Clinical trial results:
Diagnostic accuracy of MRI, diffusion-weighted MRI, FDG-PET/CT and Fluoro-ethyl-choline PET/CT in the detection of lymph node metastases in surgically staged endometrial and cervical carcinoma

Summary

EudraCT number	2011-001290-78
Trial protocol	GB
Global end of trial date	06 December 2018

Results information

Result version number	v1 (current)
This version publication date	02 January 2021
First version publication date	02 January 2021

Trial information

Trial identification

Sponsor protocol code	007697

Additional study identifiers

ISRCTN number	ISRCTN84527805
ClinicalTrials.gov id (NCT number)	NCT01836484
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Prof. Andrea Rockall, Imperial College London, 0044 020 7589 5111, a.rockall@imperial.ac.uk
Scientific contact	Prof. Andrea Rockall, Imperial College London, 0044 020 7589 5111, a.rockall@imperial.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 December 2018
Global end of trial reached?	Yes
Global end of trial date	06 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In patients with cancer of the womb (endometrial and cervical cancer), the detection of tumour in adjacent lymph glands (nodes) is very important for optimal treatment planning. Currently the standard method used to identify cancerous spread is to surgically remove and examine the nodes under the micrscope in order to identify tumour spread in the nodes. A technique that does not require surgical intervention would be highly desirable. Standard imaging on MRI or CT, in which size criteria are used to identify whether a node is malignant, is inaccurate.

This study will evaluate three new imaging techniques that may be used to identify malignant nodes preoperatively: (1) Diffusion Weighted MRI, (2) FDG-PET/CT and (3) FEC-PET/CT. The primary objective is to compare the diagnostic performance of each test (detection and false-positive rates) with that of the standard method (size criteria) with histology as the reference standard.

Protection of trial subjects:

Eligibility criteria for this study were selected to enhance the safety of patients in this trial. Patients were monitored for adverse events during their participation in the trial. Any serious adverse events were recorded until 28 days after the last administration of the PET tracer. A Data Monitoring Committee was appointed to monitor safety during the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 162
Worldwide total number of subjects	162
EEA total number of subjects	162

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	86
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Women with histologically confirmed endometrial or cervical carcinoma who complied with the study entry criteria were recruited at six centres in the UK between 06Jun2012 and 27Jul2017.

Pre-assignment

Screening details:

162 patients were registered for the trial of which 150 were found to be eligible.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	DW-MRI - primary reference standard

Arm description:

The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy.

Arm type	Imaging technique (no IMP)

No investigational medicinal product assigned in this arm

Arm title	FDG-PET/CT - primary reference standard

Arm description:

The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy

Arm type	Experimental
Investigational medicinal product name	Fluorodeoxyglucose (FDG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered prior to PET/CT scan with activity of 18F-FDG between 200MBq and 400MBq, +/- 10% of the local diagnostic reference level based on scanner performance and patient body weight.

Arm title	FEC-PET/CT - primary reference standard

Arm description:

The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy

Arm type	Experimental
Investigational medicinal product name	Fluoro-ethyl-choline (FEC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Administered prior to PET/CT scan with activity of 18F-FEC between 200MBq and 300MBq, +/- 10% of the local diagnostic reference level based on scanner performance and patient body weight.

Number of subjects in period 1	DW-MRI - primary reference standard	FDG-PET/CT - primary reference standard	FEC-PET/CT - primary reference standard
Started	118	118	52
Completed	118	118	52

Baseline characteristics

Reporting groups[1]	
Reporting group title	DW-MRI - primary reference standard
Reporting group description:	
The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy.	
Reporting group title	FDG-PET/CT - primary reference standard
Reporting group description:	
The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy	
Reporting group title	FEC-PET/CT - primary reference standard
Reporting group description:	
The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The primary analysis of this data is based on the subset of patients who are assessable by the primary reference standard. This is all patients who underwent both DW-MRI and FDG-PET/CT imaging and had definitive histology obtained by lymphadenectomy. Data is presented for patients in the subset.

