraph 28 and Schedule 1 Part 2 of the Medicines for Human Use (Clinical Trials) Regulations, 2004, and the Clinical Trials Directive (2001/20/EC) elsewhere in the EU and follow the principles of research governance.

17.1 Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number will be collected to enable tracing through national records, if required. The personal data recorded on all records will be regarded as confidential, and to preserve each patient's anonymity, only their initials and trial number will be recorded on CRFs. The patients will be identified within the CRFs by the use of a unique trial number allocated to them upon entry into the study.

The Principal Investigator (or designee) at each site must keep a log of patients' trial numbers, names, addresses and hospital numbers. The Principal Investigator must ensure that patient confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

The SCTRU will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified. Patients will only be referred to by Trial Number and Initials in any essential trial related correspondence, including Case Report Forms.

All patient identifiable data will be handled, computerised and stored in accordance with the GDPR and Data Protection Legislation and PHS Data Protection Policy.

17.2 Informed Consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever they want. This will not prejudice the patient's subsequent care.

Documented informed consent must be obtained for all patients included in the study before they are enrolled or randomized. This must be done in accordance with the national and local regulatory requirements and must conform to guidelines on Good Clinical Practice. That is, "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

All Patient Information Sheets & Informed Consent Forms will be version controlled and dated and this information will always be stated in any communication with ethics committees.

18. DISSEMINATION, OUTPUTS, PUBLICATION POLICY AND ANTICIPATED IMPACT

All presentations and publications relating to the trial must be authorised by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by the Trial Management Group representatives from SCTRU and high accruing clinicians. The trials offices and all participating Centres and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning their patients, which is directly relevant to the questions posed in the trial, until the main results have been published.

The TMG will seek PPI input to develop a dissemination plan so that patients/caregivers understand the findings and can engage confidently with clinicians. The dissemination plan will also include a requirement to offer the results of the study and its lay summary to patients/next of kin.

19. RESEARCH GOVERNANCE

Trial Organisation

Chief Investigator – The Chief Investigator will have overall responsibility for the design, co-ordination and management of the study. These include:

- Trial authorisation including responsibility for the protocol and obtaining approvals
- Ensuring that the trial is conducted according to Good Clinical Practice (GCP)
- Assessment of SAEs and providing a prompt response as to whether the SAE is a SUSAR.

Clinical Trials Unit – The Sponsor has delegated the responsibility for overall project management, data management and monitoring to the Scottish Clinical Trials Research Unit (SCTRU), based in Edinburgh. Responsibilities include:

- Assistance with completion of the IRAS form and REC communication
- Production of trial specific documentation (i.e. CRFs)
- Assistance with site activation procedures within centres
- Data management
- Financial Management
- Monitoring
- Pharmacovigilance – Reporting of serious adverse reaction (SAR)s / SUSARs

Statistical Analysis – Jade Carruthers, based at SCTRU, Edinburgh will undertake the final analysis or the secondary efficacy endpoint arising for this study.

Sponsor – PHS will act as study sponsor. Central study co-ordination, data collection, monitoring and organisation of the data for the statistical analyses will be undertaken by SCTRU, which has processes in place to ensure that the study will not open to recruitment until appropriate approvals and authorisations have been obtained from the independent research ethics committee, and NHS Research and Development departments.

Local Project Teams – These will consist of oncologists (responsible for introducing the patient to the study and ensuring eligibility and consent), Research Nurse (responsibilities include patient recruitment and co-ordination of all aspects of data collection), other health care professionals and administrative staff. Centres are specifically responsible for conducting the trial in accordance with the protocol, Standard Operating Procedures (SOPs), the trial agreement and Good Clinical Practice.

