

TRIAL SYNOPSIS

Title:	A Phase III randomised study of Folic Acid supplementation in the management of Menopausal symptoms in cancer survivors and healthy postmenopausal women (FOAM Trial)
Trial Design:	National, phase III, multicentre, double-blind, placebo controlled, randomised trial
Primary Objectives:	To assess the efficacy of folic acid supplementation in terms of relief of the frequency and severity of vasomotor symptoms as compared to placebo
Secondary Objectives:	<ol style="list-style-type: none"> 1. To study the efficacy of folic acid supplementation in terms of other menopausal symptoms as compared to placebo 2. To study the efficacy of folic acid supplementation on quality of life (QoL) domains as compared to placebo 3. To explore the effect of folic acid in various prognostic subgroups: <ul style="list-style-type: none"> • Healthy women v cancer survivors (breast or endometrial cancer survivors) • Body Mass Index (BMI): ≤ 30 v >30
Exploratory Translational Objectives:	<ol style="list-style-type: none"> 1. To assess the effect of folic acid supplementation on the blood level of serotonin and nor-adrenaline 2. To measure the correlation between clinical improvement, serum folic acid levels and blood levels of serotonin and nor-adrenaline 3. To assess the effects of folic acid supplementation on urine levels of 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy 4-hydroxy phenyl glycol (MHPG) metabolites
Primary Outcome Measures:	Change in Hot Flush Score at 12 weeks from randomisation. A validated composite score B calculation based on frequency and severity as reported by patients in weekly Sloan Diaries
Secondary Outcome Measures:	<ol style="list-style-type: none"> 1. Change from randomisation in Hot Flush Score at weeks 4, 8 and 12 as calculated using the composite score B 2. Change from randomisation in frequency of hot flushes (mild, moderate and severe) at weeks 4, 8 and 12 as calculated using frequency score B 3. The percentage of responders at weeks 4, 8 and 12; defined as a reduction in Hot Flush Score of $\geq 50\%$ from randomisation as calculated using composite score B 4. Change from randomisation in longitudinal QoL data as measured by the Utian Quality of Life (UQoL) Scale at weeks

	<p>4, 8 and 12</p> <p>5. Change from randomisation in other menopausal symptoms using the Greene Climacteric Scale at weeks 4, 8 and 12</p> <p>6. Investigate effects in specific prognostic subgroups of:</p> <ul style="list-style-type: none"> • Healthy women v cancer survivors (breast or endometrial cancer survivors) • BMI ≤ 30 v >30
Exploratory Translational Outcome Measures:	<ol style="list-style-type: none"> 1. Change from randomisation in whole blood levels of serotonin, plasma nor-adrenaline and serum folic acid at week 12 2. To measure the correlation between clinical improvement (if any) and whole blood levels of serotonin, nor-adrenaline, and serum folic acid at week 12 3. Change from randomisation in urine levels of 5-HIAA and MHPG metabolites at week 12
Patient Population:	Postmenopausal women either healthy or breast and endometrial cancer survivors with early onset of menopausal symptoms
Sample Size:	236
Trial Duration:	24 months
Trial Treatment	<p>Arm 1: Folic acid (5mg) tablet, once daily by mouth for 12 weeks</p> <p>Arm 2: Folic acid-matched-placebo, once daily by mouth for 12 weeks</p>
Inclusion Criteria:	<ol style="list-style-type: none"> 1. Postmenopausal women* either healthy or breast / endometrial cancer survivors with early onset of menopausal symptoms. Postmenopausal is defined as: <ol style="list-style-type: none"> i. 12 months of spontaneous or induced amenorrhoea; OR ii. 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy. 2. Experiencing ≥ 50 hot flushes per week, as quantified from daily patient Sloan Diary recordings for 7 days after consent and prior to randomisation 3. Being ≥ 40 and ≤ 70 years of age 4. Willing to participate in the trial and given informed consent
Exclusion Criteria:	<ol style="list-style-type: none"> 1. Baseline red cell serum folic acid level above the normal

laboratory range (3.1 to 20.0µg/L)

2. Smoking >5 cigarettes per day
3. Intestinal malabsorption e.g. coeliac, tropical sprue or Crohn's disease
4. Known chronic renal impairment or failure
5. Known established chronic conditions mimicking climacteric presentation e.g. poorly controlled hypertension, hyperglycaemia or thyroid instability
6. Pernicious anaemia due to vitamin B12 deficiency
7. Alcohol consumption more than 14 units per week
8. Women with pheochromocytoma or other medullary tumours or carcinoid syndrome
9. Known allergic reactions and/or hypersensitivity to folic acid
10. Women who are, in the opinion of the treating physician, unlikely to be able to give informed consent or successfully complete the trial intervention and procedure
11. Participation in another clinical trial within the last 4 weeks prior to enrolment
12. Administration of the following drugs during study and for the specified number of weeks prior to study entry:
 - a) 24 weeks prior to randomisation:
 - Bevacizumab (Avastin)
 - Trastuzumab (Herceptin)
 - b) 8 weeks prior to randomisation:
 - HRT (women on oestrogen implants are excluded from trial entry)
 - Herbal remedies
 - Heparin
 - c) 6 weeks prior to randomisation:
 - Tamoxifen
 - Fluoxetine
 - Venlafaxine
 - d) 4 weeks prior to randomisation:
 - Phenytoin
 - Phenobarbitol
 - Primidone
 - e) 2 weeks prior to randomisation:
 - Warfarin
 - Sertraline
 - Mianserin

- Mirtazapine

f) 1 week prior to randomisation:

- Raloxifen
- Chronic use of NSAIDs (including high dose Aspirin* and Cox-2 inhibitors)
- Methotrexate
- Fluorouracil
- Trimethoprim
- Co-trimoxazole
- Chloramphenicol
- Sulfasalazine
- Mesalazine
- Paroxetine
- Duloxetine
- Clonidine

*low dose Aspirin (75mg daily) is not prohibited

g) Stop prior to study entry:

- Cholestyramine
- Antacids (containing aluminium or magnesium)
- Vitamin containing zinc or folic acid

Trial Office Contact Details:

FOAM Trial Office, CRCTU, Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT

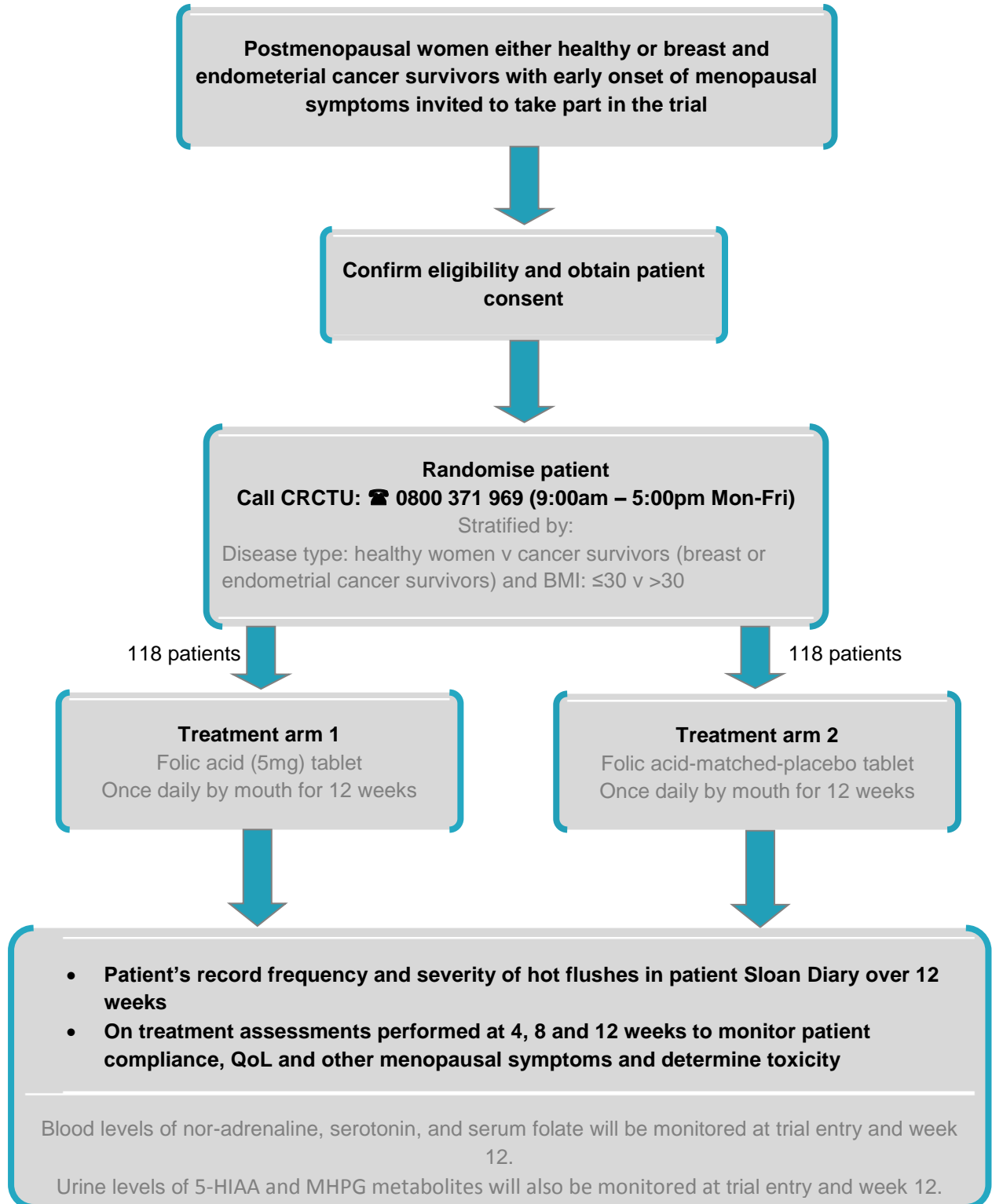
☎ 0121 414 3792

📠 0121 414 8392 or 0121 414 3700

✉ Foam@trials.bham.ac.uk

TRIAL SCHEMA

FOAM is a multicentre, phase III, double-blinded, placebo-controlled, randomised trial to directly compare 5mg folic acid with placebo in reducing the frequency and severity of hot flushes. Postmenopausal women both healthy and cancer (breast and endometrial) survivors will be randomised on 1:1 basis between folic acid (5mg) tablets or placebo tablets daily for 12 weeks.



SCHEDULE OF ASSESSMENT

	Screening		Treatment Visits			
	Pre-screening Visit	Screening Visit	Trial Entry* (Baseline)	Week 4*	Week 8*	Week 12*
Obtain Informed Consent	X					
Distribution of Screening Sloan Diary ¹	X					
Review of Medical History		X				
Review of Concomitant Medication		X	X	X	X	X
Calculation of BMI		X				
Assessment of Inclusion and Exclusion Criteria		X				
Collection of Patient Sloan Diary		X		X	X	X
Blood sample collection for measurement of serum folate		X				X
Confirmation of Eligibility			X			
Randomisation			X			
Distribution of On-treatment Sloan Diary ²			X	X	X	
Dispense and commence trial medication			X			
Blood sample collection for measurement of plasma nor-adrenaline and whole blood serotonin			X			X
Urine sample collection for measurement of 5-HIAA and MHPG			X			X
Completion of Greene Climacteric Scale ³			X	X	X	X
Completion of Utian Quality of Life Scale ³			X	X	X	X
Review of Adverse Events (AEs) and Serious Adverse Events (SAEs)				X	X	X
Review of treatment compliance				X	X	X

Keys:

* Visit only applicable to patients that meet the eligibility criteria

¹ Screening Sloan Diary to be completed by the patients at home on a daily basis for 7 days

² On-treatment Sloan Diary to be completed by the patients at home on a daily basis for duration of the trial

³ Scales to be completed by patient in clinic at the defined visit