Reporting group values	DW-MRI - primary reference standard	FDG-PET/CT - primary reference standard	FEC-PET/CT - primary reference standard
Number of subjects	118	118	52
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	64	64	63
full range (min-max)	24 to 83	24 to 83	24 to 80
Gender categorical Units: Subjects			
Female	118	118	52
Male	0	0	0

Reporting group values	Total		
Number of subjects	118		
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median full range (min-max)	- 		
Gender categorical Units: Subjects			
Female	118		
Male	0		

End points

End points reporting groups

Reporting group title	DW-MRI - primary reference standard
Reporting group description:	
The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy.	
Reporting group title	FDG-PET/CT - primary reference standard
Reporting group description:	
The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy	
Reporting group title	FEC-PET/CT - primary reference standard
Reporting group description:	
The primary reference standard includes all eligible patients who underwent both DW-MRI and FDG-PET/CT and had nodal histology obtained by lymphadenectomy	

Primary: Comparing sensitivity of imaging techniques with nodal size

End point title	Comparing sensitivity of imaging techniques with nodal size[1]
End point description:	
Sensitivity and false-positive rates for each imaging technique were calculated using strictly confirmed nodal histology as the reference standard. By specifying a cut-off value for diagnosis based on nodal size that matched the false-positive rate of each imaging technique, we could compare the sensitivity of each imaging technique with nodal size while assuming them to have equal false-positive rates. For each imaging technique assessed, the nodal size cut-off which provided a false-positive rate closest to the imaging technique was >10mm. Paired comparisons of sensitivity were performed only in patients with confirmed positive histology.	
End point type	Primary
End point timeframe:	
Each patient underwent imaging before having lymphadenectomy.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: McNemar p-values from comparing sensitivity of each imaging technique with nodal size (10mm cut-off) are as follows:
DW-MRI - p=0.22
FDG-PET/CT - p=0.017
FEC-PET/CT - p=0.13

End point values	DW-MRI - primary reference standard	FDG-PET/CT - primary reference standard	FEC-PET/CT - primary reference standard	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[2]	30[3]	12[4]	
Units: patients				
+ve imaging/+ve nodal size	11	7	4	
+ve imaging/-ve nodal size	5	12	4	
-ve imaging/+ve nodal size	1	0	0	
-ve imaging/-ve nodal size	13	11	4	

Notes:

[2] - Only patients with confirmed positive histology included in this analysis.

[3] - Only patients with confirmed positive histology included in this analysis.

[4] - Only patients with confirmed positive histology included in this analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day of consent until 28 days after the last administration of the PET tracer.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	All patients who received any trial scan

Reporting group description: -

Serious adverse events	All patients who received any trial scan		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 147 (6.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Wound infection			

subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	3 / 147 (2.04%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pelvic infection			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All patients who received any trial scan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 147 (22.45%)		
Vascular disorders			
Lymphoedema	Additional description: Reported as Mild lymphodema - right groin		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
General disorders and administration site conditions			
Oedema	Additional description: Reported as edema limbs and Localised edema Groin (right).		
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	19 / 147 (12.93%)		
occurrences (all)	21		
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Psychiatric disorders			
Mood altered			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Investigations			
Blood glucose increased	Additional description: Reported as High glucose and FDG scan not undertaken as blood sugar too high.		
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		
Urine output decreased	Additional description: Reported as Reduced urinary output.		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Residual urine volume increased	Additional description: Reported as Self catheterisation post op high residuals.		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Atrial fibrillation	Additional description: Reported as Fast AF		

subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Nervous system disorders			
Facial paralysis	Additional description: Reported as bells palsy		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Depressed level of consciousness			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Presyncope	Additional description: Reported as Vasovagal reaction.		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	6 / 147 (4.08%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 147 (3.40%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Rash	Additional description: Reported as Rash - trunk and limbs.		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Oliguria			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Reported as knee pain.		
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Infections and infestations			
Pelvic infection			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	6 / 147 (4.08%)		
occurrences (all)	6		
Wound infection			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed occurrences (all)	1 / 147 (0.68%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2012	Change in Sponsor name to Barts Health NHS Trust
30 August 2012	Removal of quality of life objective. Updates to image analysis scale. Inclusion of tissue banking of lymph nodes.
17 June 2013	Inclusion criteria clarification. Update to Informed Consent Procedures. Update to Enrolment Procedures. Inclusion of the dynamic FEC-PET/CT protocol. Removal of FEC safety assessment. Tissue banking made optional for sites to take part.
01 May 2014	PET tracer doses: incorporation of +/- 10% diagnostic reference level (DRL). NCRI PET – sending scans for central review instructions update (appendix). Tissue banking – addition of primary tissue as well as lymph nodes. SAE reporting clarification. IMP clarifications.
31 October 2017	Allowing post-surgical imaging review without obtaining further consent in patients with positive imaging and negative histology and patients for whom histology was not performed but all mandatory imaging was done.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported