MRC Clinical Trials Unit

FOCUS4

Efficacy and Mechanism Evaluation programme

NHS National Institute for Health Research

CANCER RESEARCH UK

UNIVERSITY OF OXFORD

FOCUS4 – Molecular selection of therapy in colorectal cancer: a molecularly-stratified randomised controlled trials programme

Master Protocol

Registration of patients and generic trial governance issues related to the FOCUS4 Trials Programme

Version:	**1.0**
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Date:	04/2/13

GENERAL INFORMATION

This document was constructed using the MRC CTU Protocol Template Version 4.0. The Master Protocol describes the overall plan and structure for FOCUS4, and, together with the separate trial protocols for each of the randomised trials, encompasses the protocol for the FOCUS4 Trials Programme. FOCUS4 is coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU), and these documents provide information about procedures for entering patients into FOCUS4.

The FOCUS4 Trials Programme protocols should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting the protocols, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the FOCUS4 Trial team at the MRC CTU, London, UK, to confirm they have the most up-to-date version.

COMPLIANCE

The FOCUS4 Trials Programme will be conducted in compliance with the approved protocol, the 1996 version of the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), EU Directives 2001/20/EC Article 2 and 2005/28/EC and subsequent amendments, their implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

SPONSOR

The MRC is the sponsor of FOCUS4 and MRC CTU has been delegated responsibility for the overall management of the FOCUS4 Trials Programme. Queries relating to MRC sponsorship should be addressed to the Director, Professor Max Parmar, Regional Centre London, Aviation House, 125 Kingsway, London, WC2B 6NH, UK or via the FOCUS4 Trial Team.

FUNDING

The FOCUS4 Trials Programme is jointly funded by the NIHR/MRC Efficacy and Mechanism Evaluation (EME) programme and Cancer Research UK (CRUK). Additional funding and support has been provided from collaborating pharmaceutical companies, see individual trial protocols for details.

AUTHORISATIONS AND APPROVALS

This FOCUS4 Trials Programme and all current trials within it were approved by **[*Insert Info*]** and is part of the National Cancer Research Network (NCRN) portfolio. Subsequent trials will all be submitted for approvals.

TRIAL REGISTRATION

The FOCUS4 Trials Programme has been registered with the ISRCTN Clinical Trials Register, where it is identified as **[*Insert Info*].**

TRIAL ADMINISTRATION

Please direct all queries to the Trial Manager at MRC CTU in the first instance; clinical queries will be passed to the Clinical Trial Physician or the Chief Investigators via the Trial Manager.

For full details of all trial committees, please see section 14 and Appendix VI.

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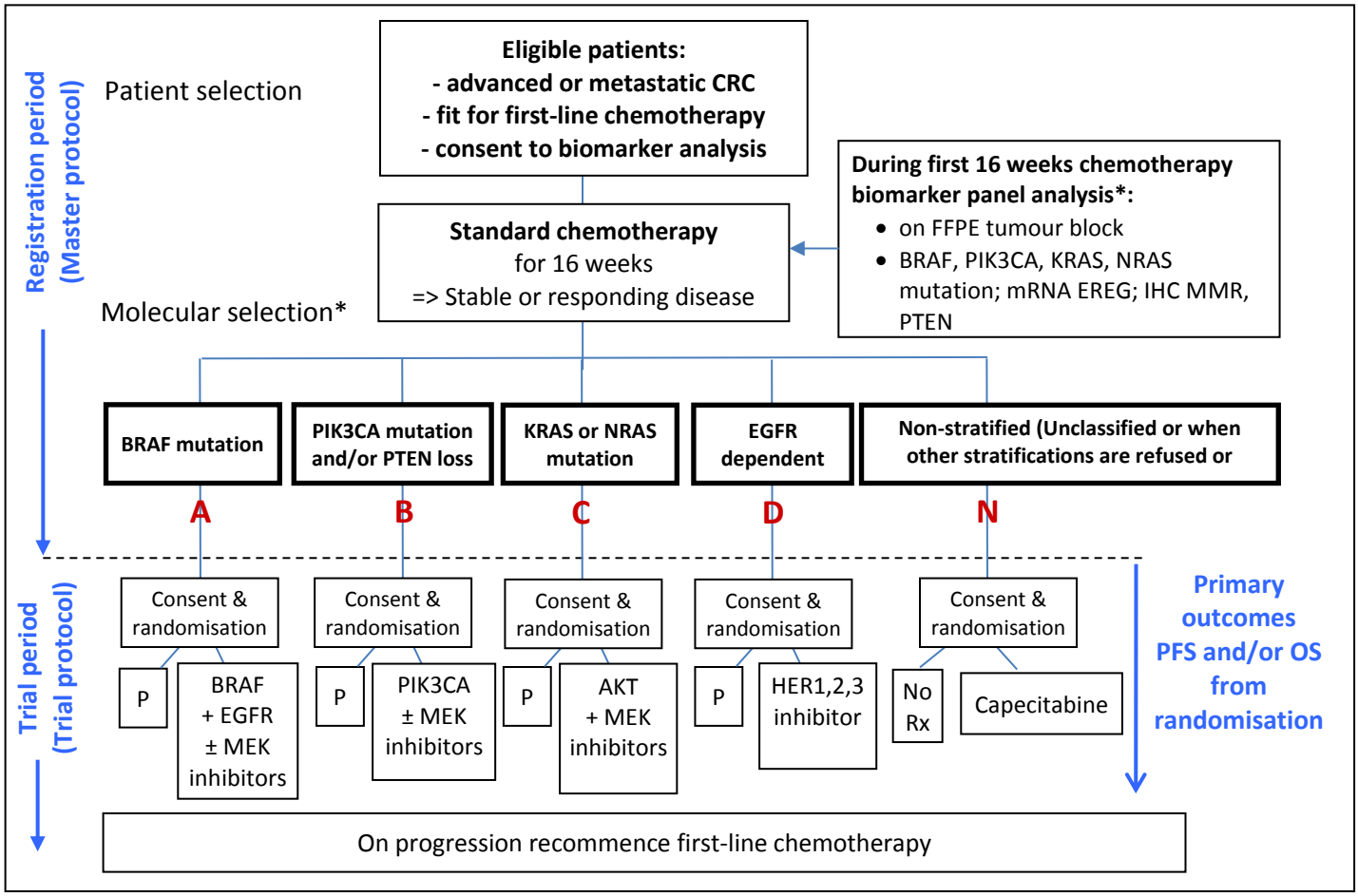
SUMMARY OF TRIAL

FOCUS4 STRUCTURE AND SCHEMA

FOCUS4 is a molecularly stratified, multi-arm, multi-stage (MAMS) design, multi-site randomised trials programme for patients with colorectal cancer (CRC). During the initial registration period, all patients are treated with standard chemotherapy and considered for a standard treatment break if they have responding or stable disease after 16 weeks of chemotherapy. During the registration period, biomarker testing will be performed on their original tumour specimens to determine which specific drug(s) may be most appropriate to test during interruption of chemotherapy after 16 weeks. The patient will then be offered entry into a specific trial on the basis of their molecular cohort. Each of these trials (which are each identifed by a unique letter) will be double blind and placebo controlled for oral agents but may be modified for intra-venously administered agents as a double blind placebo design may not be appropriate or acceptable to patients. A separate specific trial protocol will describe the procedures for that trial (see Figure 1: FOCUS4 Trials Programme Schema). As new agents are tested within each molecular cohort of the FOCUS4 Trials Programme a new letter is assigned to that trial.

Figure 1: FOCUS4 Trials Programme Schema - registration, randomisation and treatment



** The molecular cohorts are arranged in a hierarchy from left to right. For example a patient with both a PIK3CA mutation and a KRAS mutation will be classified into the PIK3CA mutation cohort.*

Due to the molecularly stratified nature of the research questions, the FOCUS4 protocol is separated into sections:

- **FOCUS4 Master Protocol:** this is the main overarching protocol which describes the registration period - identification of patients, biomarker testing and initial 16 weeks of standard therapy. It will also cover aspects such as trial governance generic to all trials within the FOCUS4 Trials Programme.
- **FOCUS4 Trial Protocols:** Following the biomarker panel results, patients are allocated into a series of individual randomised trial comparisons. Initially these are effectively randomised phase 2 trials, but within the multi-stage statistical design, each can independently roll forward into a randomised phase 3 trial if the early data indicate there is sufficient treatment activity according to pre-specified criteria.

The molecular cohorts are defined by somatic (tumour) genetic changes with expected predictive and/or prognostic implications. The strength of prognostic effect and the molecular targets of the novel agents to be tested dictate a natural hierarchy to the molecularly stratified cohorts. These are as follows, with any patient with the defining mutations (regardless of other molecular findings) assigned to the corresponding active cohort:

- Patients with BRAF-mutation – first trial **FOCUS4-A**
- Patients with PIK3CA mutation or major PTEN loss – first trial **FOCUS4-B**
- Patients with either KRAS or NRAS mutation – first trial **FOCUS4-C**
- EGFR dependent patients (wild type BRAF, PIK3CA, KRAS, NRAS) – first trial **FOCUS4-D**
- Patients unclassified or unable/unwilling to enter their relevant molecular trial – **FOCUS4-N**

For example, a patient with PIK3CA mutation *and* KRAS mutation will be classified into the the PIK3CA mutation cohort. As and when some agents fail to demonstrate sufficiently encouraging activity, other novel agents may be available for testing in these molecular cohorts; these agents will be assigned new designations as FOCUS4-E, -F, *etc.* For the current status of the trials within the FOCUS4 Trials Programme please refer to the the FOCUS4 website, www.focus4trial.org.

The trials in the molecular cohorts will be adaptive in design such that pre-specified interim analyses will be performed to identify therapies that appear to be having a strong or weak treatment effect. Therapies that do not demonstrate a sufficiently strong effect (according to pre-specified thresholds) will be dropped and alternative available therapies will replace them for that cohort (under new designations as explained above).

Another adaptive aspect of the design is that, for therapies that demonstrate a strong treatment effect in a biomarker-selected cohort, further testing will be undertaken in patients whose biomarker profile does *not* direct them to that cohort, thus determining whether the therapy effect is specific to the original molecular cohort selection.

If in the future strong evidence emerges, from within or outside this trial, for new or alternative stratified molecular cohorts based upon alternative robust biomarkers, the design allows for these to be added by amendment to the stratified structure.

FOCUS4 COMMON TERMINOLOGY

Table 1: A description of terms used commonly throughout the FOCUS4 Trials Programme

TERM	MEANING
FOCUS4	The whole FOCUS4 Trials Programme
Master Protocol	The FOCUS4 Master Protocol describes the procedures for patient identification, registration, biomarker testing and initial 16 weeks of standard therapy procedures. It also contains generic information relating to all trials in the FOCUS4 Trials Programme.
FOCUS4-A Trial	The name for a specific trial (letter A onwards)
Trial Protocol	The protocol for a specific trial (letter A onwards)
Molecular cohort	The molecular sub-group determined from the biomarker tests performed on the tumour sample sent off at registration. The molecular cohort classification when FOCUS4 opens is: • BRAF mutation • PIK3CA mutation and/or PTEN loss • KRAS or NRAS mutations • EGFR dependent (wild type for all mutations above)
Biomarker defined cohort	Same as molecular cohort
Stage I, II, III or IV	The interim analysis stages in the MAMS design.
Phase 2 or 3	The phases of the trial: Phase 2 includes stages I and II Phase 3 includes stages III and IV
Step 1 or 2	The patient information and consent steps for registration (Step 1) and randomisation (Step 2)
Period	Registration or trial period
Level	Refers to the categorisation of participating trial sites into levels 1, 2 or 3. Initial treatment for some molecular cohorts may be limited to higher level sites.

FOCUS4 DETAILED SUMMARY TABLE

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
ACRONYM	FOCUS4
Long Title of Trials Programme	Molecular selection of therapy in colorectal cancer: a molecularly stratified randomised controlled trials programme
Note	This protocol is the FOCUS4 Master Protocol. Patients will be registered into the FOCUS4 Trials Programme and subsequently randomised into a trial available for their molecular cohort. These trial protocols will have the acronyms of FOCUS4-A trial, FOCUS4-B trial etc., and are provided as separate protocol documents.
Version	1.0
Date	1st February 2013
MRC CTU ID	CR13
ISRCTN #	(To be applied for)
NCT #	(To be applied for)
EudraCT #	2012-005111-12
CTA #	
REC #	13/SC/0097
Type of Participants to be Studied	Adult patients with inoperable advanced or metastatic colorectal cancer (CRC) who are suitable for intermittent chemotherapy.
Study Design	The FOCUS4 Master Protocol describes the registration period - identification of patients, biomarker testing and initial 16 weeks of standard therapy prior to entry into any of the FOCUS4 Trials. Patients undergoing 16 weeks of first-line chemotherapy for CRC will be registered and asked for consent to send their tumour block sample for biomarker panel assessment. The results of this assessment will be used to classify patient into one of several possible molecular cohorts. Patients are offered entry into the trial available for their molecular cohort. Each trial within these patient molecular cohorts will aim to be double blind and compare an intervention with a placebo control and have its own dedicated trial protocol. A fifth trial (FOCUS4-N) will run concurrently for patients whose biomarker panel results are unclassifiable; for those whose molecular cohort is temporarily not open for recruitment, and for any patients unable or unwilling

	to travel. (For safety reasons, agents for some cohorts will initially be available only at a limited number of trial sites). FOCUS4-N will answer a conventional (not molecularly stratified) chemotherapy question comparing capecitabine against no treatment; unlike the other trials, this chemotherapy comparison will not be blinded or placebo controlled. FOCUS4 is a rolling trials programme that utilises the MAMS design. A maximum of 4 staged interim analyses are proposed for each trial: Stage I (safety), Stage II (lack of sufficient activity), Stage III (efficacy for PFS) and Stage IV (efficacy for OS). Stages I and II would be regarded as equivalent to a conventional phase 2 study and Stages III and IV a phase 3 study. Results at each stage will be reviewed confidentially by an Independent Data Monitoring Committee (IDMC) but results at the end of stage II (phase 2) may be released by the IDMC to allow an open decision to be made on whether to proceed to stage III (phase 3). In addition, if the novel agent is showing sufficiently strong activity, it may be tested in patients who are not selected for that molecular cohort to ascertain whether the action of the novel agent is specific to that biomarker classification. The four molecular cohorts are organised into a hierarchy of classification (see Trial Schema and explanation above) and are described below along with FOCUS4-N. Specific agent(s) are detailed separately in each of the trial protocols. The trials listed below are the current trials planned for each molecular cohorts at the time of writing of this Master Protocol: ***Cohort: BRAF mutant tumours*** Trial name: FOCUS4-A Intervention(s): Specific BRAF mutated kinase inhibitor in combination with panitumumab (an EGFR targeted monoclonal antibody) with or without MEK inhibitor. Control: Dual placebo ***Cohort: PIK3CA mutant tumours and/or loss of PTEN IHC*** Trial name: FOCUS4-B Intervention(s): Dual PIK3 / mTOR inhibitor monotherapy Control: Dual placebo. ***Cohort: KRAS or NRAS mutant tumours***