20. FINANCING AND INSURANCE

This study is funded by National Institute for Health Research (NIHR) and the IMP (micronised progesterone/placebo) is provided by Besins Healthcare (UK) Ltd. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

Appendix 1 – The Principles of ICH Good Clinical Practice

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

    This principle applies to all records referenced in this guideline, irrespective of the type of media used.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

    Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

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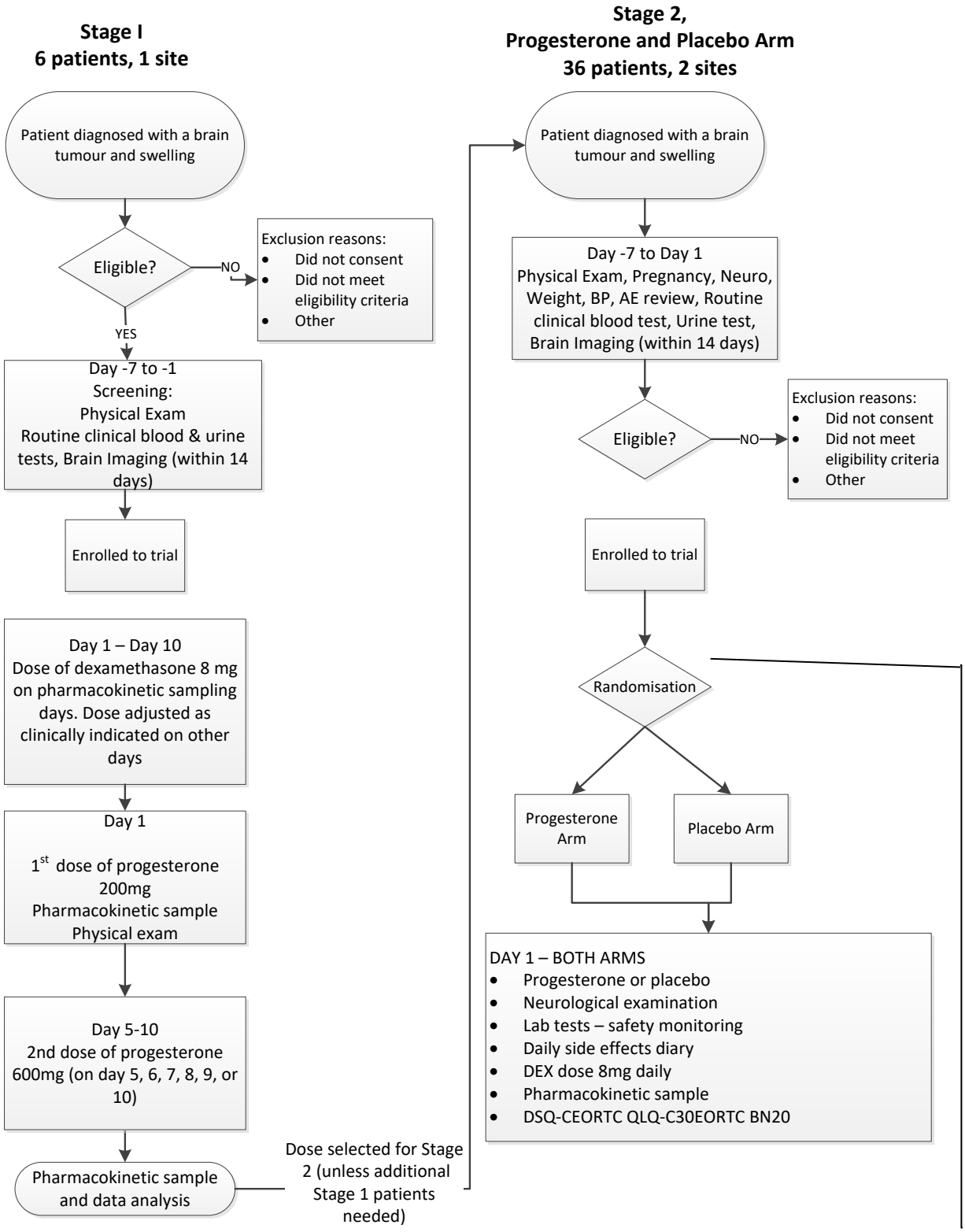
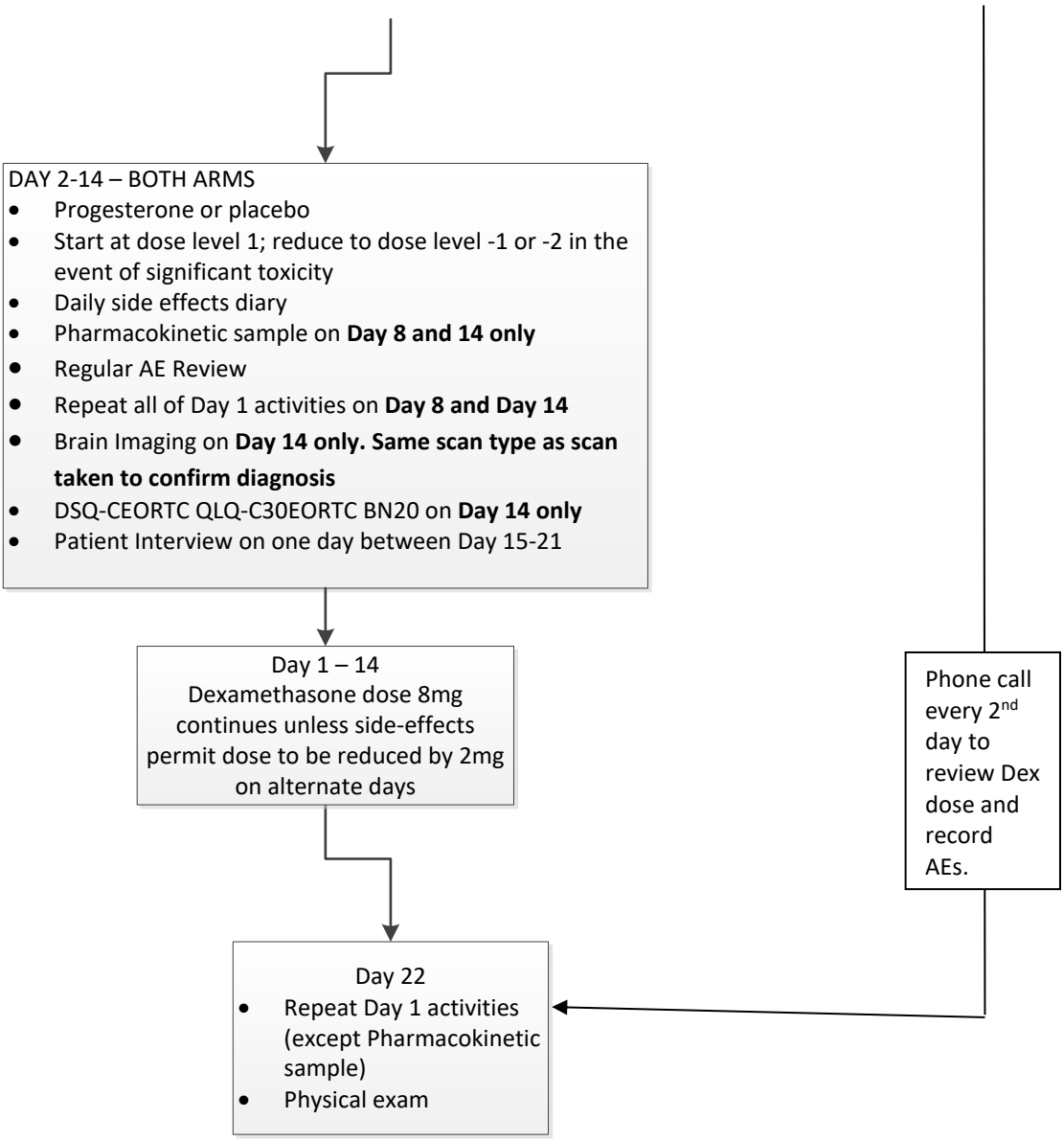
Appendix 3 – Patient pathway



