



FALCON

(Short title: Fluciclovine (^{18}F) PET/CT in biochemicalAL reCurrence Of prostate caNcer)

A phase 3, open-label study to assess the clinical utility of Fluciclovine (^{18}F) PET/CT in patients with prostate cancer with biochemical recurrence after radical treatment

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Conflicts of Interest

Blue Earth Diagnostics Ltd is responsible for the manufacture of fluciclovine (^{18}F).

Protocol Signature Page

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1. SYNOPSIS

Study Title	A phase 3, open-label study to assess the clinical utility of fluciclovine (¹⁸ F) PET/CT in patients with prostate cancer with biochemical recurrence (BCR) after initial treatment	
Internal ref. no. / short title	Fluciclovine (¹⁸ F) PET/CT in biochemical <u>AL</u> reCurrence <u>Of</u> prostate ca <u>N</u> cer (FALCON); BED-004	
Study Design	This is a phase 3, open-label study to confirm the clinical benefit of fluciclovine (¹⁸ F) PET/CT in patients with biochemical recurrence of prostate cancer (BCR).	
Study Participants	Patients with BCR being considered for radical salvage treatment (with curative intent), having had primary radical curative therapy performed at least 3 months before enrolment.	
Planned Sample Size	Recruitment of 180 patients with anticipation of 171 patients completing the trial.	
Planned Study Period	Patients will be followed up for treatment outcome and standard of care investigation results for up to 7-8 months after completion of treatment plan. Duration on study will be up to 7-8 months after completion of treatment plan.	
	Objectives	Endpoints
Primary	To assess the clinical impact of fluciclovine (¹⁸ F) PET/CT in affecting management decisions in patients with BCR being considered for radical salvage treatment (with curative intent).	The record of the revised management plan post fluciclovine (¹⁸ F) PET/CT scan in comparison to the pre-scan intended management plan.
Secondary	<ol style="list-style-type: none"> To assess possible improvement in outcome of radical salvage treatment based on fluciclovine (¹⁸F) PET/CT being included in the assessment. To assess the prostate specific antigen (PSA) threshold for positive lesion detection by fluciclovine (¹⁸F) PET/CT in BCR To assess the safety of fluciclovine (¹⁸F) injection in patients undergoing PET/CT 	<ol style="list-style-type: none"> The proportion of patients who have a sustained response to radical salvage therapy. PSA levels in relation to scan positivity will be analysed to determine the optimal PSA threshold for detecting recurrent PCa by fluciclovine (¹⁸F) PET/CT. Safety will be assessed from data on the occurrence of adverse events (AEs) and changes in clinical laboratory tests, vital signs, injection-site status, and physical examination findings from the

		time of administration of fluciclovine (¹⁸ F) injection throughout the study period.
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2. ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
C.I.	Confidence Interval
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NRES	National Research Ethics Service
PET	Positron Emission Tomography
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
US	Ultrasound

3. BACKGROUND AND RATIONALE

Prostate cancer (PCa) is the commonest cancer in males in the UK, accounting for 25.9% of total malignancies in men in 2012, with an age-standardised incidence of 174.7 per 100,000 males [1]. It is the second commonest cause of male cancer deaths [2] with a recurrence rate of 20-30% in patients who have received primary radical treatment [3].

The diagnosis of PCa is often made following the detection of elevated prostate-specific antigen (PSA) and / or an abnormal digital rectal examination, with confirmation of diagnosis by prostate biopsy. PSA is used as a tumour marker and its levels are positively correlated with the risk of metastatic disease or subsequent disease progression.

The primary treatment of PCa can be divided into radical and non-radical treatment, the former applicable to patients with localised non-invasive disease. Radical primary treatment options include radical prostatectomy (RP), radical external beam radiotherapy (RRT) and brachytherapy. Following radical treatment, patients undergo surveillance via PSA measurement. Detection of PSA post radical therapy (at least 6 weeks post treatment in the case of RP), or an initially falling and then rising PSA are evidence of biochemical disease relapse, BCR. Depending on clinical factors and local practice, patients may undergo imaging, usually a bone scan and or pelvic MRI, to confirm the sites and extent of disease relapse.

3.1 Conventional Imaging in BCR

Standard imaging investigations are an isotope bone scan to evaluate for bony metastatic disease [4] and MRI / CT to assess for local / nodal recurrence [5]. However, BCR after RP or RRT precedes clinical metastases by 7-8 years on average, rendering the diagnostic yield low in asymptomatic patients [6]. EAU guidelines recommend these tests only be performed in patients with BCR who have a high baseline PSA (> 10 ng/mL) or a high PSA velocity (> 0.5 ng/mL/month) or in patients with symptoms of bone disease. The positive detection rate of these investigations are poor below these thresholds [7, 8]. In BCR patients with PSA ≤ 10 ng/ml, Dotan et al [9], only 4% of patients had positive bone scans. Studies have shown CT to be positive in only 11–14% of men with BCR after RP [8, 10]. The diagnosis of nodal involvement on conventional cross-sectional imaging (CT / MRI) is based primarily on nodal size, which is known to be inaccurate, with pooled sensitivities of 39% and 42% for MRI and CT respectively and pooled specificities of 82% in both modalities [11]. As such, the utility of imaging and type of investigation in BCR varies across the UK.

3.2 FDG PET-CT Imaging in BCR

The uptake of FDG is low in prostate cancer and its use as an imaging agent in PET-CT in prostate cancer has been shown to be of limited value [12, 13]. Several radionuclide tracers have been developed for clinical use in prostate cancer. The most well-established tracers in clinical use within Europe are choline-based PET radiotracers.

3.3 Choline PET/CT

The concept of using radiolabelled choline in the imaging of prostate cancer is based on the overexpression of choline kinase by prostate cancer cells, a property shared with other tumour types [14]. Two different forms of radiolabelled choline are in current use, ^{11}C -choline and ^{18}F -fluorocholine. With the latter, two chemically variant compounds are commercially available, ^{18}F -fluoromethylcholine and ^{18}F -fluoroethylcholine. No in vivo studies directly comparing the different forms of radiolabelled choline have been published.

Choline PET/CT has better diagnostic performance in detecting sites of recurrent prostate cancer than conventional imaging and ^{18}F -FDG PET/CT. Evangelista et al [15] pooled data from 2 studies (n=89) comparing ^{11}C -choline to ^{18}F -FDG PET/CT in detecting prostate cancer metastases. In ^{11}C -choline and ^{18}F -FDG PET/CT scans respectively, they reported pooled sensitivities of 65.1 % (95% C.I. 53.8–75.2 %) and 39.8 % (95% C.I. 29.2–51.1 %), and pooled specificities of 83.3 % (35.9–99.6 %) and 83.3 % (35.9–99.6 %). Von Eyben et al [16] pooled data from 7 studies (n=280) comparing choline PET/CT to bone scintigraphy. Choline PET/CT yielded positive results for more patients [127 (45%) vs. 46 (16%), odds ratio (OR) 2.8, 95% C.I. 1.9–4.1]. In a cohort of 109 BCR patients with negative conventional imaging (transrectal US, MRI, abdominopelvic CT, bone scintigraphy), Giovacchini et al reported positive ^{11}C -choline PET/CTs in 11% [17].

The adoption of choline PET/CT has also been shown to have clinical impact. In a recent retrospective multicenter study, Ceci et al [18] reported ^{11}C -choline PET/CT led to a major clinical impact change in management in 18% of patients, with an overall management change in 46.7%. Von Eyben et al 2014 pooled data from 15 studies (n=938) evaluating the impact of choline PET/CT on changing treatment in prostate cancer [16]. They reported 41% of patients undergoing a change in treatment. Based on a secondary pooled analysis restricting this cohort to patients with BCR [19-22], 40% underwent a change in treatment. Furthermore, patients with negative choline PET/CT results had better BCR-free, disease-free and treatment-free survival rates than those with positive findings. Choline PET/CT positivity/negativity was the only significant predictor of treatment-free survival.

In the same meta-analysis, PSA response following a change in treatment based on choline PET/CT results was evaluated using pooled data from 10 studies (n=404) [16]. This demonstrated 25% of patients having a complete PSA response. Treatments included salvage lymphadenectomy (LND) and pelvic radiotherapy.

Despite better diagnostic performance compared to conventional imaging, choline PET/CT still suffers from suboptimal sensitivity. Whenever choline-PET/CT identifies a suspected lesion, almost twice as many metastases are present [23], an observation reflected in data from recent meta-analyses. Von Eyben et al [16] pooled data from 11 studies (n=609) evaluating the performance of choline in detecting lymph node metastases in BCR – with histological correlation. Pooled sensitivity was 59% (51%–66%) and specificity was 92% (89%–94%). Hence, choline cannot adequately characterise the extent of nodal disease in BCR.