	Trial name : FOCUS4-C Intervention(s): Dual pathway inhibition using an AKT inhibitor and MEK inhibitor Control: Dual Placebo ***Cohort: EGFR dependent (BRAF, PIK3CA, KRAS, NRAS wild type)*** Trial name: FOCUS4-D Intervention(s): HER1, 2 and 3 inhibitor Control: Placebo ***Cohort: Non-stratified (patients whose biomarker panel results are unclassifiable or who are unable or unwilling to enter the trial available in their molecular cohort or the trial for their molecular cohort is not open to recruitment at that time).*** Trial name: FOCUS4-N Intervention(s): Capecitabine Control: Active monitoring (treatment break)
Study Hypothesis	The primary objectives are to test: 1) In the interval following standard first-line chemotherapy, does the proposed intervention improve PFS compared with the control group in the biomarker-defined cohort? 2) Do the biomarkers used identify one or more patient cohorts with greater responsiveness to therapy than an unselected group?
Primary Outcome Measure(s)	There are no primary outcome measures for the registration period as no interventions are being compared during this period. The primary outcome measure for the subsequent trials that commence at the end of the registration period will be progression -free survival (PFS) which includes death from any cause as well as CT scan evidence that there is disease progression according to RECIST criteria. Analysis will be timed from randomisation with the baseline CT scan performed just prior to randomisation. An additional primary outcome of overall survival may be evaluated for trials that progress to Stage III.
Secondary Outcome Measure(s)	1) Safety, toxicity, response, tumour shrinkage. 2) Quality of life (QL) may be assessed in any molecularly stratified trial where the release of interim results at the end of stage II leads to a decision to continue the trial to stage III. However, QL data may be collected at other stages if it is deemed to be important for that specific trial. QL will be assessed throughout FOCUS4-N from

	randomisation onwards.
Randomisation	Randomisation into any trial will not occur until the end of the 16 week registration period. Minimisation with a random element will be used for patient allocation and the randomisation ratio will be defined within each trial protocol. Generally this will be 2:1 in favour of the novel therapy (unless agent supply is limited or there is a 3-way randomisation).
Number of Patients to be Studied	FOCUS4 is a rolling trials programme that utilises the MAMS design. The following numbers indicate the cumulative number of patients required to evaluate the current intervention up to the end of each interim analysis stage. Actual sample sizes may vary for each trial within these cohorts and are detailed in the specific trial protocols: • BRAF mutant = 61 (stage I), 97 (II), 139 (III), 301 (IV) • PIK3CA mutant/PTEN loss = 170 (I),264 (II), 373 (III), 264 (IV) • KRAS/NRAS mutant = 177 (I), 273 (II), 378(III), 574 (IV) • EGFR dependant (wildtype) = 180 (I), 275 (II), 381(III), 547 (IV) • FOCUS4-N Trial: Target up to 643 patients.
Duration	7 years (4 to 5 years recruitment)
Ancillary Studies/Substudies	1) Biomarker development studies for mRNA based stratification in the all-wildtype cohort 2) Fresh tumour biopsies at randomisation and on progression from patients giving consent and with accessible tumour 3) Circulating Tumour DNA analysis 4) Sequencing of genes in candidate pathways from FFPE 5) Pharmacogenomic sub-studies 6) Pharmacodynamic sub-studies (for given cohorts)
Sponsor	Medical Research Council
Funder	NIHR/MRC EME programme and CR-UK
Chief Investigators	Overall: Professor Tim Maughan and Dr Richard Wilson Each individual trial: FOCUS4-A: Professor Gary Middleton FOCUS4-B: Dr Harpreet Wasan FOCUS4-C: Dr Richard Wilson FOCUS4-D: Dr Richard Adams FOCUS4-N: Professor Tim Maughan
Current Status of FOCUS4 Trials	Please refer to FOCUS4 website at: http://www.focus4trial.org/ (to be registered)

ASSESSMENT SCHEDULE DURING REGISTRATION PERIOD

Figure 2: Registration Period GANTT Chart (the grey shading provides a guide to when each task may be performed but some flexibility exists around these timelines)

(This is also provided in Section 6.1 on page 33)

Registration period → **Trial period (see trial protocol)** →

WEEK	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
First-line chemotherapy#		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■				
Check registration eligibility criteria Δ	■	■	■	■	■	■	■	■	■	■	■	■	■								
PIS1Δ	■	■	■	■	■	■	■	■	■	■	■	■	■								
RegistrationΔ		■	■	■	■	■	■	■	■	■	■	■	■								
Biomarker sample sent Δ		■	■	■	■	■	■	■	■	■	■	■	■								
CT scan §	■								■								■				
RECIST response									■								■				
PIS2 ∞										■	■	■	■	■	■	■	■				
Check specific trial eligibility criteria										■							■	■			
Baseline assessment †																	■	■			
Wash out from first-line chemo‡																■	■	■			
Randomisation¥																		■	■		
*Optional Assessments**																					
Blood (Genomic DNA) *	■																	■	■		
Blood (Circulating DNA) *	■																■	■	■		
Tumour biopsy *																	■	■	■		

Key to symbols

\# *Regime determined locally for 16 treatment weeks (± 2 weeks) but overall time from start of treatment to end of last cycle of up to 20 weeks is acceptable. Beyond 20 weeks, please contact the MRC CTU office to determine whether the patient is eligible for any of the trials.*

Δ *PIS1, registration and biomarker sample can be completed at any time up to weeks 1-12 of the 16 weeks of first-line chemotherapy*

§ *Mandatory CT scan within 4 weeks prior to standard chemotherapy, recommended interim CT scan after 8 weeks chemotherapy; mandatory CT scan after 16 weeks chemotherapy*

∞ *PIS2 can be given when biomarker result is known and interim CT scan shows SD, PR or CR*

† *Baseline assessments must be done within 1 week prior to randomisation – see specific trial protocol for list of tests required.*

‡ *Wash out period of 3 weeks between end of 16 weeks first-line chemotherapy and start of allocated trial therapy*

¥ *Randomisation must be within 4 weeks of 16 week CT scan*

* *Not required if patient has withheld consent for molecular research tumour biopsy or there is no tumour accessible for percutaneous biopsy*

CONTENTS

ABBREVIATIONS AND GLOSSARY

Term	Definition
aCRC	Advanced Colorectal Cancer
AE	Adverse Event
ADL	Activities of Daily Living
ALP	Alkaline Phosphatase (also known as ALKP)
ALT	Alanine Transaminase
AR	Adverse Reaction
AREG	Amphiregulin
APC gene	Adenomatous Polyposis Coli Gene
AST	Aspartate Transaminase
AZ	AstraZeneca
BD or BID	Twice Daily
Biomarker defined cohort	The molecular sub-group determined from the biomarker tests performed on the tumour sample sent off at registration. The molecular cohort classification when FOCUS4 opens is: • BRAF mutation • PIK3CA mutation and/or PTEN loss • KRAS or NRAS mutations • EGFR dependent (wild type for all mutations above)
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BSA	Body Surface Area
CEA	Carcino-embryonic Antigen
CF	Consent Form: - CF1 = for registration - CF2 = for randomisation - CF3 = for optional biopsy sub-study
CFI	Chemotherapy Free Interval
CI	Chief Investigator
CI	Confidence Interval
Cohort	Molecular Cohort
COIN	Continuous chemotherapy plus cetuximab, or Intermittent chemotherapy with standard continuous palliative combination chemotherapy with oxaliplatin and a fluoropyrimidine in first line treatment of metastatic colorectal cancer
COIN-B	Intermittent chemotherapy plus continuous or intermittent cetuximab in the first-line treatment of advanced colorectal cancer
CR	Complete Response (RECIST)
CRC	Colorectal Cancer
CRF	Case Report Form
CRN	Clinical Research Network
CRP	C-Reactive Protein

Term	Definition
CR-UK	Cancer Research UK
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Awards and Advisory Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical trial of an investigational medicinal product
CTU	Clinical Trials Unit
DH	Department of Health
DM	Data Manager
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DPA	(UK) Data Protection Act
DUSP4 & 6	Dual Specific Phosphatases 4 & 6
ECG	Electrocardiogram
ECMC	Experimental Cancer Medicine Centre
EDTA	Ethylene Diamine Tetraacetic Acid
EGFR	Epidermal Growth Factor Receptor (also HER-1 and Erb1)
EME	Efficacy Mechanism Evaluation
EREG	Epiregulin
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FBC	Full Blood Count
FFPE	Formalin Fixed Paraffin Embedded
FOCUS4	The whole FOCUS4 Trials Programme
FOLFIRI	5FU, folinic acid and Irinotecan
FOLFOX	5FU, folinic acid and Oxaliplatin
5FU	5-Fluorouracil
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GP	General Practitioner
GSK	GlaxoSmithKine
HER	Human Epidermal Growth Factor Receptor (family of EGFR, HER-2, HER-3, HER-4). In non-human species, often termed as Erb-B (1-4) but these are standardised to EGFR and HER (2-4) in the FOCUS4 Protocols
HR	Hazard Ratio
IB	Investigator Brochure
IBW	Ideal Body Weight
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product

Term	Definition
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
IWRS	Interactive Web Response System
ITT	Intention-to-Treat
LDH	Lactate Dehydrogenase
Level	Refers to the categorisation of sites into levels 1, 2 or 3
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
LSA	Lack of Sufficient Activity
LVEF	Left Ventricular Ejection Fraction
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
m^2	Metre-squared
MAMS	Multi Arm Multi Stage
Master Protocol	The FOCUS4 Master Protocol describes the procedures for patient identification, registration, biomarker testing and initial 16 weeks of standard therapy procedures. It also contains generic information relating to all trials in the FOCUS4 Trials Programme.
mCRC	Metastatic Colorectal Cancer
Mg	Magnesium
mg	Milligrams
MHRA	Medicines and Healthcare products Regulatory Agency
ml	Millilitre
mmHg	Millimetres of Mercury
MMR	Mis-matched Repair
Molecular cohort	The molecular sub-group determined from the biomarker tests performed on the tumour sample sent off at registration. The molecular cohort classification when FOCUS4 opens is: • BRAF mutation • PIK3CA mutation and/or PTEN loss • KRAS or NRAS mutations • EGFR dependent (wild type for all mutations above)
MRC	Medical Research Council
MRC CTU	Medical Research Council Clinical Trials Unit
MREC	Main Research Ethics Committee
mRNA	Messenger Ribonucleic Acid
mSec	Millisecond
MTD	Maximum Tolerated Dose
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network

Term	**Definition**
NHS	National Health Service
NHSCR	National Health Service Central Register
NHS-IC	National Health Service Information Centre
NIHR	National Institute for Health Research
NIHR CSP	National Institute for Health Research Co-ordinated System for gaining NHS Permission
NIMP	Non-Investigational-Medicinal Product
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
ONS	Office of National Statistics
OS	Overall Survival (an additional potential primary outcome)
OxMdG	Oxaliplatin , 5FU and Folinic acid
PALS	Patient Advice and Liaison Services
PD	Progressive Disease (RECIST)
Period	Registration or trial period
PFS	Progression-Free Survival (the primary outcome)
PH	Proportional Hazards
Phase 2 or 3	Phases of the trial: Phase 2 includes Stages I and II Phase 3 includes Stages III and IV
PI	Principal Investigator
PIK3CA	Phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha
PIS	Patient Information Sheet: - PIS1 = for registration - PIS2 = for randomisation - PIS3 = for optional biopsy sub-study
PR	Partial Response (RECIST)
PS	Performance Status
PTEN	Phosphatase and Tensin homolog
QA	Quality Assurance
QC	Quality Control
QL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumors
RGC	Research Governance Committee
RGF	Research Governance Framework (for Health and Social Care)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Stable Disease (RECIST)
SNP	Single-Nucleotide Polymorphism
SOP	Standard Operating Procedure

Term	**Definition**
SPC	Summary of Product Characteristics
Stage I, II, III or IV	Interim analysis stages in the MAMs design
Step 1 or 2	The patient information and consent steps for registration (step 1) and randomisation (step 2)
SUSAR	Suspected unexpected serious adverse reaction
TCGA	The Cancer Genome Atlas
TGF	Transforming Growth Factor
TKI	Tyrosine Kinase Inhibitor
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
Trial Protocol	The protocol for a specific trial (letter A onwards)
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
U&Es	Urea and Electrolytes
UKCRN	UK Clinical Research Network (now the NIHR CRN)
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WT	Wild type
XELOX	Xeloda (Capecitabine) plus Oxaliplatin

1 INTRODUCTION AND SCIENTIFIC BACKGROUND

1.1 DISEASE SETTING AND TRIAL CONTEXT

Over 16,000 people die of colorectal cancer (CRC) per annum in the UK (Cancer Research UK (CR-UK) Cancer Stats 2010), most of whom die with metastatic disease[1]. The use of EGFR-targeted therapy has led to the discovery of the importance of BRAF, PIK3CA, KRAS and NRAS mutations in prediction of lack of response to EGFR-targeted therapy[2]. Major challenges now face oncologists in identifying effective treatments for patients with CRC following the limited benefits shown for bevacizumab and cetuximab and the failure of multiple other agents in recent commercial trials. A more selective approach is urgently required.

The NCRI Colorectal Cancer Clinical Studies Group has delivered a step-wise programme of clinical trials including developments both in biomarker selection and therapeutic intervention. FOCUS4 is the next trial in that process and will provide a structure for the rapid identification of the patients whose tumours can be characterised either on the basis of the presence of specific mutations or on the basis of validated biomarkers which characterise biological cohorts. FOCUS4 will characterise the tumours and stratify all patients who are eligible and consenting into a clinical trial which, by being a component of a large national study, will adapt efficiently to refinement of biomarker data and will enable rapid accrual even in rare subtypes such as those with BRAF mutation who only comprise 8% of the metastatic CRC population.

This programme of trials is needed now because the convergence of molecular understanding of the disease and the clinical development of a wide range of targeted therapies demands the evaluation of new therapies within subsets of the population whose tumours are more likely to benefit. In addition, following the failure of many classic trials to show benefit for a new treatment in colorectal cancer we clearly need a new paradigm to attempt to make progress. The concept of one research question for all patients is outdated in colorectal cancer, as in breast cancer and as will increasingly be the case across all oncology.

1.2 RESEARCH LEADING TO THE PROPOSED TRIAL

1.2.1 MOLECULAR CLASSIFICATION OF COLORECTAL CANCER

There is a great deal of research activity under way to clarify the molecular variability in CRC. The Cancer Genome Atlas (TCGA) Network have published an indepth molecular characterisation of colon and rectal cancer[3]. A key driver of CRC is the *wnt* pathway which is affected in nearly every case of CRC, and can be disregulated at many points but most commonly at the APC gene. The TGF-β pathway which is a negative regulator of cell growth is deficient in many of the cancers. Both of these pathways converge to drive increased expression of the *myc* oncogene which seems of central

importance in colorectal cancer. Unfortunately agents targeting these pathways are still in early development so cannot be used in this trial currently.

In FOCUS4, patients will be allocated into trials initially defined by four specific molecular cohorts with another cohort for patients whose cancer could not be classified into a specific molecular cohort. Cohorts may change as data become available during FOCUS4. Data from the COIN Trial[4] have been used to determine the prevalence and prognosis of patients *with normal platelets* in each of the molecular cohorts and thus, the figures below differ from those presented in the literature. Therefore, the initial five molecular cohorts are:

BRAF mutation

These mutations are more frequent in the presence of microsatellite instability and arise more commonly in right sided colon carcinomas and have a reasonably consistent gene expression signature[5].

Prevalence: In the MRC COntinuous or INtermittent (COIN) trial[4], 8% of patients had BRAF mutations.

Prognosis: Patients with this molecular classification and with normal platelets in the intermittent arm of the COIN Trial had a median overall survival (OS) of 14.8 months and a median progression-free survival (PFS) of 3.1 months. In the complete-break intermittent arm of the COIN-B Trial[6], such patients had a median OS of just 5.0 months and a PFS of just 1.9 months, albeit with low patient numbers, indicating that prognosis is potentially very poor among patients with BRAF mutations.

PIK3CA mutation or profound loss of PTEN function

These mutations lead to activation of the AKT signalling network and about half the patients also have KRAS mutations in the tumour. In addition, about 10% of patients have a loss of PTEN function by various mechanisms including mutation, methylation silencing of the promoter and microRNA inhibition. The TGCA report[3] has identified increased signalling through the IGF receptor due to amplification of IGF2 as an important additional driver within this pathway.

Prevalance: PIK3CA mutations have been identified as one of the commonest mutations in cancer and were identified in 13% of patients in the COIN trial. Patients with PIK3CA or PIK3R1 mutations or profound loss of PTEN function account for about 20 to 30% of the CRC population and have activated AKT signalling.

Prognosis: Patients with this molecular classification and with normal platelets in the intermittent arm of the COIN Trial had a median OS of 16.9 months and a median progression-free survival of 2.7 months. These figures were similar whether or not a KRAS/NRAS mutation was also present. (PIK3CA mutation data are not available in the COIN-B Trial.)

KRAS or NRAS mutation

Expression profile analysis shows a variation in gene expression patterns in tumours with KRAS mutation with signalling down the canonical RAS-RAF-MEK-ERK pathway dominating in about a quarter, signalling through the PIK3-AKT-mTOR pathway in others and diverse signalling in other tumours[7].

Prevalance: In the COIN trial, 44% of patients exhibited either KRAS or NRAS mutations, rising to 52% of those who also exhibited PIK3CA mutation.

Prognosis: Patients with this molecular classification and with normal platelets in the intermittent arm of the COIN Trial had a median OS of 18.4 months and a median PFS of 3.0 months. In the COIN-B Trial the equivalent figures were 11.0 months and 2.8 months.

EGFR dependent (wild-type for all the above mutations)

Patients with these tumours are wild type for BRAF, PIK3CA, KRAS and NRAS and do not have loss of PTEN and include the subset of patients who respond best to EGFR targeted monoclonal antibodies. In addition, mutations or amplification in *HER2* occur in around 5% and over-expression of *HER3* in around 50% of these patients.

Prevalance: In the COIN Trial, 42% of patients were free from all four above mutations.

Prognosis: Patients with this molecular classification and with normal platelets in the intermittent arm of the COIN Trial had a median overall survival of 19.1 months and a median progression-free-survival of 3.3 months. In the COIN-B Trial the equivalent figures were 20.0 months and 4.4 months, albeit with low patient numbers, indicating that prognosis is potentially good among such patients.

Non-stratified group (unclassified)

About 2% of patients' tumours cannot be classified successfully and these patients will be included into this group. In addition, this cohort will include those patients eligible for trials which are suspended between novel therapy evaluations or patients who chose not to participate in their specific molecular trial due to reasons such as distance to an experimental therapy centre. Once a patient enters a particular trial, they would not be able to enter another FOCUS4 Trial at another time.

The identification of novel biomarkers and their link to selection of patients for specific therapy is however a fast moving field. An essential feature of this trial is that it will allow introduction of novel biomarkers once they have been sufficiently validated, to identify newly characterised tumour subgroups for evaluation of therapies hypothesised to be effective in the identified patient sub-populations. Thus the trial incorporates some biomarkers that are accepted (KRAS mutation), some reaching general consensus (BRAF mutation) and others for which further development and refinement is required (PTEN, mRNA for epiregulin) but can be accomplished within the trial itself.

This trial is structured to provide an overarching recruitment and biomarker identification strategy, linked to a series of randomised comparisons between novel and control treatments for the identified sub-populations. During the trial some of these interventions may be shown to have a lack sufficient activity and these will be withdrawn after interim analysis and replaced by new agents or by new biomarker-defined groups. Others which are successful at interim analysis will proceed to the next stage.

Within the individual trials for each molecular cohort, the novel therapy comparisons will be double blind and placebo controlled. FOCUS4-N will allocate patients to either capecitabine or no treatment and thus will be an open, unblinded trial. Standard objective measurements of tumour response and toxicity grading will be used as well as nurse-assessed toxicity scores. Tumour responses will be documented on CT scans and disease response will be evaluated according to RECIST criteria. Quality of life may be evaluated in any trial that continues beyond stage II evaluation and will be evaluated throughout FOCUS4-N.

1.2.2 MAINTENANCE TREATMENT IN THE INTERVAL AFTER FIRST-LINE CHEMOTHERAPY

In FOCUS4, novel agents will be used in the interval off chemotherapy treatment. There are three reasons for chosing this setting:

1) The COIN Trial, which randomised 1630 patients, tested whether intermittent chemotherapy is non-inferior to continuous chemotherapy[4]. Median survival in the per-protocol population of COIN (n=978) was 19·6 months with continuous chemotherapy and 18·0 months with intermittent chemotherapy, HR 1·087 (80% CI 0·986-1·198), the upper limit being just above the predefined non-inferiority critical value of 1·162. Sub-group analyses identified that a raised baseline platelet count (>400x10^9/L in 28% patients, n=271) was the only variable associated with a significant survival advantage from continuous chemotherapy (p-value for interaction=0·003; HR for intermittent vs continuous=1.24 among patients with raised platelets, p=0.002) and these patients will be excluded from the proposed study. COIN demonstrated that patients with normal baseline platelets gain the benefits of intermittent chemotherapy, of less time on chemotherapy, improved quality of life and less toxicity without loss of survival. These are the patients who will be eligible for FOCUS4.

   However, the finding that patients with high platelets (>400x10^9/L) fare less well with a treatment break has not been validated or tested in a new patient group. Steps are currently being taken to collate the international datasets to test this finding in other completed trial datasets. Despite data from COIN, COINB, OPTIMOX 1 & 2, Nordic VII, GISCAD & TTD, the evidence to support the predictive value of raised platelets with respect to intermittent therapy is weak. Two more trials expected to report in coming months may help confirm the result one way or another. If the finding is supported by these data, the high platelet exclusion criterion will be maintained in FOCUS4. If the result is not supported, this exclusion criterion will be removed via a protocol amendment.

2) The proposed agents are currently in a relatively early point in their clinical development and in any other settings than FOCUS4 they would only be tested after resistance/failure of (at least) first-line chemotherapy and usually in combination with other known active chemotherapy, which requires completion of dose-finding studies in combination. In FOCUS4, promising new agents can be tested immediately as monotherapies or dual novel therapies in patients who have not already developed chemotherapy resistance. Therefore the plan is to evaluate the novel therapies in the chemotherapy-free interval following 16 weeks of combination chemotherapy in biomarker-defined cohorts of patients.

   This approach has been piloted in the COIN-B Trial in which FOLFOX (OxMdG) plus cetuximab chemotherapy was used as an intermittent strategy, comparing no therapy in the interval with cetuximab maintenance in the interval. This trial was presented at 2011 European Multidisciplinary Cancer Congress (ECCO-ESMO)[6]. It has shown that cetuximab maintenance in the interval when used in patients with KRAS wild type tumours was associated with an improvement in progression-free survival from 3.1 to 6.0 months (HR = 0.67 (95% CI 0.46 to 0.98); p=0.040). This is a useful proof of principle that the FOCUS4 design will be able to test the efficacy of targeted agents in a molecularly-selected population in the interval following first-line chemotherapy.

3) The use of novel therapies as single agents or in novel-novel combinations is likely to yield a clearer and more reliable signal of activity than combining concurrently with first-line combination chemotherapy, where unexpected interactions (including apparent interference with benefit) have been frequently seen to occur.

1.2.3 FEASIBILITY OF FOCUS4 BASED UPON THE PREVIOUS FOCUS 3 STUDY

FOCUS4 builds on the recently completed feasibility study of molecular selection of therapy in advanced colorectal cancer, MRC FOCUS 3[8]. FOCUS 3 has demonstrated that it is possible to collect samples from a national multi-centre trial and perform biomarker analysis and return results to the trials centre in 10 working days in 74% and in 21 days in 99% of cases. It also showed that with well-designed, staged, patient information sheets, patients are very willing to join a seemingly complex randomised trial of therapies based on molecular selection.

1.3 RESEARCH OBJECTIVES

The primary objectives of FOCUS4 are to answer the following research questions:

1.3.1 CLINICAL BENEFIT

In the interval following standard first-line chemotherapy, do the proposed interventions improve progression-free survival compared with placebo in the biomarker-defined cohorts?

The scientific rationale for each of the individual trials and the intervention is given in the specific trial protocols. The specific agents and the biomarker definition of the molecular cohorts may change as subsequent FOCUS4 trials are introduced. This master protocol will continue to apply as the over-arching trial protocol.

1.3.2 TRIAL DESIGN IMPROVEMENT

In the FOCUS4 Trials Programme, patients will be registered with newly-diagnosed advanced or metastatic disease from colorectal cancer, undertake a centralised biomarker panel and allocate patients into the most appropriate trial based on the results of the biomarker analysis. Some trials will adapt over time (as, for example, when an agent has successfully passed the stage II interim analysis and further testing will incorporate a larger sample size and be tested in patients ***not*** selected on the basis of the biomarker profile; or alternatively when an agent has not proved promising and a potentially superior agent has become available for testing; or alternatively when a new robust biomarker profile with an appropriate molecular targeted agent for it becomes available). The individual trial protocols are intended to be used along with this Master Protocol, which will remain the overall guide to the study.

During the course of the FOCUS4 Trials Programme, there will be times when not all trials will be open in the molecular cohorts but a current list of open trials will be be available on the FOCUS4 website. Patients who are classified into any cohort for which a trial is not currently open will be offered entry into the FOCUS4-N trial or, if appropriate, entry into one of the other molecular cohort trials where they are selected for that mutation (eg. patients with both a KRAS and a PIK3CA mutation will join FOCUS4-C if FOCUS4-B is not currently open).

1.3.3 BIOMARKER RESEARCH

1. *Biomarker development programme for EGFR dependent cohort:*

   What is the optimal algorithm for stratification of the EGFR dependent cohort, (AREG, EREG, DUSP4, DUSP6 mRNA expression) and what optimal cut points should be used? What is the impact of mutation or amplification in HER2 or over-expression of HER3?

2. *Fresh tumour biopsies before randomisation and on progression:*

   Does detailed molecular analysis of biopsies from unresected primary tumour or metastases following initial chemotherapy (prior to interval) result in better selection of therapy than the targeted biomarker analysis on diagnostic material taken before initial chemotherapy?

   Do such analyses comparing biopsies on progression with those taken at randomisation reveal mechanisms of resistance to therapy?

3. *Circulating tumour DNA analysis:*

   Does sequential assessment of circulating tumour DNA from plasma for the presence of somatic mutation provide early information on resistance and/or document specific mechansims of resistance to the investigational therapies?

4. *Sequencing of genes in candidate pathways from FFPE:*

   Does a more detailed genetic analysis of archival tumour result in an ability to provide more detailed and accurate molecular stratification?

5. *Pharmacogenomic sub-studies:*

   Germline DNA will be collected.

6. *Pharmacodynamic sub-studies (for given cohorts):*

   Further details will be provided in specific trial protocols.

2 SELECTION OF SITES/CLINICIANS

2.1 CATEGORISATION OF SITES

The MRC, as trial Sponsor, has overall responsibility for site and investigator selection. FOCUS4 includes the use of novel therapies (either single agent or combinations of agents) in a widely dispersed collaborative group of sites. For each novel therapy arm, in collaboration with the company providing the novel agent(s), a safety assessment has been performed and will be updated when required. On the basis of this safety assessment, for some novel therapies, more intensive surveillance will be required for an initial period of administration. In order to be confident and to ensure the confidence of the collaborating pharmaceutical companies, patients allocated to those interventions will need to be referred to an Experimental Cancer Medicine Centre (ECMC) or a site assessed to be equivalent, i.e. a site with the required facilities and experience. This is due to the limited experience with some of these novel agents at the time of starting FOCUS4, eg. only 50-100 patients already treated with the agent(s) in phase I/II trials. However some therapies will not require referrals such as in the FOCUS4-N trial, or with others as experience is gained both within and outside the FOCUS4 trial. The FOCUS4 Trial Management Group (TMG) has identified three categories of sites (Levels 1, 2 and 3) and each FOCUS4 Trial protocol will state the activities for each individual trial which may be undertaken at the different levels. Sites participating in the trial will be assessed through the FOCUS4 site set up process and those invited to participate in the trial will be allocated into one of the following three levels:

2.1.1 LEVEL 1 SITES

All level 1 sites will be able to participate in patient registration; recruitment and administration of treatment for the FOCUS4-N trial; referral of patients to level 2 and 3 sites for randomisation to the other FOCUS4 trials; and follow-up for novel agents where sufficient preliminary data are available to confirm safety on a per patient basis.