Appendix 3 – Patient pathway (Cohort 2 continued)



Appendix 4 – Stage 1: Schedule of activities

Dosing		Day 1	Day 2	Day 3	Day 4	Day 5/6/7/8/9/10[5]	Post-trial
Dexamethasone – non IMP	≥4mg-12mg for ≥48 hours	8mg	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated with exception of the day progesterone is given when the dose will be 8mg	As clinically indicated
Progesterone - IMP		200mg				600mg given on one of the above days	
Activity/Day	≤ 7 days prior to progesterone						
Symptom directed physical examination	X	X					
Weight/BMI	X						
BP, pulse, temp	X						
Medical History	X						
Full blood count	X						
Clotting profile	X						
Urea and electrolytes	X						
Pregnancy check	X						
Fasting glucose	X						
Progesterone PK blood samples		X[1]				X[2]	
AE review and Dex dose review		X	X	X	X	X	
Concomitant Medications Review	X	X				X[3]	
CT/MRI brain[4]	X						

[1] = At baseline (pre-dosing with progesterone); t = 1, 2, 3, 4 and 6 hours (all +/- 15 minutes); then 10 and 24 (both +/- 2 hours) after administration of progesterone.
[2] = At PK sampling day (one day between days 5-10) (pre-dosing with progesterone); t = 1, 2, 3, 4 and 6 hours (all +/- 15 minutes); then 10 and 24 (both +/- 2 hours) after administration of progesterone.
[3] = On PK sampling day only
[4] = CT/MRI brain – Within 14 days of screening visit

[5] = Patients will be contacted by the Research Team 30 days after their 2nd dose of progesterone, to confirm if patient has experienced any SAEs. Patients will also be asked to contact the Research Team should they experience any side effects up to and including 30 days after their 2nd dose of progesterone (days 35-40). In addition, any events occurring more than 30 days after final IMP that are deemed to be related to the IMP should be notified to PHS by emailing phs.sctru@phs.scot.

Appendix 5 – Stage 2: Schedule of activities

Dosing	Day -2 and -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Days 15 - 21	Day 22[8]
Dexamethasone (mg) – non IMP	8	8	8	6#	6#	4#	4#	2#	2#	0#	0#	0#	0#	0#	0#	As clinically indicated	As clinically indicated
Micronised progesterone/ placebo t.d.s. - IMP		*	*	*	*	*	*	*	*	*	*	*	*	*	*		
Activity	**Day -7 to Day -1**																
Symptom directed physical examination	X	X							X						X		X
Medical History	X																
Pregnancy[5]	X																
Neuro. exam[1]		X							X						X		X
Weight/BMI		X							X						X		X
BP, pulse, temp		X							X						X		X
AE review and Dex/IMP dose review	X		X		X		X		X		X		X		X	X[7]	X
Concomitant Medications Review	X	X							X						X		X
Full blood count	X	X							X						X		X
Clotting profile	X	X							X						X		X
U & E, LFT, Ca	X	X							X						X		X
Hormone profile[2]		X													X		

Progesterone/placebo PK blood samples[3]		X							X						X		
Side-effects diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Interview[4]																X	
DSQ-C		X													X		
EORTC QLQ-C30		X													X		
EORTC BN20		X													X		
CT/MRI brain[6]	X														X		

On Day 3 to day 14, if clinically appropriate, the dexamethasone dose will be reduced by 2mg/day on alternate days and can be discontinued if indicated. See Appendix 7 Drug Table Stage 2 for further detail
* Dose determined in Stage 1 and modified as per protocol
[1] Neurological assessment will also be completed at any time dexamethasone dose needs to be increased
[2] Patient will be asked to fast (water only) and avoid taking their dexamethasone and progesterone/placebo before the blood sample is taken between 8.00am – 10.00am. After which they should take their prescribed dexamethasone and progesterone/placebo. "Hormone bloods" include: cortisol, glucose, testosterone, lipids; HbA1c, TSH, free T4, FSH, LH, oestrogen, IGF-1.
[3] Trough progesterone and dexamethasone levels. Prior to dose of progesterone (or placebo) and dexamethasone. These will be between 8.00am-10.00 am where the patients will already be delaying taking the medication.
[4] To be completed once between Day 15 and Day 21. Approximately 15 patients will be approached for the patient interview.
[5] WOCBP – Woman of child bearing potential only
[6] CT/MRI brain – Within 14 days of screening visit.
[7] Alternate days.
[8] Patients will be contacted by the Research Team on Day 44 to confirm if patients has experienced any SAEs. Patients will also be asked to contact the Research Team should they experience any side effects up to and including Day 44. In addition, any events occurring more than 30 days after final IMP that are deemed to be related to the IMP should be notified to PHS by emailing phs.sctru@phs.scot.

Appendix 6 – Stage 1: Drug table

Day	DEX dose – non IMP	PROG dose - IMP	
1[1]	8mg	200mg	PK sampling
2	as clinically indicated		
3	as clinically indicated		
4	as clinically indicated		
5 - 10[2]	8mg on a single day as clinically indicated other days	600mg on a single day	PK sampling

[1] Day 1 is a FIXED dose of 8mg Dexamethasone and 200mg Progesterone.
[2] The second FIXED dose of 600mg of Progesterone can be taken on any day between day 5 to day 10; on that day the dose of dexamethasone will be 8mg. On other days the dexamethasone dose will be determined clinically.

Appendix 7 – Stage 2: Drug table

Day	DEX dose[1] (non IMP)	PROG/Placebo dose[2] (IMP)	
1	8mg	Xmg	Dose of progesterone (Xmg) will be determined by the pharmacokinetic results of Stage 1
2 – 14	as clinically indicated, using Prossper DEX dosing	as defined by Stage 1. As clinically indicated, using Prossper PROG/Placebo dosing	
15	as clinically indicated, at clinicians discretion		
16	as clinically indicated, at clinicians discretion		
17	as clinically indicated, at clinicians discretion		
18	as clinically indicated, at clinicians discretion		
19	as clinically indicated, at clinicians discretion		
20	as clinically indicated, at clinicians discretion		
21	as clinically indicated, at clinicians discretion		
22	as clinically indicated, at clinicians discretion		

[1] DEX dosing - 8mg, 6mg, 4mg, 2mg, 0mg

From Day 3-14, if clinically appropriate, the dexamethasone dose can be reduced by 2mg/day on alternate days, and can be discontinued if indicated. Should symptoms of raised intracranial pressure recur, the dose of dexamethasone will be increased by 4mg (i.e. to 2mg above the dose at which the patient's symptoms had been controlled).

[2] PROG dosing - 600mg t.d.s, 400mg t.d.s, 200mg t.d.s

Any patient unable to tolerate the initial Progesterone/placebo dose would have the dose reduced; if that reduced dose is not tolerated, it will be reduced further. If this second dose is not tolerable, the patient will be withdrawn from the study.

Appendix 8 – Principal Investigator Declaration

PROSSPER

PROgesterone as a **S**teroid **SP**aring agent against o**E**dema occurring with secondary b**R**ain cancers

Principal Investigator Declaration

I acknowledge receipt of version <#> date <dd/mmm/yyyy> of the PROSSPER trial protocol (REC approved <dd/mmm/yyyy>) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern.

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please retain original declaration form in the Investigator Site File and return a copy to:
PROSSPER Team
Scottish Clinical Trials Research Unit
Public Health Scotland
Gyle Square
1 South Gyle Crescent
Edinburgh
EH12 9EB
Email: phs.prossper@phs.scot