In the context of primary prostate cancer, Evangelista et al [24] pooled data from 10 studies (n=441) evaluating the performance of choline in detecting lymph node involvement. This also yielded a relatively poor pooled sensitivity of 49.2% (95% C.I., 39.9-58.4%), with a higher specificity of 95% (95% C.I., 92-97.1%).

While it performs better than conventional imaging counterparts, the detection rate of choline PET/CT remains poor in the setting of relatively low PSA and slow PSA kinetics. Husarik et al and Castellucci et al reported a moderate and low detection rate in case of PSA value <2 ng/mL and <1.5 ng/mL (71.4% and 28%), respectively [25, 26]. The detection rate of metastases has been described to range between 20% and 36% in patients with PSA <1 ng/mL, compared to 63%-83% where PSA levels exceed 3 ng/mL [27-29]. In a cohort of 109 BCR patients with negative conventional imaging (TRUS, MR, abdominopelvic CT, bone scintigraphy), Giovacchini et al reported a higher rate of positive ¹¹C-choline PET/CTs with higher PSA [17]. Imaging was positive in 3 of 65 (5%), 4 of 26 (15%) and 5 of 18 patients (28%) with PSA between 0.2 and 1, between 1 and 2, and greater than 2 ng/ml, respectively.

As with other diagnostic tests, choline PET/CT is liable to produce false positive findings. This is reflected in the aforementioned diagnostic performance parameters and has been described in a number of entities. These included increased choline uptake within: the prostate in benign prostatic hypertrophy (BPH) [30], lymph nodes due to inflammation [31, 32], the prostate bed due to post-surgical scarring and inflammation post-RP/RRT [33], bones due to degenerative change or recent fractures [34].

The two different forms of radiolabelled choline, ¹¹C-choline and ¹⁸F-fluorocholine, have individual drawbacks. ¹¹C-choline exhibits early accumulation in small bowel limiting pelvic analysis [35]. The short 20-minute half-life of ¹¹C limits the use of ¹¹C-choline to centres with an on-site cyclotron and radiopharmacy facilities. Its short half-life also limits the scope for obtaining delayed acquisitions to improve tumour-to-background ratio. The latter can be performed with ¹⁸F-fluorocholine, which has a longer half-life of 110 minutes. This also makes it a more widely distributable tracer. However, high urinary tract uptake and excretion of ¹⁸F-fluorocholine into the urinary bladder limits assessment of the prostate bed [36].

3.4 Conventional and Emerging Radical Salvage Options in BCR

The options for radical salvage therapy (with curative intent) in BCR remain controversial [5]. In the context of prior RP, the main option is salvage radiotherapy (SRT) to the prostate bed. In patients with intact prostates, having had prior primary RRT or brachytherapy, a wider range of options for salvage therapy with curative intent are available. These include salvage radical prostatectomy, salvage cryotherapy, salvage brachytherapy and salvage HIFU [5].

The described therapies are local treatments, directed at the prostate / prostate bed. Based on current mainstream practice, the presence of disease outside the prostate bed precludes radical salvage therapy. Paradoxically, current NICE guidelines recommend against the use of conventional imaging in patients being considered for radical salvage therapy [37], unless symptomatic. This may be rationalised by the observation of more favorable outcomes from radical salvage therapy at low PSA levels, particularly SRT [38], and foreknowledge of the poor diagnostic performance of conventional imaging at such PSA levels. While this in itself underpins the need for an imaging test to accurately detect extra-prostatic disease and thus prevent unnecessary radical salvage treatment, there is an emerging role for salvage treatment of limited nodal disease, with several reports of promising clinical endpoints based on early results. This has been described in the form of salvage pelvic lymphadenectomy (LND) or targeted pelvic radiotherapy, the latter afforded by the advent of more sophisticated techniques, namely intensity modulated radiotherapy (IMRT) and stereotactic beam radiotherapy (SBRT).

Rigatti et al [39] evaluated the effect of salvage LND in 72 patients with BCR post-RP, who had choline-positive lymph nodes on PET/CT. They reported a complete PSA response in 56.9% of patients and 5-year recurrence-free and cancer-specific survival of 24% and 75% respectively. The mean PSA in this cohort was 1.5 ng/ml. In 47 patients with BCR and a history of RP or RRT and choline-positive nodal disease, Jilg et al [40] evaluated the impact of salvage LND (with adjuvant radiotherapy in a subset). Similar outcomes were reported, a complete PSA response in 46% and 5-year recurrence-free and cancer-specific survival of 25.6% and 77.7% respectively.

Alongi et al [41] described an overall response rate of 82% (over a median follow-up of 195 days) to SBRT of isolated lymph node metastases in 34 patients with previously radically treated PCa. In a cohort of 24 patients with BCR and up to 3 synchronous bone or nodal metastases treated with SBRT, Berkovic et al [42] reported a median delay in commencing ADT of 38 months (95% C.I. 18–58 months). In another cohort of 34 patients with BCR and isolated disease recurrence (in various sites) on imaging, robotic SBRT resulted in a progression-free survival of over 40% at 30 months, and complete PSA response in over 60% treated with SBRT alone [43].

3.5 Rationale for accurate imaging in BCR

As mentioned previously, the presence of disease outside the prostate bed precludes radical salvage therapy based on mainstream practice. In addition, more favorable outcomes from salvage therapy are observed at low PSA levels [38], when the diagnostic performance of current imaging options is poor. Conversely, the presence of a high PSA is associated with an increased risk of metastatic disease [44], the presence of which precludes the option of radical salvage therapy. Herein lies the ongoing need for an imaging test to detect sites of recurrent disease earlier and with greater accuracy, to aid clinical management in patients with BCR.

3.6 Fluciclovine (¹⁸F) PET/CT

Fluciclovine (¹⁸F) is a synthetic amino acid ([¹⁸F]1-amino-3-fluorocyclobutane 1-carboxylic acid) developed by Shoup et al as a PET radiotracer for visualising malignant tumours [45]. The concept of using radiolabeled amino acids for the imaging of cancer is based on the increased metabolic demand of tumour cells, with enhanced channelling of amino acids into select metabolic pathways and increased expression of amino acid transporters to acquire these substrates. It is thought to be taken up by PCa cells via the ASCT2 and LAT1 amino acid transporters, and is not metabolised upon internalisation [46].

In 2007, Schuster et al first described the use of fluciclovine (¹⁸F) PET/CT in PCa in 15 patients with either primary disease or BCR [47]. This yielded promising findings of accurate nodal staging and identification of disease sites in patients with proven recurrence. This group have gone on to expand their work in a single centre study, evaluating the diagnostic performance of fluciclovine (¹⁸F) PET/CT compared to that of ¹¹¹In-capromab pendetide SPECT/CT in BCR. The latter is a radionuclide tracer licenced and established as standard of care for PCa imaging in the USA, but has been shown to have low sensitivities, with dismal detection of bone metastases [48]. Based on their latest published results in May 2014 from a cohort of 93 patients [49], fluciclovine (¹⁸F) PET/CT demonstrated a significantly higher accuracy, detecting more prostatic and extra-prostatic disease, and effectively up-staging 25.7% of cases. With specific regards to extra-prostatic disease (n=70), fluciclovine (¹⁸F) PET/CT detected disease in 18 more patients compared to ¹¹¹In-capromab pendetide (22 vs 4). Fluciclovine (¹⁸F) PET/CT had 55.0% sensitivity, 96.7% specificity,

72.9% accuracy, 95.7% positive predictive value (PPV) and 61.7% negative predictive value (NPV) compared to ¹¹¹In-capromab pentetide with 10.0%, 86.7%, 42.9%, 50.0% and 41.9%, respectively. Histological proof was obtained for majority (96.1%) of the lesions which had fluciclovine (¹⁸F) positivity.

In the largest cohort to date of intra-individual comparison of fluciclovine (¹⁸F) to ¹¹C-choline PET/CT, Nanni et al compared diagnostic performance between the two tracers in 28 patients with BCR after RP, in a single-centre study [50]. In the setting of relatively low PSA levels (mean 2.9 ng/mL, range 0.2- 14.6), the positive detection rate was found to be higher in fluciclovine (¹⁸F) compared to ¹¹C-choline PET/CT (35.7% vs 17.8%). Specifically, the detection rate was higher at PSA levels ≤ 1 ng/mL and > 2 ng/mL, and similar at levels between 1 – 2 ng/mL. All choline-positive lesions were also fluciclovine-positive. Fluciclovine (¹⁸F) PET/CT was positive in an additional 5 patients who had negative ¹¹C-choline PET/CTs. The tumour-to-background ratio (TBR) of fluciclovine (¹⁸F) was greater than ¹¹C-choline in 83.3% of lesions. There were also fewer false positive findings on fluciclovine (¹⁸F) PET/CT. Increased choline uptake by liver angiomas and several inflammatory inguinal lymph nodes were fluciclovine-negative. The same trend of higher detection rates across all PSA levels, and higher TBR in fluciclovine (¹⁸F) PET/CT compared to ¹¹C-choline PET/CT in a larger cohort of 50 patients was more recently presented by the same group [51].

Compared to its radiolabelled choline counterparts, fluciclovine (¹⁸F) also has a more favourable biodistribution. It has minimal renal excretion and associated bladder activity, and low homogeneous activity in the bowel [52]. Furthermore, being an ¹⁸F labelled tracer, it is a distributable product which does not have to be manufactured on-site.

With a high positive predictive value (95.7%) for extra-prostatic disease, almost entirely confirmed by histology, and a higher detection rate than choline, fluciclovine (¹⁸F) bears hallmarks of a competitively diagnostic agent in BCR. The impact of fluciclovine (¹⁸F) PET/CT on clinical management of patients with BCR remains to be defined, as is the PSA level associated with probability of a positive scan. Furthermore, the encouraging results on diagnostic performance observed at two expert centres need to be corroborated with larger multi-centre data, in order to formally validate its clinical utility for medical practice.

3.7 Proposed Research

In the setting of growing single-centre evidence of superior diagnostic performance of fluciclovine (¹⁸F) PET/CT in BCR, our primary aim is to assess its clinical impact on treatment decisions in a multi-centre study in patients with BCR being considered for radical salvage treatment (with curative intent). In addition, we aim to further characterise its diagnostic performance, afforded by larger numbers of patients from multi-centre recruitment. We also aim to assess the effect of PSA level on probability of lesion detection by fluciclovine (¹⁸F).

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints
<p>Primary Objective</p> <p>To confirm the clinical benefit of fluciclovine (¹⁸F) PET/CT in affecting management decisions in patients with BCR being considered for radical salvage treatment (with curative intent).</p>	<p>The record of the revised management plan post fluciclovine (¹⁸F) PET/CT scan in comparison to the pre-scan intended management plan.</p>
<p>Secondary Objectives</p> <ol style="list-style-type: none"> 1. To assess possible improvement in outcome of radical salvage treatment based on fluciclovine (¹⁸F) PET/CT being included in the assessment. 2. To assess the prostate specific antigen (PSA) threshold for positive lesion detection by fluciclovine (¹⁸F) PET/CT in BCR 3. To assess the safety of fluciclovine (¹⁸F) injection in patients undergoing PET/CT 4. 	<ol style="list-style-type: none"> 1. The proportion of patients who have a sustained response to radical salvage therapy. 2. PSA levels in relation to scan positivity will be analysed to determine the optimal PSA threshold for detecting recurrent PCa by fluciclovine (¹⁸F) PET/CT. 3. Safety will be assessed from data on the occurrence of adverse events (AEs) and changes in clinical laboratory tests, vital signs, injection-site status, and physical examination findings from the time of administration of fluciclovine (¹⁸F) injection throughout the study period. 4. .

5. STUDY DESIGN

5.1 Summary of Study Design

This will be an open-labelled, multi-centred study in the UK. The study group will include up to 180 patients with a diagnosis of BCR of previous radically treated PCa, and who are being considered for radical salvage therapy. Patients will have a fluciclovine (¹⁸F) PET/CT scan in addition to standard work-up for radical salvage therapy. The clinical utility of fluciclovine (¹⁸F) PET/CT will be assessed by recording changes to the recommended management plan influenced by the scan result.

Eligible patients who have expressed interest in the study will be provided detailed information about the study to consider participation, and means to communicate with the study team to discuss and raise any queries regarding participation. If the patient would like to take part, an enrolment visit (Visit 1) will be organised. Written informed consent, study registration and screening (including baseline blood tests and electrocardiogram [ECG]) will be performed on the same visit. The visit is also a further opportunity to ensure all queries about the study have been addressed.

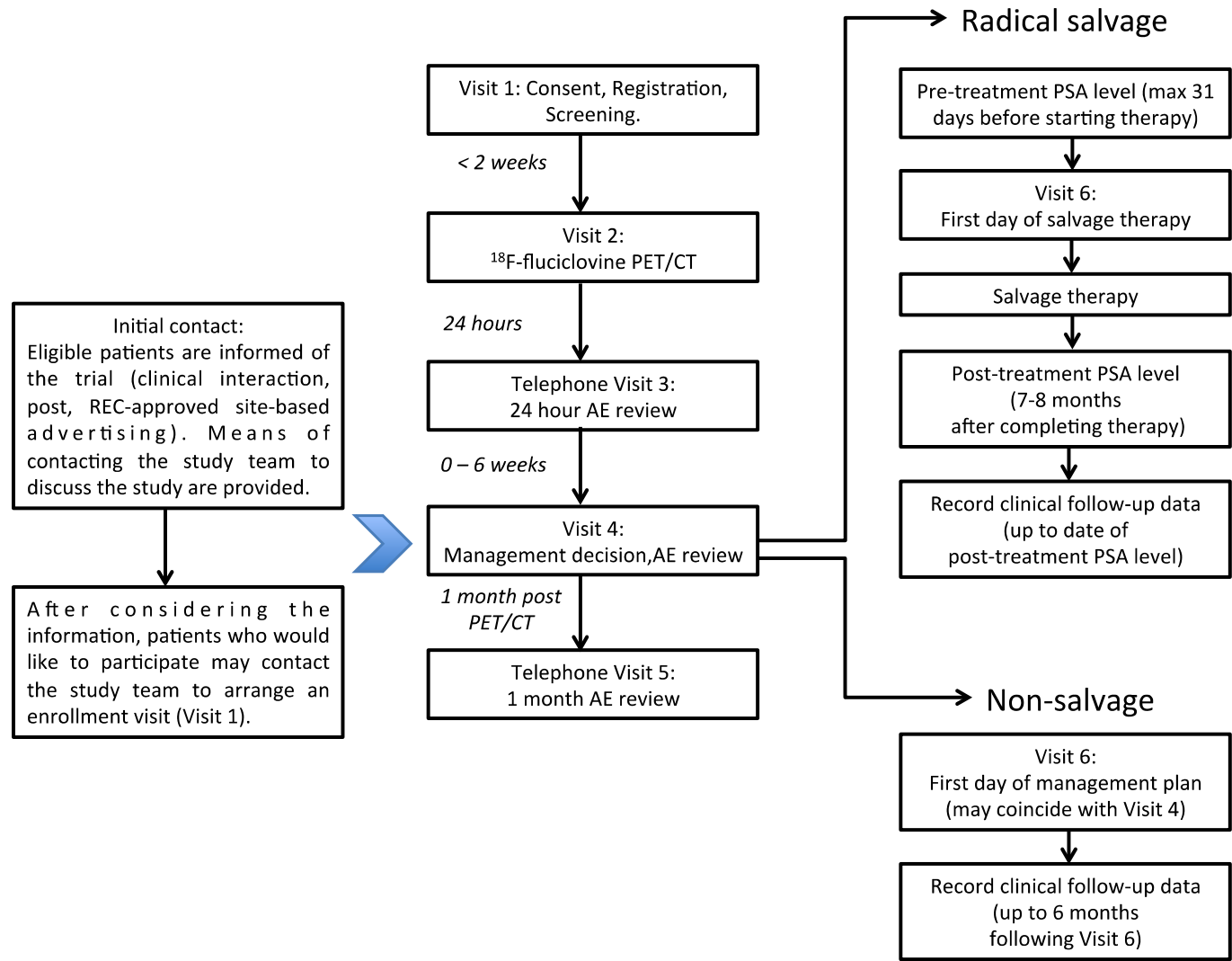
At the baseline imaging visit (Visit 2), participants will undergo routine medical screening approximately 1 hour prior to receiving fluciclovine (¹⁸F) injection and undergoing PET/CT imaging. Vital signs and the

injection site will be monitored regularly for 2 hours after administration of fluciclovine (^{18}F). In the absence of AEs, patients may be discharged 2 hours after administration. Participants will receive a telephone consultation 24 -72rs after completion of fluciclovine (^{18}F) PET/CT to review any AEs that have occurred in the interim following discharge (Telephone Visit 3). Furthermore, participants will attend a subsequent hospital outpatient appointment (Visit 4) after the scan to discuss their test results and treatment options, and undergo post-imaging blood tests and ECG, during which they will have a further opportunity to report any AEs. Participants will receive a second telephone consultation 1 month after completion of fluciclovine (^{18}F) PET/CT to review any AEs that have occurred in the interim (Telephone Visit 5). Subsequent hospital visits for treatment and assessing response to treatment will be performed as part of routine standard of care.

Participation in Visit 1 should take 30 minutes to 1 hour. Visit 2 will take approximately 3 hours from the point of commencing medical screening to being discharged. Visit 4 will take approximately 30 minutes and may vary depending on practice of the participant's clinical team. Telephone consultations will take approximately 15 minutes.

In patients who receive radical salvage therapy (regardless of fluciclovine (^{18}F) PET/CT result), PSA should be assessed a maximum of 31 days before therapy and at least once between 7-8 months after treatment completion. Where possible, this should be arranged to coincide with treatment-associated hospital visits as per standard of care. If these cannot be incorporated into the hospital visits, a minimum of one, maximum of two extra visits will be required for these PSA tests.

5.2 Summary Flow Chart of Study Design



6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Participants with a diagnosis of BCR of previous radically treated PCa, aged ≥ 18 years old, being considered for radical salvage therapy (with curative intent).

6.2. Inclusion Criteria

- (1) The subject is a male ≥ 18 years old.
- (2) The subject has had an original diagnosis of PCa and underwent radical curative therapy at least 3 months before enrolment, and has been diagnosed with BCR on the basis of:
 - a. Post RRT / brachytherapy: Increase in PSA level ≥ 2.0 ng/mL above the nadir level after radiotherapy (RT) or brachytherapy (ASTRO-Phoenix criteria) [53], or
 - b. Post RP: EITHER two consecutive rises in PSA and final PSA > 0.1 ng/mL OR three consecutive rises in PSA. This definition is also applicable to subjects with PSA persistence post RP (where the PSA fails to fall to undetectable levels).
 - i. In addition, the subject post RP, should have a PSA doubling time of ≤ 15 months OR PSA level ≥ 1.0 ng/mL at time of recruitment. The PSA doubling time will be calculated using the Memorial Sloan Kettering Cancer Center nomogram (<http://www.mskcc.org/nomograms/prostate/psa-doubling-time>), based on a minimum of two PSA levels within 12 months of screening, taken after the last recorded nadir PSA available at time of screening.
- (3) The subject has not had previous recurrences of PCa, i.e. this is the first diagnosis of BCR.
- (4) The subject is being considered for radical salvage therapy.
- (5) The subject is able and willing to comply with study procedures, and signed, dated and timed informed consent is obtained before any study-related procedure is performed.
- (6) The subject's Eastern Cooperative Oncology Group [ECOG] performance status 0-2.
- (7) The subject should not have received androgen-deprivation therapy within 3 months of screening.
- (8) The subject has a normal or clinically acceptable medical history and vital signs findings at screening (up to 14 days before administration of study drug).

6.3. Exclusion Criteria

- (1) The subject has been previously included in this study.
- (2) The subject has received, or is scheduled to receive, another investigational medicinal product (IMP) from 1 month before to 1 week after administration of fluciclovine (¹⁸F) injection.
- (3) The subject has known hypersensitivity to fluciclovine (¹⁸F) injection or any of its constituents.
- (4) The subject has had a choline PET/CT scan within 3 months of the screening visit.
- (5) The subject has bilateral hip prostheses.

7. STUDY PROCEDURES

7.1. Recruitment

The trial will be advertised in the clinical centres participating in the study using REC approved advertising materials explaining the study and providing contact information for the local study team. In addition, potential participants will be identified from their local urology MDT meeting and during outpatient oncology or urology appointments. They will be approached by a member of their clinical team within the hospital setting and be informed of the trial, or be sent information, the patient information sheet (PIS) by post. The PIS will also provide contact details for the study team should the potential participant wish to initiate contact.

If a patient expresses an interest in the study to their clinical team within the hospital setting, they will be given a PIS and will be asked to give their permission to be contacted by the study team. If this permission is given, the referring clinical team member will complete a referral form to the study team with the patient's contact details.

Upon establishing contact with the study team to indicate interest in the study, a concise explanation of the study will be provided to the patient (as detailed in section 7.2). Patients will be encouraged to raise any queries they have about the study to aid their decision regarding participation. They will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. This may involve more than one contact with the study team. When the patient has decided to participate in the study, an enrolment visit (Visit 1) will be arranged. Enrolment will involve checking that the patient is eligible for the study, completion of informed consent, study registration and screening. The patient's hospital notes will be made available for screening purposes. The visit is also a further opportunity to ensure all queries about the study have been addressed.

7.2. Informed Consent

The participant must personally sign and date the REC approved version of the Informed Consent form before any study specific procedures are performed. If an amendment is made to the informed consent document during the study, patients still being followed up in the study will be informed of the changes made to the document and will be asked to consent to continued participation in the trial.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, trained in GCP and informed consent procedures, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

7.3. Screening and Eligibility Assessment

Prior to registration or any study measures being undertaken, eligibility will be checked as detailed in section 7.1 and documented informed consent will be completed as detailed in section 7.2.

All participants will undergo clinical assessment including medical history and baseline study measures (section 7.5) over Visits 1-2 as outlined below and in Appendix A (Schedule of Study Procedures): -

7.4. Randomisation, blinding and code-breaking

All participants will receive fluciclovine (¹⁸F) injection.

7.5. Baseline Assessments

Visit 1 (after successful screening and patient informed consent obtained)

Demographics

The participant's age will be recorded.

Medical History

This forms part of the participant's routine clinical care, consisting of significant past medical history and drug history including known drug allergies.

PSA level

The dates and levels of the participant's PSA from the date of radical therapy will be recorded. These values will be obtained from the participant's hospital records. A repeat PSA level will be measured at time of screening at the same time as the clinical laboratory tests are taken.

PCa treatment history

Specific details on the treatment history for PCa will be recorded. This will include the date of initial PCa diagnosis, initial tumour stage and Gleason score, dates of radical treatment and adjuvant treatment (if given), date of BCR diagnosis. This information will be obtained from the participant's hospital records.

Imaging history

The nature, date and outcome of imaging examinations performed up to 3 months before screening will be recorded. This information will be obtained from the participant's hospital records.

Intended management plan

The management plan, based on pre-existing clinical information including results of conventional imaging, will be recorded. This information will be obtained from the participant's hospital records or MDT records.

ECG

An ECG will be performed.

Vital Signs

Sitting blood pressure and heart rate will be recorded.

Urine

Patients will be asked to provide a mid-stream specimen of urine to be tested with urine dipstick (leucocytes, nitrites, pH, protein, ketones, glucose, bilirubin, blood, urobilinogen). If the sample is positive for leucocytes or nitrites, the sample should be sent for urine microscopy and culture and if the

patient has symptoms of a urinary tract infection, this should be treated according to local guidelines prior to PET/CT. Fluciclovine (^{18}F) PET/CT can be performed during such treatment.

Clinical laboratory tests

Blood samples for clinical laboratory tests will be taken and sent for analysis at the local hospital. This will consist of haematology (red blood cell count, haemoglobin, white blood cell count with automated differential count, platelet count and haematocrit), biochemistry (electrolytes (sodium, potassium, calcium, chloride), urea, creatinine, total bilirubin alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine transaminase (ALT), creatine kinase (CK), lactate dehydrogenase (LDH), albumin, total protein).

Visit 2 (day of Fluciclovine (^{18}F) PET/CT)

Vital signs

The sitting blood pressure and resting heart rate of the participant will be recorded.

Height and weight

The participant's height and weight will be measured.

Post-screening pre-administration events

A review of the participant's medical history will be performed to check for new health-related events and changes to concomitant medications since the screening visit.

7.6. Fluciclovine (^{18}F) PET/CT

The PET/CT will be acquired on the highest quality scanner available in the participating institution. The participant will be required to fast for at least 4 hours prior to the scan, drinking only sips of water within 4 hours of the scan if needed for administration of medications, and not exercise from the day before the scan through to the time of the scan. The participant will be cannulated, preferably in the right arm, and receive one dose of fluciclovine (^{18}F) diluted up to 10 mL injected by intravenous push (5-10 seconds) via the cannula with arms down followed by $\geq 10\text{mL}$ flush [54]. The participant will be scanned in the supine position in the direction of mid-thigh to skull base, with the arms positioned overhead following the dose and flush. The uptake time should be 3 to 5 minutes with a goal of 4 minutes from the end of the dose. For the PET acquisition, participants will be imaged for approximately 25 minutes. For the CT parameters, a high-quality unenhanced CT will be employed. Further details on the PET/CT acquisition will be given in the Study Imaging Manual.

Vital signs, examination of the injection site and review of AE/SAEs will be performed immediately post scan and at 60(± 5) minutes, 90(± 5) minutes and 120(± 5) minutes post-injection. All images obtained during the trial will be retained for use in this research and may be used for future approved research studies.

Analysis

Image interpretation will be based on guidelines derived from an international fluciclovine (^{18}F) reader consensus meeting held in June 2014 [54]. All readers will undergo training in interpretation of fluciclovine (^{18}F) scans, and will have a training set available for reference.