These sites will be responsible for:

- Discussion of FOCUS4 with the patients
- Obtaining informed consent for biomarker analysis
- Registration of patients into the FOCUS4 Trials Programme
- Identification of an FFPE block containing tumour by the pathologist and sending the block for biomarker analysis to one of the referral laboratories
- If the site can deliver standard chemotherapy, then the first 16 weeks of treatment (prior to randomisation) can be given at the site
- CT scans to be performed prior to start of standard chemotherapy, at an interim timepoint (8 weeks recommended) and 16 weeks, with ability for electronic transfer of scans to other sites

  IMPORTANT NOTE: The FOCUS4 trials are investigating efficacy in terms of repeated measurements from CT scans. Therefore the local investigators must consider the CT

scanning facilities in their area and ensure that the scanners used throughout the patient's follow-up, provide consistent and comparable measurements. Ideally all CT scans should be performed using the same scanner but some flexibility can exist if different scanners are known to have very similar specifications and scanning protocols and radiologists in all sites can confidently report response according to RECIST version 1.1 criteria.

- Initiation of consent process for patients prior to referral to Level 2 or 3 sites for experimental trial participation. Final consent must be completed at the Level 2 or 3 site.
- Randomisation of patients into the FOCUS4-N Trial
- Treatment and follow-up of patients randomised into the FOCUS4-N Trial
- Obtaining consent and performing additional research biopsies for patients entering FOCUS4-N
- Treatment and follow-up of patients whose novel agent treatment has been shown to be sufficiently safe and appropriate for continuation at Level 1 sites
- Randomisation, treatment and follow-up of patients randomised into FOCUS4 trials of novel agents against placebo when these have been approved for use at Level 1 sites

2.1.2 LEVEL 2 SITES

In addition to performing the level 1 site activities for its its own local population, these sites will also be responsible for:

- Assessing patients for eligibility for randomisation into the specific FOCUS4 trials open at level 2 sites
- Obtaining informed consent for randomisation, including for additional research biopsies
- Randomisation of patients into the specific FOCUS4 trials open at level 2 sites
- Arranging collection and sending of research biopsies (if consented to by the patient)
- Initiation of consent process for patients prior to referral to Level 3 sites for experimental trial participation. Final consent must be completed at the Level 3 site
- Administration of trial treatments that have been approved for use at level 2 sites
- Follow-up of patients until their novel agent has been shown to be sufficiently safe and appropriate, at which point follow-up may be continued at their original referring site if not the level 2 site.

2.1.3 LEVEL 3 SITES

These include ECMCs or those with equivalent experimental treatment experience. They will be able to perform all the responsibilities of the Level 1 and 2 sites as above. In addition, in collaboration with the early phase trials unit in the site, they will initiate and administer the high risk novel therapies deemed by safety review to require experimental treatment site support.

In addition to performing the Level 1 and 2 site activities for its own local population, these sites will also be responsible for:

- Assessing patients for eligibility for randomisation into the specific FOCUS4 trials only open at Level 3 sites
- Randomisation of patients into the specific FOCUS4 trials open at Level 3 sites

- Administration of trial treatments that have been approved for use at Level 3 sites
- Follow up of all patients until their novel agent has been shown to be sufficiently safe and appropriate, at which point follow-up may be continued at their original referring site if not the Level 3 site.

2.2 SITE AND INVESTIGATOR INCLUSION CRITERIA

For a site to be identified as being compliant with the inclusion criteria, a site evaluation form must be completed and the site may require a visit or teleconference from relevant members of the TMG to finalise their assesssment. Once this has been completed and level of site determined, the FOCUS4 team will provide the site with the FOCUS4 Trials Programme documentation for their R&D approval and MRC CTU accreditation documents. Sites must complete the FOCUS4 programme accreditation documentation (as referred in Section 2.5) at the same time as applying for their local R&D approval through the Integrated Research Application System (IRAS).

2.2.1 LEVEL 1 SITE INCLUSION CRITERIA

Requirements for all sites to participate as level 1 sites are as follows:

a. The institution regularly undertakes the treatment of patients with advanced or metastatic CRC
b. Patients must be under the care of a consultant medical or clinical oncologist
c. Willingness to refer patients in the higher risk trials onward to a level 2 or 3 site (where applicable) until the therapy is deemed to be sufficiently safe and appropriate for that patient. Identification of the most appropriate Level 2 or 3 site and agreement with that site to accept referrals for FOCUS4 (this may be on a patient by patient basis)
d. Agreement by the local pathology department that they will identify and send a FFPE block containing maximum viable tumour to the central laboratory. All participating sites will need to provide confirmation from the lead colorectal pathologist and/or Head of Histopathology Service that a FFPE tumour block will be released following patient registration and sent to the designated laboratory for central biomarker panel testing. To that end, an identified secretarial or technical contact person and their fax and telephone numbers and the name of the designated pathologist with their written agreement of participation will be required from all sites before being accredited to participate in the trial
e. For administration of the standard first-line chemotherapy, normal practice requirements should be followed. Treatment must be administered in a dedicated oncology facility where, in addition to specialist nursing and junior medical staff, the consultant medical or clinical oncologist is routinely on-site and available to discuss/assess patients prior to treatment. Defined arrangements must be in place for the management of acute complications of the standard chemotherapy in weeks 1-16. These may include admission to the designated facility at the site or Unit under the direct supervision of the consultant oncologist, haemato-oncology colleague or general medical service, but should not include admission under the surgical service
f. Pharmacy support for treatment allocation of novel therapies and trial administration. The FOCUS4 pharmacist will sign an agreement to confirm that local hospital systems are in place to

cover drug ordering, drug receipt, drug storage and dispensing, and will enable accurate traceability of all drugs used in the trial

g. Research nurse support for informed consent and on trial data entry and collection. All Serious Adverse Events (SAEs) will be reported immediately to the MRC CTU (within one working day of the investigator becoming aware of the event). The initial SAE report shall be promptly followed by detailed written reports
h. The site has an adequate number of qualified staff and adequate facilities for the foreseen duration of FOCUS4 to conduct the trial properly and safely according to the FOCUS4 Trials Programme protocol
i. All staff assisting with FOCUS4 are adequately informed and trained about the FOCUS4 Trials Programme protocols, the investigational products and their FOCUS4 related duties. Staff will participate in mandatory initial and ongoing training for the FOCUS4 Trials Programme and each trial as required
j. FOCUS4 will be conducted in accordance with the current protocols
k. FOCUS4 will be conducted in compliance with the principles of GCP and all applicable regulatory requirements
l. The site will permit monitoring and auditing by the MRC CTU and inspection by the appropriate regulatory authorities and applicable pharmaceutical companies if required. Direct access will be made available to all trial related sites, data/documents and reports
m. The site will maintain a trial site file, which will contain essential documents for the conduct of the FOCUS4 Trials Programme
n. All FOCUS4 data will be submitted in a timely manner and as described in the protocol. Individual sites may be suspended from recruitment of new patients if data returns are poor or if trial conduct is violated in other ways
o. No trial data on FOCUS4 patients within their site will be disclosed without the approval of the TMG and Trial Steering Committee (TSC)
p. All documents related to the FOCUS4 Trials Programme will be retained for at least 10 years after the completion of the trial
q. The ability to be able to transfer CT scans electronically to other sites if required.

2.2.2 LEVEL 2 SITE INCLUSION CRITERIA

Requirements for a site to participate as a level 2 site in addition to the requirements of a level 1 site:

a. Experience with novel tyrosine kinase inhibitor (TKI) studies in phase 2 studies in the site
b. Willingness to refer patients in the higher risk trials onward to a level 3 site until the therapy is deemed to be sufficiently safe and appropriate for that patient to be treated at their level 2 site. Identification of the most appropriate level 3 site and agreement with that site to accept referrals for FOCUS4
c. Availability of relevant non-oncology specialists with named contacts including ophthalmology, dermatology and any other needed specialty input according to the agent toxicity profile
d. Willingness to accept referrals from level 1 sites.

2.2.3 LEVEL 3 SITE INCLUSION CRITERIA

Requirements for a site to participate as level 3 site includes all the requirements of the level 1 and 2 sites and in addition:

a. Experience of conducting phase 1 and early phase 2 trials including those of novel TKIs
b. Readiness and resource to attend additional monitoring Investigator teleconferences on a fortnightly or monthly basis when the first patients are being dosed
c. Willingness to accept referrals from level 1 and 2 sites.

To participate in the FOCUS4 Trials Programme, investigators and clinical trial sites must also fulfil a set of basic criteria as well as those stated above, which have been agreed by the FOCUS4 TMG and are defined below.

2.2.4 PRINCIPAL INVESTIGATOR'S (PI) QUALIFICATIONS & AGREEMENTS

1. The site PI and all investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC and the regulatory authority.
2. The PI should be thoroughly familiar with the appropriate use of the investigational medicinal product(s) as described in the trial protocols, in the current Investigator Brochures, in the product information and in other information sources provided by the Sponsor.
3. The PI should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.
4. The PI/site should permit monitoring and auditing by the Sponsor, and inspection by the appropriate regulatory authority and if required appropriate pharmaceutical company.
5. The PI should maintain a delegation log of appropriately-qualified persons to whom the PI has delegated significant trial-related duties.
6. The PI should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.2.5 ADEQUATE RESOURCES

1. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (that is, the investigator regularly treats the target population).
2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely. Further resources will be required for level 2 and 3 sites, and will be assessed prior to accreditation.
4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5. The site should have sufficient data management resources to allow prompt data entry to the MRC CTU. Sites that have previously participated in MRC CTU-coordinated trials should have a proven track record of good data return and have adequate facilites and staffing for remote data entry.

2.3 SITE AND INVESTIGATOR EXCLUSION CRITERIA

Lack of any of the inclusion criteria as defined in Section 2.2.

2.4 PATIENT REFERRALS BETWEEN DIFFERENT LEVELS OF SITES

If patients at level 1 sites are eligible and willing to enter a trial which requires level 2 or 3 site responsibility, the patient must be referred to the relevant clinic at the most appropriate level 2 or 3 site. If the patient is ineligible or unwilling to enter a trial which requires level 2 or 3 responsibility, randomisation into the FOCUS4-N Trial can be offered instead. A list of level status of activated sites at any given time may be obtained from the Trial Manager or can be found on the FOCUS4 website. The decision on which Level 2 or 3 site to refer to can be discussed with the patient but where possible it is recommended that existing standard referral pathways are used to ensure efficient referrals between sites.

If the patient from a level 1 or 2 site agrees to referral to a level 2 or 3 site, the level 2 or 3 site will be responsible for final informed consent, randomisation and administration of trial therapy. Full details and assessment schedules can be found in the FOCUS4 trial protocols.

Once a patient has been randomised into a trial, CT scans will be required at 8 week intervals to document disease status, until progression has been documented. Consistency between measurements is of paramount importance in assessing disease progression and therefore, the local investigators must consider the CT scanning facilities in their referral area and ensure that the scanners used throughout the patient's follow-up, provide consistent and comparable measurements. Ideally all CT scans should be performed using the same scanner but some flexibility can exist if different scanners are known to have very similar specifications and scanning protocols and radiologists in all sites can confidently report response according to RECIST version 1.1 criteria.

For all patients referred to a level 2 or 3 site, surveillance should be continued at that site until the therapy is deemed to be sufficiently safe and appropriate for that patient. At this point, their surveillance may revert back to the original level 1 site. Once a trial therapy has been used in sufficient patients, and following central safety review, further patients may be treated in level 1 sites for that novel therapy. This will be explained in detail in each FOCUS4 trial protocol. Information on the current status of FOCUS4 trials will be communicated to sites and can be found on the FOCUS4 website.

2.5 APPROVAL AND ACTIVATION

2.5.1 REQUIRED ACTIVATION DOCUMENTATION

Each selected clinical trial site must complete the required FOCUS4 activation documents prior to accreditation. These are:

- Site evaluation form – this will be used to determine the level of site and may require an evaluation visit to assess facilities and resource. Following this sites will be notified of their category assessment.
- Signed Clinical Trials Agreement between the MRC and the hospital NHS trust.
- Confirmation of favourable ethics opinion (applied for by the MRC CTU). The site must receive a copy of this confirmation for their local site file
- The Clinical Trial Authorisation (CTA) for FOCUS4 requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating site principal investigators. Trial staff at the MRC CTU will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering patients (see below).
- Confirmation of R&D approval for the trial.
- CV of Principal Investigator and co-investigators (or confirmation that these are held on site).
- Signed agreement from Lead Colorectal Pathologist and/or Head of Histopathology Service with contact details of designated secretarial or technical person at each site.
- Signed document by pharmacist to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, accurate traceability of all drugs used in FOCUS4 .
- Normal value(s) and range(s) for medical, laboratory and other technical procedure(s) and test(s) included in the protocol as required.
- Contact details and a signature and delegation log for all FOCUS4 personnel at the site. The MRC CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the trial site file at the site and also at the MRC CTU.
- Investigator statement signed by Principal Investigator at the site. This verifies that the site is willing, and able to comply with the requirements of the trial.
- A copy of the most recent version of the patient information sheets (PIS), GP letter and consent form on local headed paper.

2.5.2 REQUIRED SITE TRAINING

Prior to any site opening to recruitment, each site will also be required to have **at a minimum** a site PI, one research nurse and a pharmacist to participate in FOCUS4 training. This training may be incorporated through attendance of the FOCUS4 Investigator launch meeting, a site initiation visit or participation in an appropriate training teleconference. It will be the responsibility of those who attend the training to disseminate the training to other site personnel.

The training for each site may differ depending on how it has been categorised for treatment administration and there may be further specific requirements for individual trials. If applicable, this will be explained in further detail in the individual trial protocol. If a substantial amendment or new trial is started, the FOCUS4 TMG will determine if further training is required for any new procedures and will notify the applicable sites.

2.5.3 ACTIVATION

Following receipt of the above documents at the MRC CTU and all required training being performed, written confirmation of FOCUS4 activation will be sent to the PI and all relevant site personnel. This will confirm the site's assessment of level, and therefore which trials they are activated to participate in. At activation, sites will also be notified of which central laboratory to send their blocks for biomarker panel assessments. An accreditation pack will be provided to the site containing documents for FOCUS4 when they are activated.

The site pharmacist will also be informed of the site's activation, to which trials they are activated and be sent the pharmacy packs containing required relevant information in regards to initial and subsequent drug orders.

Following substantial amendments and future trials opening, sites will be notifed of relevant documents and training required and if and when they are able to participate. Further accreditation packs may be circulated as a result to update trial documentation.

Following activation to FOCUS4:

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor, the regulatory authority(ies) and the main REC.
2. The PI or delegate should document and explain any deviation from the approved protocol, and communicate this with the trial team at the MRC CTU.

3 SELECTION OF PATIENTS FOR REGISTRATION

3.1 NUMBER OF PATIENTS

FOCUS4 aims to randomise 1536 patients across all molecular cohorts over four years, although the overall sample size is dependent on the staged outcomes in each randomisation. To randomise 1536 patients, it is expected that ~3400 patients will need to be screened for registration into FOCUS4. For sample size calculations, please refer to Section 9.3 or the statistical sections in each trial protocol.

3.2 PATIENT SCREENING AND INFORMATION AND CONSENT PROCEDURE

The process for giving information to patients about this study has a staged approach to reduce the possibility of information overload. A two-step process has been designed and patients will be given a folder with a section for each patient information sheet (PIS) and consent form to be stored.

3.2.1 PATIENT INFORMATION SHEET 1 (PIS1)

This PIS contains information about the nature of the research being considered and the need for further analyses of tumour tissue, with consent for release of an archival tumour block for molecular analyses. This will usually be given at the first consultation with the oncologist when the diagnosis of advanced or metastatic disease has been discussed. However, provision of PIS1 and registration can occur after commencement of standard chemotherapy and up to 12 weeks into the chemotherapy regimen *providing the patient meets all the registration eligibility criteria prior to starting their first-line chemotherapy*. Registration during these first 12 weeks allows a minimum of 4 weeks for biomarker assessment before the 16 week CT scan is performed. If possible, consent should also be obtained at registration for collection of blood samples for additional bowel cancer research but this is optional (see Section 4.6 and question 8 on the Registration Consent Form (CF1)).

Space is provided for the patient to document any questions that they have, and to serve as a reminder to discuss them with the oncologist at their next appointment. Therefore, this first PIS is as simple and minimal as possible whilst providing sufficient information for the patient to give informed consent for registration and release of the tumour block. Once written consent for registration, and eligibility has been confirmed (through completion of the Registration Eligibility Checklist), the patient is registered with the MRC CTU via the MACRO Registration database (for instructions, please refer to the FOCUS4 MACRO EDC guidelines) and a unique registration number is allocated to that patient.

3.2.2 PATIENT INFORMATION SHEET 2 (PIS2)

PIS2 is specific to each trial and contains standard clinical trial information on randomised controlled trials, general issues regarding possible unwanted side-effects and toxicity from

treatment and further details of the potential advantages and disadvantages of the arms between which the patient will be randomised. PIS2 can only be provided when the following results have been obtained:

i) The biomarker panel results are complete and the MRC CTU has informed the site which molecular cohort the patient is from and thus which molecular trial they are eligible for.
ii) An interim CT scan (recommended 8 weeks after the start of first-line chemotherapy) indicating that the patient has stable or responding disease and is therefore more likely to be stable and responding by the 16 week scan.

Once both these results are known, the information and consent procedure for a specific trial can commence and the specific PIS2 for that trial can now be given. If at this stage it becomes clear that the patient does not wish to or will not be able to travel to another site for their treatment or they are not showing enthusiasm for enrolment in their specific molecular trial, then the alternative option of FOCUS4-N must be discussed with the patient and they must be provided with PIS2 for the FOCUS4-N Trial (PIS2-N).

Once the 16 week CT has been performed, if this confirms the patient still has stable or responding disease, the patient can be offered entry into their relevant molecular trial or FOCUS4-N. For patients who did not consent to the collection of a blood sample for other bowel cancer research at registration, they should be asked again if they are prepared to consent to this just prior to randomisation. In addition, the 16 week CT scan can be used to determine whether the patient has sufficient tissue for an optional fresh tumour biopsy. If so, then the patient must be provided with PIS3 for the optional biopsy collection. For patients who agree to this additional procedure, the biopsy consent form (CF3) must be signed and the biopsy will need to be scheduled to take place before any trial treatment is started. The optional biopsies can be consented and performed in all sites.

Patients wishing to receive all information about all the available trials before providing consent for the release of a tumour tissue block, may receive all of the patient information sheets at their first appointment if they wish.

See Figure 3.1 and Figure 3.2 for a flow-chart illustrating the consent process according to site level.

The PIS1 is provided in Appendix I and the CF1 in Appendix II. For PIS2, please refer to the specific trial protocol for each individual trial.

The PI or delegated staff at site must keep a patient screening log of all patients being considered for FOCUS4 registration for the site. A registration log and randomisation log should in addition be maintained for FOCUS4 for patients registered and randomised. Reasons for non-inclusion should be listed in these logs which will be provided to sites at activation.

Figure 3.1: Patient Consent Process for level 3 and level 2 sites where the patients' molecular cohort trial is available

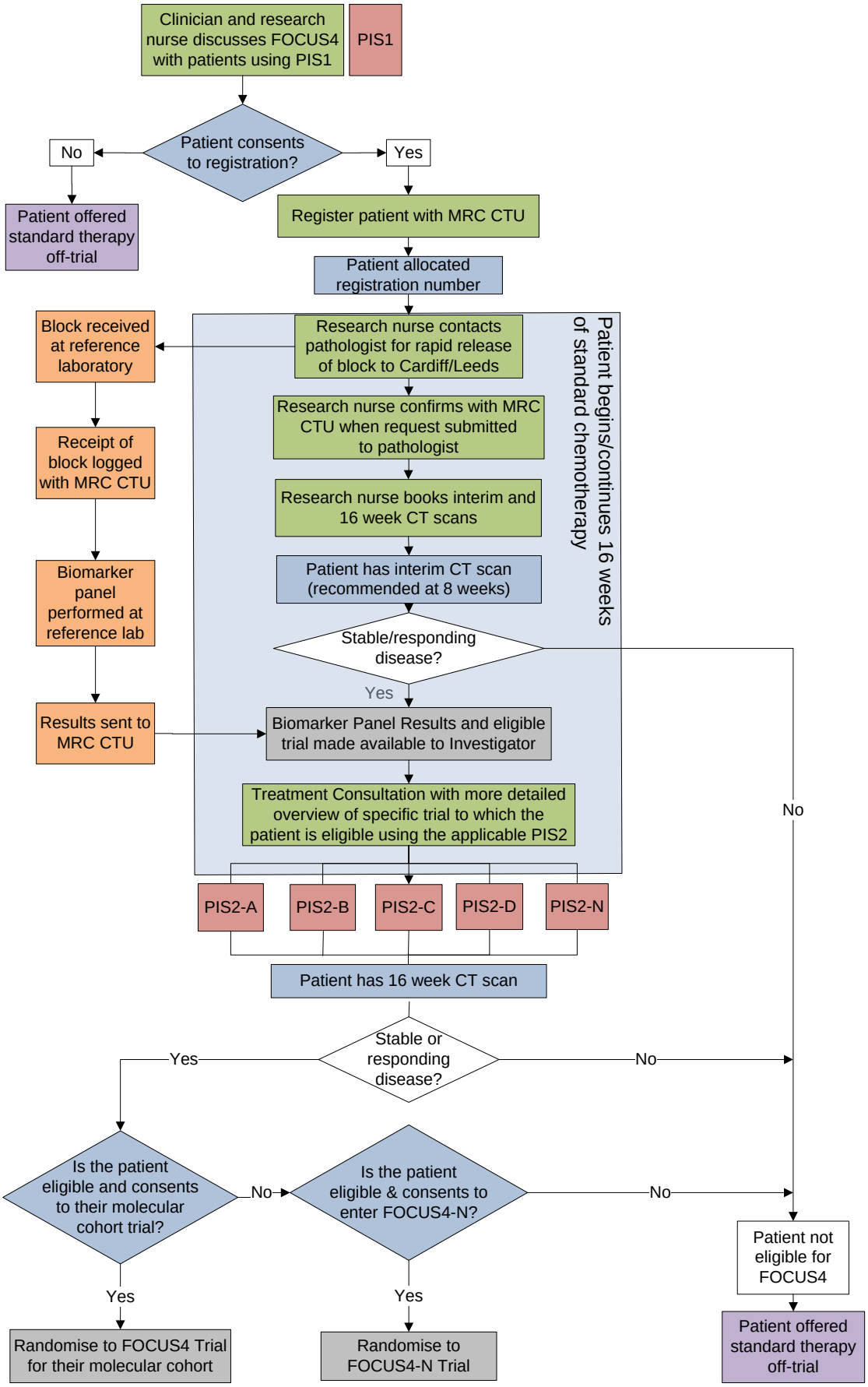
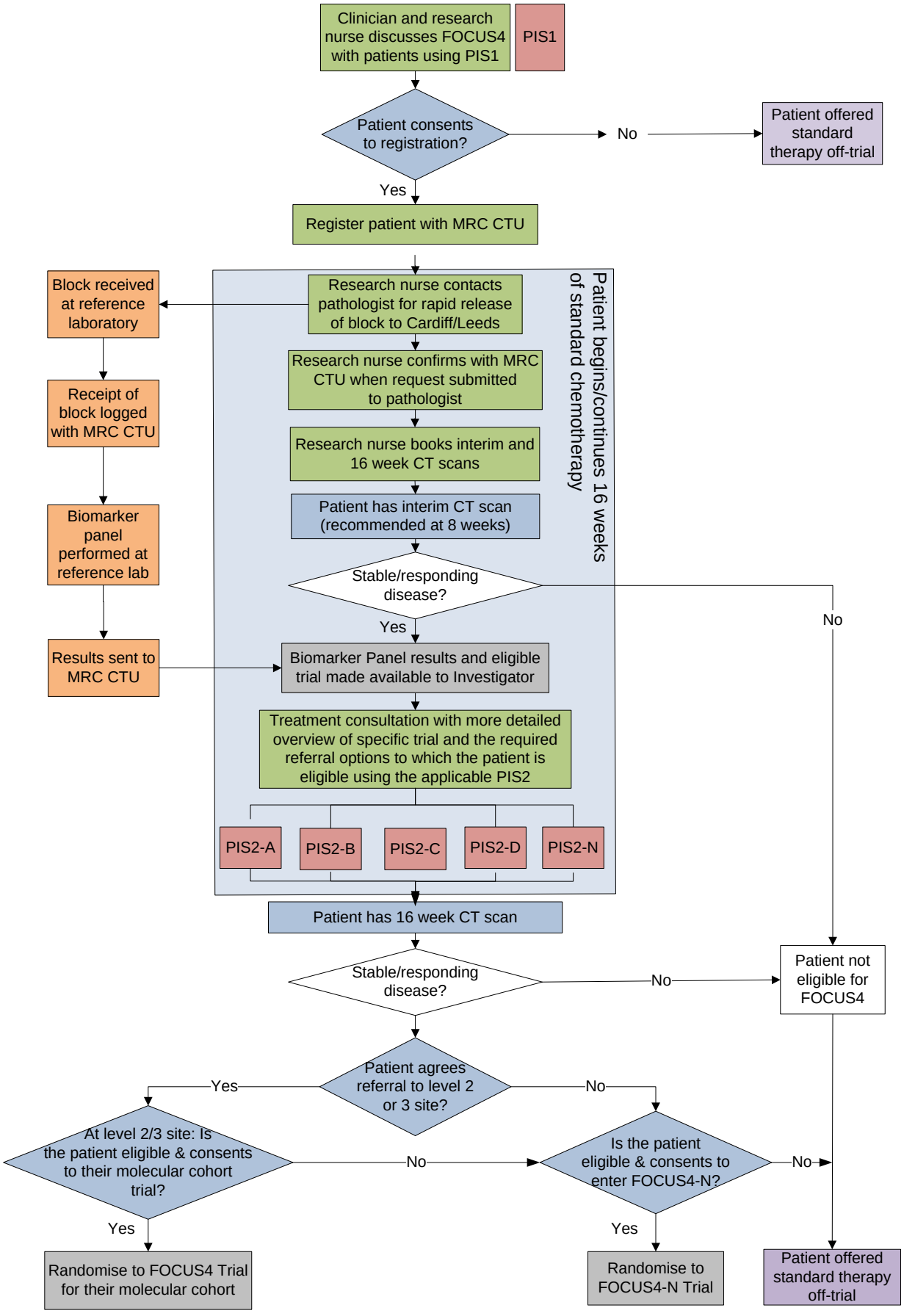


Figure 3.2: Patient Consent Process for level 1 and level 2 sites where the patients' molecular cohort trial is NOT available



3.3 PATIENT INCLUSION AND EXCLUSION CRITERIA FOR REGISTRATION

There will be **no exceptions** or waivers to eligibility requirements at the time of registration or randomisation. Questions about eligibility criteria should be addressed prior to attempting to register or randomise the participant.

The eligibility criteria for both registration and randomisation for the FOCUS4 Trials Programme have been carefully considered. The eligibility criteria are the standards used to ensure that only appropriate patients are considered for this study. Patients not meeting the criteria should not join the Trial. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Participants will be considered eligible for **registration** into FOCUS4 if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below. The Registration Eligbility Checklist should be completed to confirm eligibility and signed by the registering investigator. A copy of the signed form must be submitted to the Trial Team at the MRC CTU.

Please note for each trial, additional randomisation eligibility criteria will exist that will need to be checked if the patient progresses to randomisation. For these please refer to the specific trial protocol.