Primary evaluation and reporting of the PET/CT scan will be site-based (as per standard of care). The clinical team should make the revised treatment decision on the site-based report.

The fluciclovine (^{18}F) PET/CT scan will be centrally reported at the end of the study, blinded to the original report. Copies of the fluciclovine (^{18}F) PET/CT will be transferred from the host site for this purpose. Copies of the original report will also be transferred, as this data will be used to determine inter-reader agreement.

Prospective central review of scans will also be permitted where a second opinion is sought by a reader prior to issuing the report. This can be arranged ad hoc by contacting the co-ordinating investigator, sponsor or chief investigator.

7.7. Subsequent Visits

At each subsequent visit for the first 4 weeks following fluciclovine (^{18}F) PET/CT, study patients will be asked whether they have had any:

- Hospitalisations
- Consultations with other medical practitioners
- Disability or incapacity or other adverse event that has occurred since their last visit

24 (+ 4)-72 hours after fluciclovine (^{18}F) PET/CT (Telephone Visit 3)

A review of AE/SAEs will be performed via telephone consultation.

Outpatient appointment to review fluciclovine (^{18}F) PET/CT and revise management (Visit 4)

It is recommended that this outpatient appointment is scheduled approximately 2 weeks after the fluciclovine (^{18}F) PET/CT scan (Visit 2), although a window of 0-6 weeks is permitted depending on local clinical practice. The clinical team will then record whether the pre-scan management plan will be unchanged or altered based on the new information provided by the fluciclovine (^{18}F) PET/CT, and the reason for the decision. It is recognised that the revised management plan may be decided on before the outpatient appointment and this is permitted.

Examples of a change in proposed management plan include changing of treatment types and/or approaches (including change to radiotherapy plans), and recruitment into another clinical trial. The patient may enter another clinical trial as part of the management plan influenced by the PET/CT findings. Where an additional diagnostic procedure (e.g. imaging or biopsy) is performed in light of the PET/CT findings, the results of these should be considered prior to recording the revised management

plan, and this should be recorded on the CRF. The exception to this is where choline PET is performed in addition to fluciclovine (¹⁸F) PET/CT (see section 7.7).

The revised management plan will be discussed between the clinical team and participant, and the agreed management decision recorded. If the revised management plan and agreed management decision are different, the reason for the decision, including the influence of other standard of care assessments performed outside the trial protocol, will be documented.

The participant will also have an opportunity to report any AEs. A repeat set of clinical laboratory tests, urine dipstick analysis and ECG will also be performed during Visit 4 as part of a review for AEs.

1 month (+7 days) after fluciclovine (¹⁸F) PET/CT (Telephone Visit 5)

A review of AE/SAEs will be performed via telephone consultation.

First day of new management plan (Visit 6)

This will be performed as per standard of care and may be the same date as Visit 4, if the new management plan is commenced on the same day as the agreed treatment decision. During this visit, the investigator will record the date of management starting (to determine when follow-up information should be collected as detailed in the next heading “Clinical follow-up”).

Where patients are commencing radical salvage therapy, the investigator will also ensure that a pre-treatment PSA has been measured and recorded up to 31 days before this date.

All patients who receive radical salvage therapy

In this patient group, PSA will be measured a maximum of 31 days before therapy and at least once between 7-8 months after treatment completion. Where possible, this should be arranged to coincide with treatment-associated hospital visits as per standard of care. If these cannot be incorporated into the hospital visits, a minimum of one, maximum of two extra visits will be required for these PSA tests.

If the actual treatment received by the subject differs to the plan agreed at Visit 4, then this will be recorded on the “End of study” CRF (see the next section “Clinical follow-up”), along with the reason.

Clinical follow-up

Following instigation of their management plan, patients will be seen for follow-up at intervals as per standard of care and have imaging tests as clinically appropriate and per standard of care.

At the end of specified follow-up windows, follow-up information will be obtained by the local study team via attendance for imaging tests and via the GP or hospital medical care team as appropriate and entered on the “End of study” CRF. The patient will not be required to make a dedicated visit for this. The follow-up window is dependent on the type of management:

1. Radical salvage therapy: Up to the date of post-treatment PSA level check (7-8 months after completion of treatment).
2. Non-salvage management: Up to 6 months after Visit 6 (instigation of management plan).

In the event where radical salvage therapy is stopped prematurely or deemed by the clinical team to be sub-optimally delivered, the follow-up window should apply as for non-salvage management (up to 6 months from instigation of the initial management plan). The reasons for this should be recorded on the CRF as described in the prior section “All patients who receive radical salvage therapy”.

The following information will be collected for all patients:

1. Copies of imaging tests and reports, and histopathological reports for relevant endpoint analyses
2. PSA levels
3. Mortality (if applicable)
 - a. Date of death
 - b. Causes of death
 - c. Other significant conditions contributing to death
 - d. Source of report
 - e. Whether the death was expected
 - f. Whether a causal relationship to the study IMP is suspected
 - g. Name of the investigator responsible for assessing expectedness and causality (if the patient died prior to the last research scan or as a result of an ongoing reportable AE)

In addition, the following information on effect of management will be collected:

<u>Radical salvage therapy</u>	<u>Non-salvage management</u>
Effect of radical salvage therapy: <ol style="list-style-type: none"> a. Treatment response <ol style="list-style-type: none"> I. $\geq 50\%$ decline in PSA [5] \pm II. Radiological response b. Treatment failure <ol style="list-style-type: none"> I. Increase or $< 50\%$ decline in PSA \pm II. Radiological progression 	Effect of management as assessed by the clinical team: <ol style="list-style-type: none"> a. Response <ol style="list-style-type: none"> I. $\geq 50\%$ decline in PSA \pm II. Radiological response b. Stable c. Progressed <ol style="list-style-type: none"> I. PSA progression and/or II. Radiological progression d. Not assessed

7.8. Procedure for centres which perform choline PET as standard of care

In these participating centres, where the clinical team decides to investigate the subject with choline PET in addition to fluciclovine (^{18}F) PET/CT, this will be performed only after the fluciclovine (^{18}F) PET/CT report has been issued by the site, considered to formulate a revised management plan, and documented onto the appropriate CRF.

7.9. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of consent
- Loss to follow up

Withdrawal from the study will not result in exclusion of the data for that participant from analysis provided all baseline study measures have been completed.

The reason for withdrawal will be recorded in the CRF. If the participant is withdrawn due to an AE/SAE, the Investigator will arrange for follow-up visits or telephone calls until the AE/SAE has resolved or stabilised.

7.10. Definition of End of Study

The fluciclovine (^{18}F) injection administration will be followed by a follow-up period which will continue for 6 months after instigation of management plan.

The end of the trial for an individual patient is defined as 6 months after instigation of their management plan. In patients who receive radical salvage therapy, the end of the trial is defined as the date of post-treatment PSA level.

The end of the study is defined as the date of database lock for data analysis, which is anticipated to occur within 12 weeks after the last patient has completed the 6 months post treatment follow up.

8. Risks and Benefits to Trial Participants

8.1. Benefits

The research scans may provide further clinical information regarding the patient's disease status that may not have been appreciated by other standard of care tests. If such information arises, this will be reported back to the responsible clinician to help direct the patient's further management. This may provide a direct benefit to the subject

8.2. Risks

The risks from the imaging studies to subjects mainly relate to the intravenous injection and the radiation emitted by the radiopharmaceutical. Intravenous injection carries a small risk of infection and haematoma.

Assuming an average annual background radiation exposure of 2.6mSv [ARSAC 2006], the radiation exposure from an individual administration of fluciclovine (¹⁸F) Injection would be equivalent to 3.2 years of background radiation, and the associated CT transmission scans would be equivalent to about 2.7 years of background radiation.

The above estimations are based on a mean effective dose per unit administered activity of 22.1µSv/MBq [55]. An administered activity of 370 MBq will result in an effective dose of 8.2mSv. A maximum effective dose of 7 mSv would be expected due to the CT transmission scan depending on the scanner (details of scanner-specific CT effective doses will be given in the Study Imaging Manual). The effective dose due to the helical CT acquisition will be in accordance with ALARA (As Low As Reasonably Achievable).

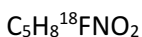
The total dose of 15.2mSv would be equivalent to 5.8 years of background radiation. This level of radiation exposure is in line with other common nuclear medicine procedures.

9. Intervention

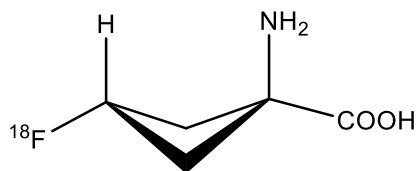
9.1. Investigational Medicinal Product

The IMP is fluciclovine (¹⁸F) injection and consists of the radiolabelled compound fluciclovine (¹⁸F) together with excipients. Fluciclovine (¹⁸F) is a radiolabelled synthetic amino acid. The radioactive isotope ¹⁸F decays with a half-life of approximately 110 minutes.

Chemical formula



Chemical structure



Chemical name

(anti)-1-amino-3-[¹⁸F]fluorocyclobutane-1-carboxylic acid.

Physiological effects

Biodistribution and radiation dosimetry studies have demonstrated physiological uptake of fluciclovine (¹⁸F) to be highest in the liver and pancreas, with rapid biological clearance [56]. There is low albeit prolonged uptake in skeletal muscle and bone marrow, with clearance dominated by the tracer half-life [56]. A 370-MBq injection of fluciclovine (¹⁸F) results in an effective dose of 8.2 mSv.

Side effects

To date, fluciclovine (¹⁸F) has been found to be well-tolerated, with all treatment emergent AEs reported during clinical studies in humans to be mild in intensity, none requiring treatment [57]. AEs reported that were considered possibly related to receipt of fluciclovine (¹⁸F) include injection site reactions (redness, pain, bruising), dysgeusia and headache [57].

Safety considerations

All participants will be carefully observed and monitored throughout the study. A panel of blood tests comprising of serum biochemistry and haematology, and an electrocardiogram (ECG), will be performed during screening and at outpatient follow-up after the PET/CT scan.

On the day of scan, there will be a minimum number of two people in attendance. This will include a doctor or allied health care professional such as a nurse or radiographer, who is solely responsible for patient monitoring, safety and well-being. They will be aware of potential risks of fluciclovine (¹⁸F) injection, and appropriately trained in how to respond to any adverse sequelae arising. The second person in attendance will be a technician/ radiologist responsible for acquiring images. In the event of any untoward medical event occurring mid-scan, staff can reach the patient immediately. As in all clinical areas throughout the participating institutions, emergency drugs and equipment are readily available and staff are trained in their use. This includes supplementary oxygen and resuscitation equipment.

Visual monitoring of the injection site and monitoring of blood pressure and heart rate will be undertaken at intervals for up to 2 hours after injection prior to discharge. After the scan, the participants will be allowed to leave the PET/CT department but remain within the host site in between the monitoring intervals. Participants will receive a telephone consultation 24 -72 hours after completion of fluciclovine (¹⁸F) PET/CT to review any AEs that have occurred in the interim following discharge. Furthermore, participants will have further opportunity to report any AEs during their outpatient follow-up appointment 14 days later and at a telephone call 1 month post scan.

Participants will be recommended not to have close contact with pregnant women or young children for 6 hours after the injection, and to drink plenty of fluids for at least 5 days after the scan to aid urinary

clearance of the tracer. These guidelines are considered as the standard of care following injection of other ^{18}F labelled tracers.

IMP preparation

The sponsor will provide fluciclovine (^{18}F) injection as a sterile solution for injection. The fluciclovine (^{18}F) injection will be manufactured to Good Manufacturing Practice (GMP) at a qualified facility.

Before approval of the batch by the Qualified Person, the suitability of each preparation will be assessed by tests including radioactivity, HPLC, and pH quality control methods, against the drug product specification according to approved standard operating procedures (SOPs) of the GMP manufacturing site.

Supply and packaging

Sites will be provided with instructions for ordering the fluciclovine (^{18}F) injection for use in the study. The site must keep records of all shipments of IMP received, dispensing and disposal/destruction performed on site. The IMP will be delivered to the site by courier from the manufacturing facility as is appropriate to each facility. Information will be provided on each shielded container giving the batch number, radioactive concentration of injection (MBq/mL) at a stated time and date, and shelf life information. To ensure timely delivery, product may be dispatched from the manufacturing site before it has been approved for use by the Qualified Person. A written agreement will be required between the investigation site and the manufacturing site in which the investigation site undertakes not to administer the drug product until it has received written confirmation from the manufacturing site that the batch has been approved by the Qualified Person. Such confirmation will be provided, for example, by fax or e-mail.

The IMP is supplied as a solution for injection, 200 MBq/ml at the reference date and time in a vial from the GMP-validated manufacturing facility. Each vial is supplied in a container providing appropriate radiation shielding. The subject dose will be drawn just before administration. The radiochemical purity of fluciclovine (^{18}F) injection is not less than 95% during the shelf life of the product.

Stability and storage

The in-use shelf life of fluciclovine (^{18}F) injection is 10 hours from the end of synthesis and must not be used beyond this limit. The expiry date and time is included on the product label. Fluciclovine (^{18}F) injection must be kept in a locked, restricted access area when not in use. Fluciclovine (^{18}F) injection should be stored at room temperature in a shielded container and in accordance with national regulations for radioactive materials. The precautions normally taken when handling radioactive materials should be observed. All non-radioactive IMP shielded containers must be returned to the sponsor/manufacturing site. Vials that are radioactive, or contained radioactive products must be destroyed at the PET centre after the study and after overall drug accountability have been completed by the sponsor or its representative. A list of IMP doses and other materials that were returned, or destroyed, must be prepared and signed by the principal investigator. An overall accountability form of the IMP will be prepared and supplied by the sponsor and completed properly. An explanation for any discrepancy must be provided.

Waste must be disposed of according to national regulations for radioactive material. The shielded container and transport case that the product is delivered in are the property of the manufacturing site. After use of the product, they must be stored securely and made available for collection on the reasonable notice of BED or the manufacturer.

IMP administration

Each individual drawn subject dose will only be administered to the subject assigned to it. No patient is to receive more than 5ml of the undiluted product.

Since the drug product vial could contain more radioactivity than is required for a 1-subject dose at the time of administration, the correct volume needs to be calculated before administration. The volume to be withdrawn and injected must be calculated from the required dose, the radioactive concentration and the reference date and time, and documented (must not exceed 5ml). After the dose has been given, subsequent doses may be withdrawn for additional subjects. When the study site receives the dose in a vial and prior to administration, the activity in the vial containing the IMP will be measured in a dose calibrator. The required dose will then be drawn into a syringe, with the activity confirmed using the same dose calibrator. Post injection, remaining activity within the syringe would be measured and the difference of pre- and post-injection syringe activities, accounting for physical decay, would be used to calculate the actual activity administered into the cannula. Appropriate dose calibrator scale factors for ^{18}F (as per manufacturer's specifications) should be applied to ensure accuracy of all activity measurements and be documented. Aseptic conditions must be observed during withdrawal of a dose from the vial, including microbial decontamination of the rubber stopper with a suitable disinfectant before removal of a dose.

Prior to PET/CT, $370 \pm 20\%$ MBq of fluciclovine (^{18}F) (not more than 5ml of product) diluted up to 10 ml with saline (sodium chloride IV infusion 0.9% w/v) will be administered. The administration will be by intravenous push (5-10 seconds) followed by a 10 ml saline flush. Fluciclovine (^{18}F) will be injected through a cannula (or indwelling catheter) with the subject lying in a supine position and in an antecubital vein or another vein that will provide access. The administration site will be evaluated pre- and post administration for any reaction (e.g. bleeding, haematoma, redness, or infection). Documentation of the IMP administered to a subject will be recorded according to standard of care and on the appropriate CRF, including date, vial number, total volume, total radioactivity, start/stop time of administration, and injection site.

Compliance with trial treatment

Participants will receive the fluciclovine (^{18}F) injection under direct supervision of study personnel. Each administration volume and total radioactivity injected will be checked. The label on the IMP container will include the batch number, expiry date/time activity in MBq, reference date/time, and volume. The batch number and volume per administration will be recorded in each subject's CRF/source document.

Concomitant medication

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the participant's records and on the appropriate CRF. Participants should be maintained on the same medications throughout the study period, if medically feasible.

10. SAFETY REPORTING

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	<p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. <p>Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.</p>
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected	A serious adverse reaction, the nature and severity of which is not

Serious Adverse Reaction (SUSAR)	consistent with the information about the medicinal product in question set out: <ul style="list-style-type: none"> • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the trial in question.
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NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

10.2. Clinical laboratory abnormalities and other abnormal assessments as AEs and SAEs

Abnormal laboratory findings or other abnormal assessments (e.g. injection site) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above. By definition, all CTCAE v4.0 Grade 3 and or 4 laboratory abnormalities should be reported as SAEs (unless specified otherwise below).

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Incidental synchronous cancers findings noted on fluciclovine (¹⁸F) PET/CT images will be reported as medical events, and qualify for reporting as AEs due to their temporal relationship to fluciclovine (¹⁸F) administration.

10.3. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.4. Procedures for Recording Adverse Events

All AEs observed by the investigator or reported by the patient up to 1 month after fluciclovine (¹⁸F) PET/CT are reported on the case report forms. A member of the research team will contact the participant by telephone 24 -72 hours and 1 month after completion of fluciclovine (¹⁸F) PET/CT to record any AEs that may have occurred after leaving the hospital. Patients will also attend a clinic visit 14 days post scan. All AEs reported by the patient will be clearly documented on the patient CRFs. The following information will be recorded: description, date of onset and end date, severity, investigator assessment of relatedness to fluciclovine (¹⁸F) injection, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

AE severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010) will be used to assess and grade event severity, including laboratory abnormalities judged to be clinically significant. The severity grading is provided below (Table 1).

Table 1. CTCAE (V4.03) AE Severity Grading

Severity (Toxicity Grade)	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If the experience is not covered in the modified criteria, the guidelines shown in Table 2 below will be used to grade severity. It should be pointed out that the term “severe” is a measure of intensity and that a severe event is not necessarily serious.

Table 2. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.
Death (5)	Death related to AE

AEs considered related to fluciclovine (¹⁸F) injection as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the investigator's clinical judgment whether or not an AE/ AR is of sufficient severity to require the patient's removal from PET/CT scanning. A participant may also voluntarily withdraw from study procedures if they tolerate it poorly. Further details of withdrawal are presented in Section 7.7.

In the event of symptoms arising, participants will be given appropriate care and medical supervision until symptoms resolve, or the condition becomes stable. Every effort will be made to gather outcome data on patients through study follow-up, or general practitioner/ hospital staff unless the participant has specifically withdrawn consent to such efforts.

10.5. Reporting Procedures for Serious Adverse Events

All SAEs following fluciclovine (¹⁸F) PET/CT must be reported on the SAE reporting form within 24 hours of the Site Study Team becoming aware of the event. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed to:

Blue Earth Diagnostics SAE E mail: Drugsafety@pharsafer.com

Tel: +44 (0) 1483 212155

Fax: +44 (0) 1483 212178

Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to the same address.

10.6. SUSAR Reporting

Blue Earth Diagnostics will be responsible for reporting of all SUSARs to the relevant Competent Authority (MHRA in the UK) and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current study.

10.7. Safety Monitoring Committee

The Sponsor will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action

- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

10.8. Development Safety Update Reports (DSURs)

In addition to the expedited reporting above Blue Earth Diagnostics will submit DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), to the Chief Investigator and to the Co-Investigator at each site. The CI is responsible for submitting these to the Ethics Committee and the Host NHS Trust.

11. STATISTICS AND ANALYSIS

Prior to the conduct of the planned interim analysis, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed for both the interim analysis and the final analysis of all study data.

11.1. Sample size

For the primary objective of treatment change evaluation, a minimum of 171 patients with complete primary endpoint data will be required to allow for a width of +/-6% in a two-sided 95% C.I. This is based on the conservative assumption that 20% of patients will have a treatment change, as fluciclovine (¹⁸F) PET/CT has been shown to upstage 25.7% of patients with recurrent prostate cancer [49], and also based on the management change studies reported on choline PET/CT (section 3). The aim is to recruit 180 patients for this trial, based on an anticipated primary endpoint drop-out rate of 5%.

11.2. Analysis of Outcome Measures/Endpoints

Evaluable patients are those that have had all baseline study measures recorded, including having had a fluciclovine (¹⁸F) PET/CT scan.

Evaluation of fluciclovine (¹⁸F) PET/CT

Evaluation of the fluciclovine (¹⁸F) PET/CT images will be primarily reviewed by site-based investigator(s) (as per standard of care). Image interpretation will be based on guidelines derived from an international fluciclovine (¹⁸F) reader consensus meeting held in June 2014. All readers will undergo training in interpretation of fluciclovine (¹⁸F) scans, and will have a training set available for reference. The investigators will have access to all the conventional imaging and medical record information.

The summary of findings will be documented on the appropriate CRF, in addition to a conventional imaging report issued as per standard of care in the respective institution.

Primary endpoint

The primary endpoint of clinical impact of fluciclovine (¹⁸F) in affecting treatment decisions will be assessed by record of the revised treatment plan post fluciclovine (¹⁸F) PET/CT scan in comparison to the pre-scan intended treatment plan.

Secondary endpoints

Improvement in outcome of radical salvage treatment based on fluciclovine (¹⁸F) PET/CT being included in the assessment.

This will be assessed as the proportion of these patients who have a treatment response or treatment failure, using the following definitions:

1. Treatment response
 - a. ≥50% decline in PSA [5] ±
 - b. Radiological response
2. Treatment failure
 - a. Increase or <50% decline in PSA ±
 - b. Radiological progression

PSA threshold

The positive detection rate will be calculated for the overall cohort and across a range of PSA values, to determine the optimum PSA threshold for lesion detection.

Safety assessment

Safety will be assessed from data on the occurrence of adverse events (AEs) and changes in clinical laboratory tests, vital signs, injection-site status, and physical examination findings from the time of administration of fluciclovine (¹⁸F) injection throughout the study period. This has been described in detail in Section 9.

11.3. Interim Analysis

A single interim analysis of the primary endpoint was performed in the first 85 evaluable patients. The number of treatment changes was greater than 45 (52.9%, with a 97.5% two-sided C.I. of 40.3%-62.3%, so the lower limit is over 40%), the trial recruitment was terminated early due to overwhelming effectiveness. If the number of treatment changes would have been 8 or fewer (9.4%, with a 97.5% two-sided C.I. of 3.6%-18.9%, so the upper limit in this population would have been below the 20% of the null hypothesis), the trial would have been terminated early due to futility.

12. DATA MANAGEMENT

12.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.2. Data Recording and Record Keeping

Database considerations

Data collection will be done using a web-based eCRF and Data management will be managed by a contracted Clinical Research Organisation. The Chief Investigator will act as Data Custodian for the trial.

Case report forms

Data collected on each subject will be recorded by the research team as accurately and completely as possible. The Investigator will be responsible for the timeliness, completeness, legibility and accuracy of the CRFs. Each patient enrolled into the study must have the correct CRFs completed and signed by the Principal Investigator (or designee). This also applies to those patients who have been withdrawn early. Please ensure that all data submitted on CRFs are verifiable in the source documentation or the discrepancies explained.

Records retention and archiving

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. These essential documents (as detailed in Section 8 of the ICH GCP Guidelines) must be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the host institution policy. Data entered onto the eCRFs will be returned to the sites in CD format and must be checked for accuracy and then held with the study files. Data will be retained on site for a minimum of 5 years. Retention and storage of scanning records for clinical scans must also follow these guidelines.

Imaging data for central review

Copies of the fluciclovine (¹⁸F) PET/CT scan and PET/CT report will be made for central review and analysis. Retention and archiving of this data will be performed according to the guidelines stipulated in this section.

13. QUALITY ASSURANCE PROCEDURES

13.1. Site Monitoring

Regular monitoring will be performed according to a Sponsor approved monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Monitoring visit reports will be sent to the site.

13.2. Central Monitoring

The study site will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. All changes to data that could influence the outcome will be queried with and approved by the study site in a timely manner. For all other data, where there is no doubt about the source of any errors, clear changes to data will be made internally without referring back to the study site staff. The trial office will be in regular contact with site personnel to check on progress and deal with any queries that they may have including those arising from data queries.

13.3. Audit and Regulatory Inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. It may also be subject to a regulatory inspection. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the trial office without delay.

13.4. Contracts / Agreements

This trial is subject to the Sponsors policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

14. ETHICAL AND REGULATORY CONSIDERATIONS

The Sponsor and Investigators will ensure that this protocol will be conducted in compliance with the UK Clinical Trials Regulations¹, the ICH guidelines of Good Clinical Practice (GCP)² and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline with Integrated Addendum E6(R2): Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 4, adopted by CPMP 9 Nov 2016.

14.1. Ethical Conduct of the trial and ethics approval

The protocol, patient information sheet, consent form and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC).

14.2. Regulatory Authority approval

This study will be conducted under a UK Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Authorisation (CTA). Approval to conduct the study will be obtained from the Responsible Authority prior to initiating the study.

14.3. Subject identification

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection act which requires data to be anonymised as soon as practical..

14.4. Early termination or temporary halt on urgent safety grounds

In cases of early termination or a temporary halt of the study due to toxicity or other safety grounds, the Chief Investigator will notify the Sponsor and Main REC within 15 calendar days of the decision giving a written explanation for the decision. In this instance, the study will not be restarted until REC & MHRA approval has been obtained for a substantial amendment.

14.5. Expenses and benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate.

14.6. Protocol Amendments

Amendments are changes made to the research following initial approval. A 'substantial amendment' is an amendment to the terms of the MHRA CTA authorisation, the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study.

Amendments will be generated and managed according to the trial office standard operating procedures to ensure compliance with applicable regulation and policies. Substantial Amendments will be sent to Blue Earth Diagnostics Ltd for review prior to submission. Written confirmation of all applicable REC, regulatory, funder and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients (see below). It is the Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented if appropriate.

14.7. Urgent safety measures

The sponsor or Investigator may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the trial office IMMEDIATELY if the study site initiates an urgent safety measure:**

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be requested by the trial office. The trial office will ensure that the urgent safety measure is reported in accordance with the current regulatory, ethical and sponsor requirements for expedited reporting and close out.

14.8. Temporary halt

The sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods for administrative reasons **or** to declare a temporary halt where necessary. For this protocol, a temporary halt is defined a formal decision to:

- interrupt the treatment of subjects already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The trial office will report the temporary halt via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

14.9. Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations require the Sponsor to notify any "serious breaches" to the MHRA within 7 days of the sponsor becoming aware of the breach. A serious breach is defined as "A breach of GCP or the trial protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

Investigators must notify the trials office at once if any serious breach of GCP is suspected.

14.10. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.11. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

14.12. Participant Confidentiality

The personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, only their participant ID number will be recorded on the CRFs. The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

15. FINANCE AND INSURANCE

15.1. Funding

This study is jointly funded by Blue Earth Diagnostics Ltd (Unit 14, Magdalen Centre, Robert Robinson Avenue, Oxford Science Park, Oxford OX4 4GA) and Innovate UK (an executive non-departmental public body, sponsored by the Department for Business, Innovation & Skills of the UK Government).

15.2. Insurance

Blue Earth Diagnostics Ltd has insurance cover for this study and will compensate patients who suffer harm from participation in the study in accordance with the ABPI guidelines. A Certificate of Insurance can be provided upon request.

16. PUBLICATION POLICY

The results of the study are intended for submitted to peer-reviewed journals such as the Journal of Nuclear Medicine, European Journal of Nuclear Medicine and Molecular Imaging and Journal of Urology with findings presented at such annual society meetings as the SNMMI, EANM, RSNA, or ASTRO. All publications will include a list of all participating PIs. The support obtained from the main research funding bodies and Sponsor will be acknowledged in any publication. No subgroup analysis can be published before the publication of the entire study. The Investigator will ensure that patients taking part in the study who are interested to learn the study findings are informed appropriately. In addition, the Sponsor will be free to use the study results, in compliance with applicable regulations and the terms of the trial agreement, to assemble supplements, amendments or other documentation required by regulatory authorities, and for other marketing or development purposes.

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18. APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Variables	Visit 1 (Screening, up to 14 days before Visit 2)	Visit 2 (Day of fluciclovine (¹⁸ F) injection and PET/CT)	Post-administration					Phone Visit 3 (24 -72 (± 4) hours after dose)	Visit 4 (Manag ement plan decision)	Phone Visit 5 (1 month ±7 days after dose)	Visit 6 (First day of management plan, <i>may be same date as Visit 4</i>)	Standard of care clinical follow-up (data entry at 6 months after starting management plan)	<i>Patients who have radical salvage therapy</i>		
			Dose	Immediately post scan	60 (±5) min	90 (±5) min	120 (±5) min						Pre-treatment PSA level (<31 days pre-therapy)	7-8 months after completing therapy	
Inclusion / exclusion criteria	X	X													
Informed consent	X														
Height, weight		X													
Medical history	X										X				
Measure PSA level	X											X		X	X
Record prior PSA levels	X										X			X	X
PCa treatment history	X														
Imaging history (3 months before to 6 months after PET/CT)	X										X			X	X
Intended management plan	X														
Concomitant medication and allergies	X	X													
Blood test	X								X						
ECG	X								X						
Post-screening pre- administration events		X													
Vital signs (heart rate and blood pressure)	X	X		X	X	X	X								
Urinalysis	X								X						
Injection site monitoring			X	X	X	X	X		X						
Imaging		X													
AE monitoring			X	X	X	X	X	X	X	X					
Revised management plan									X						
Agreed management plan									X						
Date of starting treatment											X				
Deviation from agreed management plan (if any)											X				
Treatment response assessment											X			X	X

19. APPENDIX B: Oxford site sub-study**Evaluation and optimisation of Bayesian penalised likelihood PET reconstruction for Fluciclovine (¹⁸F) whole body imaging***FALCON trial Oxford site sub-study*

Dr. Eugene Teoh, Daniel McGowan, Prof. Fergus Gleeson and Oxford FALCON trial investigators.

Background

We have recently investigated and reported on the optimisation of Bayesian penalised likelihood (BPL) reconstruction for ¹⁸F-FDG whole body oncological PET [1], and its effect on evaluating various clinical entities on ¹⁸F-FDG PET/CT [2-4]. BPL includes point spread function modeling while controlling noise through the use of a penalty term (β) [1]. One pertinent observation from our work has been of how BPL improves signal-to-noise in areas of increased tracer uptake on clinical scans, particularly in subcentimetre abnormalities [2]. This is corroborated by phantom data [1]. Our institution currently uses BPL reconstructed images ($\beta=400$) [1] for the clinical interpretation of all ¹⁸F-FDG whole body oncological PET/CT studies.

We propose to investigate the use of BPL reconstruction for Fluciclovine (¹⁸F) whole body PET, using scan data acquired in Oxford for the FALCON trial. This will be wholly performed using pre-existing scan data, so participants will not be required to make extra visits or subjected to additional study procedures.

Rationale

Currently OSEM reconstructions are standard of care worldwide, and BPL reconstruction is used with more modern PET/CT scanner reconstruction, it is important to determine if BPL improves detection. This study will address this issue.

Aims

Primary Objective	Endpoints/ Outcome measures
To evaluate the difference in image quality between BPL and standard PET reconstructions of Fluciclovine (¹⁸ F) whole body PET images.	Signal-to-noise (SNR) of background structures and areas of pathological uptake on both reconstructions.
Secondary Objectives	Endpoints
To determine the optimum penalisation factor (β) for Fluciclovine (¹⁸ F) whole body PET BPL reconstruction.	SNR of background structures and areas of pathological uptake on BPL reconstructions using different β values.
To determine the difference in positive detection rates between BPL and OSEM reconstructions.	Record of fluciclovine (¹⁸ F) positive abnormalities on both reconstructions.

Tertiary/Exploratory Objectives	Endpoints
Future study of other PET reconstruction methods (e.g. new / in development) for Fluciclovine (¹⁸ F) PET imaging	

Methodology

Optimum β

The scan data (sinograms) acquired for FALCON will be reconstructed with BPL using a range of β values. Parameters measuring the degree of tracer uptake (standardised uptake value – SUV) for background structures (blood pool, marrow and liver) and areas of pathological uptake will be measured. The SNR will be calculated using these parameters and compared between the reconstructions.

This range of reconstructions will also be visually scored by readers for image quality using previously described methodology and criteria to determine the optimum β for Fluciclovine [1].

Image quality evaluation

SUV parameters described in the former section (“Optimum β ”) will be measured in the OSEM reconstruction (current trial standard), and compared with those measured on BPL reconstruction.

Positive detection

The OSEM reconstructed images will be interpreted on day of scan, and fluciclovine (¹⁸F) positive abnormalities recorded. The BPL reconstructed images will then be reviewed by the same reader(s). Any new / change in fluciclovine (¹⁸F) positive abnormalities will be recorded and compared. This will be performed prospectively after REC and R&D approval have been obtained. Retrospective image review will be performed for all scans acquired before this time.

Receiver operating characteristic analysis will be considered to compare the two reconstructions depending on the number of cases where diagnostic performance (as laid out in the FALCON trial protocol) can be assessed.

The prospective nature of this component is partly necessitated by the use of BPL reconstruction in our routine clinical practice. As such, the BPL images will be reconstructed using a β of 400, as is used for whole body ¹⁸F-FDG and ¹⁸F-ethylcholine PET/CT scans in our institution. All readers will have the same baseline degree of competency and experience in interpreting Fluciclovine (¹⁸F) whole body PET/CT.

Where there is a change in findings, a consensus on whether this is clinically significant in such a way that would influence the patient's management, will be reached between the reader(s), the principal investigator (or a nominated investigator), and the referring investigator responsible for the patient's clinical management.

In the rare event that this is deemed to be significant, it has been agreed with the trial sponsor and Chief Investigator that:

1. the **Revised** Management Plan recorded at Visit 4 would be based on findings made on the trial standard reconstruction ie OSEM.
2. the **Agreed** Management Plan recorded at Visit 4 would be based on findings made on the BPL reconstruction.

As BPL is used as standard of care in our institution, the change in findings will be reflected in the clinical report if deemed to be clinically significant.

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