3.3.1 INCLUSION CRITERIA FOR REGISTRATION

1. Male or female patients at least 18 years old
2. FFPE tumour block taken prior to the commencement of standard chemotherapy and available for biomarker analysis
3. Histologically confirmed adenocarcinoma of the colon or rectum
4. Inoperable metastatic or locoregional disease (synchronous or metachronous)
5. WHO performance status 0, 1 or 2 (see Appendix III)
6. Unidimensionally measurable disease - RECIST 1.1 classification (see Appendix IV)
7. Have had an electronically accessible CT scan performed within 4 weeks prior to commencement of standard chemotherapy
8. Platelet count < 400 x 10^9/L **prior** to commencement of standard chemotherapy
9. For women of child-bearing potential, a negative pregnancy test and acceptable contraceptive precautions (see Appendix V)
10. Effective contraception for male patients if the risk of conception exists (see Appendix V)
11. Consent for screening of an archival FFPE tumour block for biomarker analysis
12. Patients who have already commenced on standard first-line chemotherapy may be registered for the trial during the first 12 weeks of chemotherapy (this allows 4 weeks for return of their biomarker results prior to the end of 16 weeks chemotherapy) providing they fulfilled the other registration eligibility criteria listed above **prior to starting** their standard chemotherapy

13. Patients should have sufficient capacity for informed consent
14. Patient has provided signed informed consent

3.3.2 EXCLUSION CRITERIA FOR REGISTRATION

1. Previous systemic palliative chemotherapy using a different regimen for established advanced or metastatic disease
2. Adjuvant chemotherapy given in the last 6 months
3. Patients with brain metastases
4. Pregnant and lactating women

4 REGISTRATION

4.1 REGISTRATION PROCEDURE

Prior to registration:

- Confirm the potential patient's eligibility with:
    1. History and examination
    2. Assessment of WHO performance status
    3. Assessment of eligibility criteria (see section 3.3)
- Give PIS1 and seek patient's consent for release of tumour block
- Once consent obtained, complete the Registration Eligibility Checklist which must be signed by the registering investigator and a copy submitted the Trial Team at the MRC CTU.
- Register the patient with the MRC CTU via the MACRO Registration database (please refer to FOCUS4 MACRO EDC guidelines)
- Contact pathologist to arrange for the fast-track release of the patient's tumour sample blocks to the laboratory which was assigned at accreditation (Cardiff or Leeds), and compete Biomarker Panel Sample Request Form
- If patient consents to blood sample collection, obtain the required samples as per described in section 4.6

Written informed consent to be registered in FOCUS4 must be obtained from participants, after explanation of the trial and before any trial specific procedures or any blood is taken for the trial.

It must be completely and unambigiously clear that the participant is free to refuse to participate in all or any aspect of FOCUS4, at any time and for any reason, without incurring any penalty or affecting their treatment.

At registration with the MRC CTU, a registration number will be issued. This registration number will be used to identify tumour blocks sent to the designated reference laboratory. The patient's date of birth should also be used to cross-reference the sample. No treatment or trial allocation will be performed at this point. The registration number will be a unique identifier and the primary way in which the patient will be identified and should be used in all correspondence throughout the registration and subsequent trial periods.

The original signed registration consent forms (CF1) must be kept in the investigator site file and 4 copies are made; one copy for the participant or family, one copy for the hospital notes, one copy for sending to the local pathology lab for block release and one copy to be sent to the MRC CTU for central monitoring purposes. The MRC CTU copy will be destroyed once it has been checked for correct completion.

4.2 TUMOUR BLOCK REQUEST, DISPATCH AND TRACKING PROCEDURE AFTER REGISTRATION

All patients who consent to registration in FOCUS4 require prospective testing of (as a minimum) the BRAF, PIK3CA, KRAS, NRAS, mis-match repair (MMR), PTEN immunohistochemistry (IHC) and EREG mRNA status of their primary tumour to determine their eligibility for randomisation within the FOCUS4 Trials Programme.

Receipt of these samples in an appropriate timeframe is a rate-limiting step in starting the patient's treatment within the trial so **it is very important** these blocks are sent to the designated central laboratory as soon as possible. Therefore tumour blocks will be tracked from time of patient registration to the time of patient randomisation or refusal/ineligibilty to enter a trial. All template documents will be supplied to sites at activation.

The sample handling and tracking process is as follows (please note sites will be informed if there are any changes to these procedures):

Research Nurse

- Once consent for tissue block release has been obtained and the patient has been registered with the MRC CTU, the research nurse will complete the first section of the Biomarker Panel Sample Request form.
- The Research Nurse should then immediately request the release of the block. This is performed by contacting their local pathology department contact and sending them a copy of the patient registration consent form and the completed Biomarker Panel Sample Request Form with the patient registration number.
- The Research Nurse will confirm with the MRC CTU that this request has been placed by faxing (to 020 670 4653) the completed Biomarker Panel Sample Request Form. A copy of the patient registration consent form must be sent via post to the MRC CTU (as described in section 4.1).

Local Pathologist

- The Local Pathologist must then complete the second section of the Biomarker Panel Request Form and identify the FFPE tumour block containing the **maximum quantity of viable tumour** for the patient. This block should be anonymised and should only include the FOCUS4 registration number and date of birth.
  Please note: If the patient has consented to future research using their tumour block, any further analyses will also be performed anonymously.
- The anonymised FFPE block should be sent by the pathologist or delegated staff member along with the completed Biomarker Panel Request Form and a copy of the anomymised histology report to the assigned central laboratory (as allocated at activation) immediately by First Class post.

- The Local Pathologist or delegated staff member should also fax the Biomarker Panel Sample Request Form to MRC CTU (to 020 7670 4653) in order to act as notification that the sample was sent to the designated central laboratory (Cardiff or Leeds).
- The Local Pathologist **must** keep a copy of this form for their records.

Central Laboratory

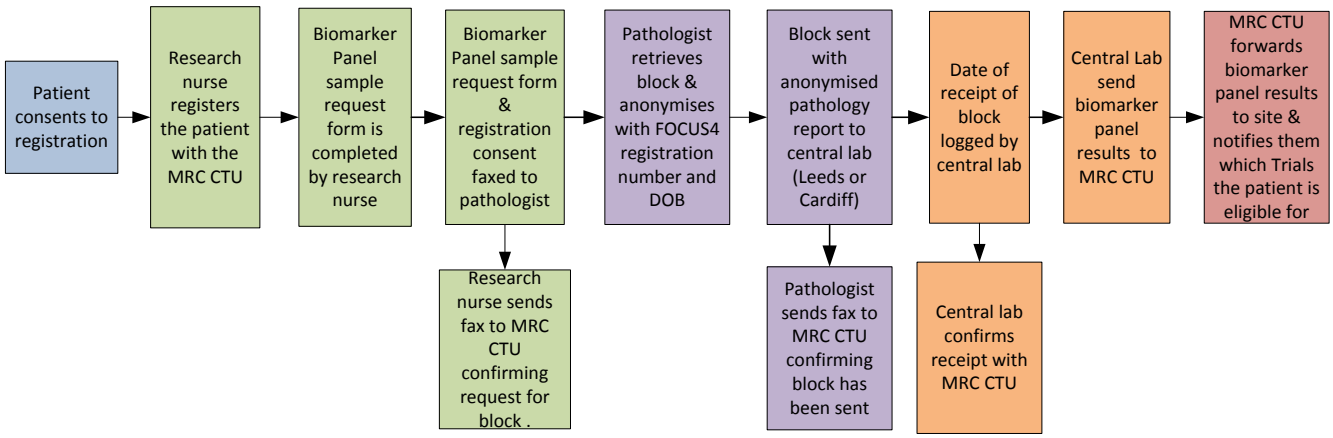
- When the block arrives at the central laboratory, their staff will inform the MRC CTU of receipt.
    - If the block has not arrived at the central laboratory within one week after registration, MRC CTU staff will contact the local pathology department and/or research nurse to establish the whereabouts of the block and rectify the situation.
- Once the biomarker panel results are available, staff at the central laboratories will inform the MRC CTU.

MRC CTU

- Upon receipt of the biomarker panel results, the MRC CTU will contact the research nurse at the relevant site and notify them which trial the patient is eligible for. A notification of the results will also be sent to the patient's clinician and pathologist for their information.

Figure 4.1 summarises the process of tracking tumour blocks.

Figure 4.1: Tumour Sample Block Request Process



All blocks will be returned at the end of the trial but the central laboratories will undertake to return the blocks at short notice if these are required for patient management.

A detailed laboratory manual has been prepared by Cardiff and Leeds laboratories. This can be supplied to your pathology department on request.

4.3 MOLECULAR TESTS RESULTS

The reference laboratories will perform a biomarker panel assessment on the FFPE tumour tissue submitted including assessment of:

- Mutations in BRAF, PIK3CA, KRAS and NRAS
- mRNA expression for epiregulin
- IHC for PTEN and MMR proteins

The results of these tests will be returned to the MRC CTU who will determine which trial the patient is eligible for. The site will be informed and the individual patients will be offered entry into the relevant trial according to the trial schema (see page v). Further details of the biomarker analyses are in the laboratory manual which is available on request from the MRC CTU.

4.3.1 FAILURE OF MOLECULAR TESTS

If the molecular tests fail completely (as occurred in 2% of instances in FOCUS 3), these patients will be offered entry into the FOCUS4-N Trial. If one or more biomarker tests fail but sufficient data have been obtained for the other biomarker tests, the MRC CTU will allocate the specific trial the patient should be offered.

4.4 CT SCAN ASSESSMENTS DURING REGISTRATION PERIOD

- The patient **must** have measurable disease by RECIST v1.1 criteria.
- CT scans must be performed:
    1. Within 4 weeks prior to the commencement of first-line chemotherapy
    2. At an interim time during the chemotherapy (recommended 8 weeks into chemotherapy) to see if the patient is responding to chemotherapy
    3. At 16 weeks to evaluate the progress of the patient's response to 16 week's first-line chemotherapy

  For those patients registered after initiation of first-line chemotherapy, during the first 12 weeks, it is required that CT scanning was undertaken within 4 weeks prior to starting first-line chemotherapy and the scan is accessible for review.
- For a patient to be eligible for randomisation they must have documented measurable disease (RECIST criteria, Appendix IV) stating SD, PR or CR after 16 weeks first-line chemotherapy. This scan must be **within 4 weeks prior to randomisation.**

IMPORTANT NOTE: The FOCUS4 trials are investigating efficacy in terms of repeated measurements from CT scans. Therefore the local investigators must consider the CT scanning facilities in their referral area and ensure that the scanners used throughout the patient's follow-up, provide consistent and comparable measurements. Ideally all CT scans should be performed using the same scanner but some flexibility can exist if different scanners are known to have very

similar specifications and scanning protocols and radiologists in all sites can confidently report response according to RECIST criteria.

4.5 PRIOR TO RANDOMISATION

- The specific trial for which the patient is eligible will be known when the biomarker panel results have been obtained. Once the 16 week CT scan has confirmed stable or responding disease, the trial inclusion and exclusion criteria must be checked for their allocated specific trial (please refer to the specific trial protocol for the criteria).
- If not already given earlier (for example following receipt of the biomarker panel results and interim CT scan RECIST assessment), the patient must be provided with PIS2 for that specfic trial. An explanation of the aims, methods, benefits and potential hazards of their specific trial must be discussed with the patient by the responsible treating clinician. The FOCUS4-N trial can be discussed as a back up or alternative trial option depending on the attitude of the patient and carer on the issues related to travel, potential toxicity or any other factors of relevance.
- At this stage, it is possible that the patient will need to be referred to a level 2 or 3 site for their treatment. A list of appropriate, activated sites for that trial at any given time may be obtained from the Trial Manager or will be available on the FOCUS4 website. This referral must be arranged promptly to facilitate a smooth transition between the end of the 16 weeks of chemotherapy and the start of the patient's randomised treatment.
- Consent for randomisation should occur at the site where the patient will receive trial treatment until the therapy is deemed to be sufficiently safe and appropriate for that patient. For all randomisation procedures and assessments please refer to each trial protocol which describes the specifics that are required.
- For patients who did not consent to the collection of a blood sample for other bowel cancer research at registration, they should be asked again if they are prepared to consent to this (see question 6 on consent forms for each trial).
- An End Of Registration form must be completed for **all registered patients** and submitted to the MRC CTU regardless of whether they are to be randomised.

Please note there is a wash out period of 3 weeks between the end of standard chemotherapy and commencement of randomised protocol treatment. This is a mandatory safety issue prior to use of novel investigational agents. Please refer to each trial protocol for specific trial details.

4.6 OPTIONAL BLOOD SAMPLES AND BIOPSY COLLECTION FOR BOWEL CANCER RESEARCH

Blood sample collection for further bowel cancer research is a recommended but optional sub-study that patients may consent to on question 8 of CF1 (see Appendix II) and on question 6 of each trial consent form (CF2). Two types of blood sample will be collected:

- One sample is for extraction of germline DNA for pharmacogenomic analysis and for comparative analysis of any genome wide analyses of tumour samples performed. The aim it to collect this from all consenting patients at registration.
- Serial samples will also be collected for analysis of circulating free tumour DNA in sites where rapid centrifugation is possible.

4.6.1 BLOOD SAMPLE FOR GENOMIC DNA

This sample can be taken at any time at or following registration to FOCUS4. A 20mL EDTA tube, labelled with the date and patient's registation trial number and initials. It is recommended that this sample is taken at the same time as the routine bloods if possible so that participants do not have to undergo additional venepunctures and as soon after registration as is convenient.

Samples must be sent immediately to the address below using the pre-paid safe boxes provided by the MRC CTU to sites at activation. In order to ensure the blood sample does not arrive at the laboratory over a weekend, the blood sample should be taken **Monday – Thursday**.

FOCUS4
All Wales Genetics Laboratory
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff CF14 4XW

4.6.2 BLOOD SAMPLE FOR CIRCULATING DNA

Blood samples for circulating DNA need to be taken more than once and should be collected for at least timepoints 1), 2) and 4) below and for as many 8 week timepoints as possible during the course of a patient's involvement with FOCUS4:

1) At registration into FOCUS4
2) Following consent to trial randomisation and before commencement of any FOCUS4 trial treatments
3) At each 8 week clinic visit just before or after the CT scan
4) On disease progression at any time during the registration or trial periods

In sites where rapid centrifuge, plasma extraction and freezing are possible a 10 ml blood sample will be taken directly into an EDTA tube. It is recommended that this sample is taken at the same time as the routine bloods if possible so that participants do not have to undergo additional venipuncture. Where this is not feasible, there may be the possibility of utilising specialised storage tubes (STRECK tubes). Frozen samples can be batched and sent frozen to the address below. Samples must be sent immediately to the address below using the pre-paid safe boxes provided by the MRC CTU to sites at activation. In order to ensure the blood sample does not arrive at the laboratory over a weekend, the blood sample should be taken **Monday – Thursday**.

FOCUS4
All Wales Genetics Laboratory
Institute of Medical Genetics
University Hospital of Wales
Heath Park
Cardiff, CF14 4XW

The protocol for handling these samples is included in the laboratory manual which is available on request.

4.6.3 BIOPSY COLLECTION

In order to investigate the critically important issue of tumour heterogeneity and its relation to responsiveness to therapy, in FOCUS4, a biopsy of accessible metastatic (or unresected primary) sites prior to randomisation and on progression is to be requested by the patient's oncology consultant or the PI at the referral level 2 or 3 centre. Investigators should review the clinical data and 16 week CT scan taken at the end of first-line chemotherapy to evaluate whether the patient has accessible tumour either by colonoscopy or per-cutaneous biopsy. Patients whose tumour is accessible to biopsy and who have consented to randomisation in one of the FOCUS4 trials should be offered this opportunity to participate in this further aspect of the trial. Such patients should be given the tumour biopsy patient information sheet about biopsy procedures following consent to be randomised in one of the FOCUS4 trials. If the patient gives consent to such a biopsy and the tumour can be safely biopsied, then a trucut, core or colonoscopic biopsy should be arranged prior to the start of trial medication for research purposes only. A repeat biopsy for these patients should also be sought at the time of tumour progression, if the patient remains fit enough for the procedure.

Patients will require standard preparation for such biopsies according to local protocols with assessment of platelet count, clotting screen and serum grouped and saved in case of need for cross matching for blood transfusion. Please see Appendix VII for the biopsy PIS (PIS3) and Appendix VIII for the biopsy consent form (CF3). Details on sample handling and curation can be found in the Laboratory user manual.

4.7 CO-ENROLMENT GUIDELINES

Patients may also be considered for entry into other clinical trials outside FOCUS4 in the following situations:

- Trials that address questions in the first 16 weeks of chemotherapy, which do not interfere with the FOCUS4 Trials Programme. This could include trials investigating surgical resection, if patients have residual measurable and non-progressive disease and have received 16 weeks chemotherapy, they would be potentially still eligible for FOCUS4. However, entry into clinical trials during first-line chemotherapy are likely to be incompatible with FOCUS4 as they may require longer durations of therapy than 16 weeks.

- Patients whose disease progressed during the 16 weeks of first-line chemotherapy are not eligible for the FOCUS4 trials, but might be appropriate candidates for other trials. The FOCUS4 TMG is keen to support such activity and would ask investigators with such proposals to discuss them with the TMG to enable optimal collaboration on such studies.
- Trials after completion of FOCUS4 treatment are also permissible, providing data related to further treatment on such studies is recorded on the FOCUS4 CRFs.

4.8 REGISTERED PATIENTS WHO DO NOT CONSENT TO RANDOMISATION

Patients may register into FOCUS4 but then decide not to consent to any FOCUS4 randomisations. The FOCUS4 TMG are interested in finding out the reasons for non-consent to the trial and this will be documented on the End Of Registration CRF. Data from molecular analyses of these patients' specimens will still be of scientific value, so at the time of non-consent, please confirm with the patient that they have or have not rescinded their consent for such studies.

5 TREATMENT OF PATIENTS DURING REGISTRATION

5.1 STANDARD CHEMOTHERAPY

No treatment or intervention is under scrutiny during the registration period of FOCUS4. Details of the treatments in each of the subsequent randomised trials stratified by molecular subgroup will be described in the relevant trial protocol (see Trial schema on page v).

During the registration period, the choice of standard chemotherapy is at the discretion of the local clinician. The planned duration of this treatment should be as near 16 weeks of treatment as possible with a window of ±2 weeks (14-18 weeks permissible). Time from first treatment to end of treatment may exceed 18 weeks up to a maximum of 20 weeks to accommodate treatment delays for resolution of toxicity. If the delay is due to a planned resection procedure and as a result treatment duration extends beyond 20 weeks, please contact the MRC CTU for advice on whether the patients is eligible for any of the trials.

Standard chemotherapy regimens that are acceptable in the first 16 weeks treatment include the following:

- FOLFOX (OxMdG)
- XELOX
- FOLFIRI (IrMdG)
- Irinotecan plus capecitabine
- Infusional 5FU plus folinic acid (MdG)
- Capecitabine
- Biological agents that are acceptable in addition to any of the chemotherapy regimens above include the following:
  - Bevacizumab
  - Cetuximab (please note that if used, the patient will not be eligible for FOCUS4-D)
  - Panitumumab (please note that if used, the patient will not be eligible for FOCUS4-D)

If the standard chemotherapy or biological agent planned is not listed above, please contact the MRC CTU to confirm use **prior** to administration.

Patients with liver only metastases and who are being treated with the intention of being made operable, but in whom the operation is subsequently considered inappropriate or is unsuccessful, may be eligible for FOCUS4 if they otherwise fulfil the entry criteria including the timelines for assessment.

Patients having resection, radioembolisation or other liver-directed therapy of liver predominant disease in whom there is remaining measurable extrahepatic disease may be entered into FOCUS4 if they otherwise fulfil all the entry criteria.

Entry into other clinical trials during first-line therapy are likely to be incompatible with FOCUS4 as they will require longer duration of therapy than 16 weeks. Please refer to section 4.7.

There must be a wash-out period of 3 weeks between end of 16 weeks first-line chemotherapy and start of allocated FOCUS4 trial therapies.

5.2 REGISTRATION DISCONTINUATION

As the patient's participation in the registration period is entirely voluntary, they may choose to discontinue their first-line chemotherapy or involvement with FOCUS4 without penalty. Although the patient is not required to give a reason for discontinuing their involvement with FOCUS4, where possible it should be documented on the End Of Registration CRF for all patients, while fully respecting their rights.

5.3 COMPLIANCE & ADHERENCE

During registration, compliance and adherence of the first-line chemotherapy will be monitored and recorded on the End Of Registration form.

5.4 REGISTRATION DATA COLLECTION

Minimal data will be collected at trial registration. Data on the type of systemic therapy used during the 16 weeks of registration will be collected and used as a stratification variable in the minimisation procedure for any subsequent trial. This will be recorded on the End Of Registration CRF along with CT assessment according to RECIST criteria of the 16 week scan, prior to randomisation into one of the available trials.

5.5 ACCOUNTABILITY & UNUSED DRUGS

No special accountability arrangements are required for the commercial stock used in the registration period of FOCUS4.

All information on accountability and unused drugs after randomisation can be found in each of the FOCUS4 Trial Protocols as specific to each trial and the trial therapies.

5.6 UNBLINDING

There is no blinding during the registration period. For specific unblinding procedures in each trial, please refer to the relevant trial protool.

5.7 OVERDOSE OF TRIAL MEDICATION

No specific data are required on overdose during the registration period as no trial medication is being tested during this time. Information on overdose of medication in any of the FOCUS4 trials is provided in the relevant trial protocol specific to its medication.

6 ASSESSMENTS DURING REGISTRATION PERIOD

6.1 ASSESSMENT SCHEDULE FOR REGISTRATION PERIOD

Figure 6.1: Registration Period GANTT Chart (the grey shading provides a guide to when each task may be performed but some flexibility exists around these timelines)

(This is also provided in in the Summary on page vii)

Registration period → **Trial period (see trial protocol)** →

WEEK	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
First-line chemotherapy#																					
Check registration eligibility criteria Δ																					
PIS1Δ																					
RegistrationΔ																					
Biomarker sample sent Δ																					
CT scan §																					
RECIST response																					
PIS2 ∞																					
Check specific trial eligibility criteria																					
Baseline assessment †																					
Wash out from first-line chemo‡																					
Randomisation¥																					
*Optional Assessments**																					
***Blood (Genomic DNA) **																					
***Blood (Circulating DNA) **																					
***Tumour biopsy **																					

Key to symbols

*Regime determined locally for 16 treatment weeks (± 2 weeks) but overall time from start of treatment to end of last cycle of up to 20 weeks is acceptable. Beyond 20 weeks, please contact the MRC CTU office to determine whether the patient is eligible for any of the trials.*

Δ *PIS1, registration and biomarker sample can be completed at any time up to weeks 1-12 of the 16 weeks of first-line chemotherapy*

§ *Mandatory CT scan within 4 weeks prior to standard chemotherapy, recommended interim CT scan after 8 weeks chemotherapy; mandatory CT scan after 16 weeks chemotherapy*

∞ *PIS2 can be given when biomarker result is known and interim CT scan shows SD, PR or CR*

† *Baseline assessments must be done within 1 week prior to randomisation – see specific trial protocol for list of tests required.*

‡ *Wash out period of 3 weeks between end of 16 weeks first-line chemotherapy and start of allocated trial therapy*

¥ *Randomisation must be within 4 weeks of 16 week CT scan*

*** *Not required if patient has withheld consent for molecular research tumour biopsy or there is no tumour accessible for percutaneous biopsy*

6.1.1 CASE REPORT FORM (CRF) RETURN TIMELINES

- A **Registration Form** should be completed prior to registration and submitted immediately to the MRC CTU.
- An **End Of Registration Form** must be completed for all patients at the end of their registration period regardless of whether they are entered into a subsequent randomised trial. This must be sent as soon as the decision has been made on whether the patient wishes to enter a specific FOCUS4 trial. This must be completed and submitted to the MRC CTU prior to any randomisation.
- For patients being randomised into a specific FOCUS4 trial, the **Randomisation Form** should be completed before the patient is randomised. Forms must be submitted immediately afterwards. These specific procedures are documented in the specific trial protocols.

6.2 PROCEDURES FOR ASSESSING EFFICACY

Efficacy is not being assessed during the registration phase but CT scans will be used to determine whether the patient receives clinical benefit from first-line chemotherapy. See Section 4.4 for when the CT scans need to be performed during the registration period. Once a patient enters a specific trial, they will have a CT scan every 8 weeks until their cancer progresses. However this is trial-specific and therefore please refer to the specific trial protocol for further details.

IMPORTANT NOTE: The FOCUS4 trials are investigating efficacy in terms of repeated measurements from CT scans. Therefore the local investigators must consider the CT scanning facilities in their area and ensure that the scanners used throughout the patient's follow-up, provide consistent and comparable measurements. Ideally all CT scans should be performed using the same scanner but some flexibility can exist if different scanners are known to have very similar specifications and scanning protocols and radiologists in all sites can confidently report response according to RECIST criteria.

6.3 PROCEDURES FOR ASSESSING SAFETY

Safety reporting is not required during the registration period of FOCUS4. Full safety reporting is required for each trial and details are provided in each trial protocol.

6.4 PROCEDURES FOR ASSESSING QUALITY OF LIFE

There will be no assessment of quality of life (QL) during the registration period. Details for collection of QL data for each trial are provided in the specific trial protocol.

6.5 EARLY STOPPING OF FOLLOW UP DURING THE REGISTRATION PERIOD

During the registration period patients may chose not to continue being involved in FOCUS4. This might include a wish to stop their first-line chemotherapy or to not receive the results of their

biomarker panel results. If this type of early stopping of follow up occurs, it must be documented on the End Of Registration CRF.

These patients should be encouraged to allow use of their data in terms of the following:

- Consent to use the data already collected during the registration period
- Consent to use the stored samples for other research
- Consent to flag the patients at the NHS Information Centre or similar approaches

If a patient would like to withdraw their consent to any of the above aspects, it must be documented on the Early stopping of follow up CRF.

6.6 PATIENT REFERRAL FOR RANDOMISATION

If a site is not open to a specific FOCUS4 trial due to their level of site categorisation, patients may be referred to another participating site to allow them to be treated on that specific trial. PIS2 may be given by the original site to allow maximum possible time to consider participation. However patients **must** be consented and randomised to the trial at the site where they will receive treatment.

After randomisation, when it is deemed safe or following completion of treatment, the patient may be referred back from the treatment site to the original site. A copy of the patient's CRFs should be provided to the orignial site and the patient will need to sign a new consent form with the original hospital headed paper. Once this has been done, the original site will take over responsibility for the patient's participation in FOCUS4. Until this has been done, responsibility for the patient's participation in FOCUS4 lies with the treatment site.

If a patient moves from the area, every effort should be made for the patient to be seen at another participating trial site. The patient's CRFs must be transferred to the new site and the patient will need to sign a new consent form with the new hospital headed paper. Once this has been done, the new site will take over responsibility for the patient's participation in FOCUS4. Until this has been done, responsibility for the patient's participation in FOCUS4 lies with the original site.

6.7 LOSS TO FOLLOW-UP

Where contact with the patient has been lost during the registration period, every effort should be made to complete the End Of Registration CRF. If the care of the patient is returned to the General Practitioner, it is still the responsibility of the investigator to ensure that the End Of Registration CRF is completed as fully as possible. If this is not possible then the patient is deemed lost to follow up and this should be documented on the End Of Registration CRF.

6.8 ASSESSMENTS AT TRIAL CLOSURE

The FOCUS4 Trials Programme will be considered closed 5 years after recruitment has been completed **and** survival data have been published. However a further non-interventional period of follow-up may occur following publication, initially via the hospital, but in the longer term may employ national registers.

7 SAFETY REPORTING

Reporting of adverse events or reactions is not required during the registration phase of FOCUS4 as standard chemotherapy is not being evaluated. Once a patient enters a randomised trial, full safety reporting is required.

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are summarised in detail in each trial protocol.

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations will be based on a formal Risk Assessment, which will acknowledge the risks associated with conduct during the registration period and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of ICH GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the registration-related activities are fulfilled. Each Risk Assessment will be reviewed by the Research Governance Committee (RGC) within the MRC CTU and this will be used to develop the Data Management and Monitoring plans, which will be kept separately. Please see each trial protocol for any specific details of its risk assessment.

8.2 CENTRAL MONITORING AT MRC CTU

Essential FOCUS4 Trials Programme issues, events and outputs will be detailed in the Data Management and Monitoring Plans. MRC CTU staff will check CRFs data for errors, inconsistencies and missing data.

8.3 ON-SITE MONITORING

The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan. This plan will also detail the procedures for review and sign-off. Further specifics for each trial will be documented in the relevant protocol.

8.3.1 DIRECT ACCESS TO PATIENT RECORDS

Participating investigators should agree to allow monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patients' consent for this is obtained as part of the patient consent process.

8.3.2 CONFIDENTIALITY

FOCUS4 plans to follow the principles of the UK Data Protection Act.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

No randomisation will occur until the end of the Registration Period. At this point, patients will be stratified into a biomarker-defined cohort and offered entry into the trial for that cohort. Within each molecular trial, patients will be randomised either to a placebo or to a new targeted agent (or targeted combination) specific to their biomarker cohort. The specific ratio to be used in each trial will be defined and justified within each trial protocol. Where possible, to maximise information on novel agents, a 2:1 randomisation ratio in favour of the novel agents will be selected, and is used in the illustrative sample size calculations in Table 9.3. For the FOCUS4-N Trial, patients will be randomised to either capecitabine or treatment break using a 1:1 ratio, as capecitabine is an established drug with known safety profile and 1:1 randomisation will maximise power for this comparison.

Each trial protocol will specify the active treatment arm(s) and allocation ratio and will generally be double-blind (apart from FOCUS4-N) with neither the patient nor the clinician aware of the patient's allocation to active or control arm. Randomisation must occur within 4 weeks of the CT scan confirming (at least) stable disease after 16 weeks of conventional chemotherapy.

All randomisations will be performed using the central randomisation service at the MRC CTU. Patients will be allocated their treatment using the method of minimisation with a random element. Minimisation will be stratified by a number of factors known to be prognostic of outcome as well as the regime used during the 16 weeks of first-line chemotherapy. A global list of minimisation factors will be agreed for all trials and some trial-specific factors will be added as necessary, eg. the FOCUS4-N trial will stratify on the biomarker profile of patients for those who choose not to go into their selected molecular trial. The agreed list of minimisation factors will be clearly specified in the statistical analysis plan.

A minimisation-based method has been selected over the more standard approach of stratified permuted block allocation to allow flexibility during the course of the trial in terms of changing minimisation factors and changing arms and biomarkers as well as helping to ensure balance for small sample sizes. After any alteration of minimisation factors, subsequent analyses would be stratified by time, before and after such a change. Providing patients are enroled at centres at random there is little risk of bias or inferiority to conventional randomisation methods.

9.2 OUTCOME MEASURES

9.2.1 PRIMARY OUTCOME

The primary outcome for all FOCUS4 Trials is progression-free survival (PFS), defined as the time to first recorded disease progression or to death from any cause, measured from the time of randomisation. Each trial utilises the Multi-Arm Multi-Stage (MAMS) trial design[9 10] with staged intermediate analyses reviewed by the Independent Data Monitoring Committee (IDMC). The first two of these analyses will be equivalent to a conventional phase 2 study to assess safety (Stage I) and lack-of-sufficient-activity (Stage II). At this point, results from Stages I and II may be released outside the IDMC and on the basis of the findings, the trial will either stop accrual or progress to continued recruitment to assess efficacy for PFS (Stage III) and, possibly, efficacy for OS (Stage IV) a potential additional primary outcome. Continuation to further accrual in these additional stages, which will be equivalent to a conventional phase 3 study, will depend on the strength of effect (MAMS-defined critical HRs) seen at the end of Stages I and II and the availability of resources to achieve adequate recruitment and follow-up, including the necessary commitment of supply of the novel agent(s).

9.2.2 SECONDARY OUTCOMES

Secondary outcomes for the trial will include evaluation of disease control, safety and toxicity starting from time of randomisation. Progression of disease will be determined using CT scans prior to randomisation and then at 8-week intervals. Safety and toxicity will be assessed at 2, 4 or 8-week intervals from the start of each trial (depending on the trial agent) as may be recommended by the TMG. Safety will be evaluated using full reporting of adverse events and reactions as described in section 7 of each protocol and the frequency of assessments may vary from trial to trial. Toxicity will be evaluated according to the risk profile for each novel agent. If necessary, additional specific safety and toxicity outcomes will be determined for each trial separately.

Quality of Life (QL) data, measured by EuroQol-5D, will only be assessed in any novel agent trial that continues into Stages III or IV. However, QL data may be collected at earlier stages if it is deemed to be important for that specific trial. QL will be assessed in all patients throughout FOCUS4-N from randomisation onwards.

9.3 SAMPLE SIZE

This will be a multi-centre trial open to all oncology centres with the appropriate experience of colorectal cancer trials in the UK. If necessary and achievable, international involvement will be considered at a later stage. The TMG has established specific site accreditation rules for both recruitment and treatment sites (see Section 2 for site eligibility) and it is expected that approximately 100 sites will participate in the trial, although not all will be eligible for administration of all treatments. All sites will be able to administer treatment for patients who enter FOCUS4-N and all sites will be able to refer patients to sites eligible for administration of novel agents.

For each biomarker-defined cohort, the assumptions for the sample size calculations are based upon the following :

- The recruitment rate for the COIN Trial, a previous trial of similar patients.
- The proportion of patients classified into each molecular cohort based upon data from COIN, COIN-B and the FOCUS 3 feasibility study.
- The survival estimates are based upon published and unpublished data taken from the COIN Trial.

9.3.1 ANTICIPATED RECRUITMENT RATE FOR EACH MOLECULAR COHORT

The COIN Trial recruited 2,445 patients over 38 months, four months ahead of schedule: an average rate of 60 patients per month. FOCUS 3 tested the feasibility of recruiting patients according to their biomarker panel classification and also managed to complete accrual on schedule by April 2011. For FOCUS4, we have assumed 70 patients will be screened for registration per month when all sites are open. Of these, it is anticipated that 32 will be eligible and consent to randomisation across all cohorts. Reasons for eligibility for randomisation are as follows:

- 72% are expected to have normal platelets → 50 patients per month;
- 90% of these will have stable or responding disease by their interim CT → 45 patients per month;
- 80% of these should have stable or responding disease by 16 weeks → 36 patients per month;
- 88% of these are likely to accept randomisation → 32 patients per month randomised.

See Table 9.1 below which provides estimates for the total number of patients recruited over four or five years. From the biomarker panel results seen in COIN and FOCUS 3, the proportion of patients expected to fall into the four molecular cohorts are also given. In this classification, there is a defined sequence of biomarker hierarchy that determines which cohort a given patient will enter. Thus, for example, and assuming all trials are open to accrual, a patient with BRAF mutation will always be placed in the BRAF cohort (regardless of PIK3CA, PTEN or KRAS/NRAS status), and a patient with PIK3CA mutation will always be placed in PIK3CA cohort (regardless of KRAS/NRAS status).

Table 9.1: Anticipated accrual for screening and randomisation across cohorts

		70 screened patients per month		
Molecular cohort	**Prevalence**	**Randomised patients/mth**	**Total over 4 years**	**Total over 5 years**
Total	**100%**	**32**	**1536**	**1920**
BRAF mutation	8%	2.6	125	156
PIK3CA mutation and/or PTEN loss	30%	9.6	461	576
KRAS or NRAS mutation	33%	10.6	509	636
EGFR dependent	27%	8.6	413	516
Unclassified	2%	0.6	28	36

9.3.2 PROPOSED SAMPLE SIZE FOR EACH MOLECULAR COHORT

All sample size calculations were performed using the nstage program in Stata Version 12.0 which uses a MAMS design incorporating multiple interim analyses for safety, lack-of-sufficient-activity (LSA) and efficacy. This allows non-beneficial comparisons to be identified and halted as soon as possible, with minimal risk of prematurely stopping beneficial comparisons by chance. To achieve this, the alpha value is set initially high (one-sided α=0.30) and is thereafter progressively lowered such that the final efficacy analyses use values of a similar magnitude to conventional statistical tests. Within each biomarker-defined trial (for each active agent vs. placebo comparison) there are four analysis stages: safety (Stage I), lack-of-sufficient-activity (Stage II), efficacy for PFS (Stage III) and efficacy for OS (Stage IV). Interim results from each stage will be reviewed by the IDMC to guide their recommendations for early termination or continuation of a trial. In addition, results may be released publically at the end of Stage II (equivalent to a phase 2 trial). Thus, the rationale for either recommending termination or continuation of the trial will be transparent to patients, clinicians and providers of the novel agent under scrutiny.

For each trial, the overall power is maintained at 80%, allowing for multiple interim analyses, with a maximum 5% two-sided overall significance level and an allocation ratio of 2:1 in favour of the active arm. This ratio has been selected because it provides more information on early safety and toxicity in the active arm. Table 9.2 summarises the median survival estimates for the control group and Table 9.3 summarises the generic sample size and timings for each biomarker cohort. Table 9.4 shows the detail of FOCUS4-D as a typical example of the assumptions made at each stage. Note that these figures are generic and relate to the molecular cohorts; the correct working figures for each trial successfully opened to randomisation are given within the relevant trial protocol where considerations specific to individual agents may have dictated some changes to the alpha level, power, target hazard ratio or allocation ratio.

Table 9.2: Accrual, PFS and Overall Survival (OS) from date of randomisation for the control group assumed for the generic sample size calculations for each cohort

Molecular cohort (Prevalence)†	Monthly randomisation accrual*	Median PFS (months)	Median OS (months)
BRAF mutation (8%)	3	3.1	15
PIK3CA mutation and/or PTEN loss (30%)	10	3.6	17
KRAS or NRAS mutation (33%)	11	3.6	18
EGFR dependent (27%)	9	4.6	19

† *Prevalence adds up to 98% as 2% of patients are expected to be unclassified*

** Uniform accrual assumed*

Table 9.3: Summary of generic operating characteristics and timelines for each cohort. (Please refer to specific trial protocol for actual operating characteristics)

Molecular cohort	Randomised allocation ratio	Phase	Outcome and stage	Target HR	Max number of events required: total (control arm)	Estimated cumulative analysis time (months)	Max number of pts required
BRAF mutation	2:1	2	PFS - I	0.5	41 (16)	20.4	61
			PFS - II	0.5	76 (28)	32.5	97
		3	PFS - III	0.5	118 (42)	46.5	139
			OS - IV (potential)	0.65	217 (79)	100.4	301
PIK3CA mutation and/or PTEN loss	2:1	2	PFS - I	0.65	107 (40)	17.0	170
			PFS - II	0.65	197 (71)	26.5	264
		3	PFS - III	0.65	303 (107)	37.2	373
			OS - IV (potential)	0.7	289 (109)	54.6	546
KRAS or NRAS mutation	2:1	2	PFS - I	0.65	109 (41)	16.1	177
			PFS - II	0.65	198 (72)	22.8	273
		3	PFS - III	0.65	302 (107)	31.4	378
			OS - IV (potential)	0.7	287 (109)	50.6	574
EGFR dependent	2:1	2	PFS - I	0.65	109 (41)	20.0	180
			PFS - II	0.65	198 (72)	30.6	275
		3	PFS - III	0.65	301 (107)	42.3	381
			OS - IV (potential)	0.7	289 (109)	60.8	547

Table 9.4: Provided as an example of the detailed generic operating characteristics for a possible trial in the EGFR dependent cohort. (Please refer to trial protocol FOCUS4-D for actual operating characteristics in this cohort)

	Stage I Safety and LSA*	**Stage II** LSA*	**Stage III** Efficacy for PFS	**Stage IV** Efficacy for OS (potential)
	Phase 2		Phase 3	
Outcome	PFS	PFS	PFS	OS
1-sided alpha	0.30	0.10	0.025	0.025
Power (overall power maintained at 80%)	0.95	0.95	0.95	0.85
Target HR	0.65	0.65	0.65	0.70
Critical HR	0.91	0.83	0.79	0.80
Time required (months)	20	11	12	19
Cumulative time (months)	20	31	42	61
Cumulative events required:	**41**	**72**	**107**	**109**
Control arm (total)	**(109)**	**(198)**	**(301)**	**(289)**
Total expected cumulative randomisations	**180**	**275**	**381**	**547**

** LSA= Lack-of-sufficient-activity*

9.4 INTERIM MONITORING & ANALYSES

9.4.1 ROLE OF IDMC

The IDMC Charter will describe the membership of the IDMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses (with a description of stopping rules and/or guidelines, if any). Please refer to Oversight and Trial committees (Section 14) for details.

Interim analysis results from each stage will be reviewed by the IDMC to guide them in making their recommendations, which include early termination or continuation of a trial. Each molecularly stratified trial is double blind but it is important that the statistician and IDMC are unblinded to the randomised allocation. This will be necessary to ensure that the HR is presented using the correct direction of effect (active relative to placebo). The turnaround time for swift and accurate interim analyses will be crucial in enabling a rapid decision from the IDMC. Therefore, resources will be focussed on prompt data collection and trial monitoring procedures for primary outcomes as well as safety and toxicity so that interim analyses can be reported quickly once the target cumulative events have been reached for each stage. Section 9.5 provides a brief summary of the statistical methods for reporting the outcome measures, but it is expected that the IDMC will use their experience and judgement to interpret the results from the primary outcome alongside the results

from other outcomes such as toxicity and safety. In particular, some flexibility may exist around the critical HR thresholds generated by the MAMS design program.

It is acknowledged that any recommendation made by the IDMC on whether to stop or continue recruitment to a trial at the end of Stage II is particularly important. Therefore, as the end of Stage II is in many ways equivalent to a phase 2 study, all results may be released publically at this point. This will provide transparency for patients, clinicians, regulatory bodies and industrial collaborators on any decision to stop or continue to Stages III and IV. In some cases, there may be justification from external sources for continuation of the trial by substituting the placebo-control arm with an active-control arm and sample size calculations would be revised accordingly. Furthermore, it is possible, if the treatment dosage and regime used during Stages I and II (phase 2) needs to be adjusted substantially for the phase 3 part of the study, it is possible that the sample size will be reset so that the later stages do not use data from Stages I and II.

9.4.2 TESTING POTENTIALLY PROMISING AGENTS IN 'NON-SELECTED' COHORTS

A further novelty of the design is that, once a treatment comparison has successfully passed the safety and LSA stages I and II in the cohort assumed to be the most responsive based on biomarker selection, the treatment effect in the cohorts ***not*** selected for that biomarker will be investigated. These 'non-selected cohorts' will be tested using a trial designed using the same randomised MAMS approach as the original selected cohort, with similar strict rules for early stopping for lack of sufficient activity, albeit seeking a possibly smaller treatment effect. Depending on the contemporaneous status of the other cohorts, the 'non-selected' cohort may encompass patients from a different cohort in which the trial for a selected agent has been stopped and as yet, a new trial has not been opened. In other circumstances, the 'non-selected' cohort may be assembled by diverting patients from the larger size cohorts that have different biomarker profiles. This would naturally introduce some delay in completion of the other biomarker-selected comparisons, but would be justified by the promising results that would at that point already have been observed with a given test agent. Because of such unavoidable uncertainties, the precise details of sample size, timings and analyses for the 'non-selected cohorts' will be assessed after discussion with the IDMC, TMG, TSC and relevant Industrial collaborator. The analysis of these non-selected groups is likely to take the form of a meta-analysis stratified by biomarker profiles with treatment effects presented within each biomarker group to see which respond and to generate an overall pooled treatment effect for the agent across all patients. As all patients will have been investigated using the same overall Master Protocol, heterogeneity between biomarker groups will help provide information on how strongly specific the new agent is to each biomarker group. All such analyses will be regarded as exploratory.

9.5 ANALYSIS PLAN (BRIEF)

Patients within each molecular trial will be analysed entirely independently of other trials. Therefore, any analysis details specific to a cohort can be found in the relevant trial protocol. Additionally, a formal Statistical Analysis Plan for each trial will be completed in advance of the first interim analysis. A broad description of what will be presented for each analysis is given below.

9.5.1 SUMMARY OF PATIENTS

The baseline characteristics of patients will be presented by randomised group to determine whether any strong imbalances are present. A flow chart will be constructed to show patient flow through the trial up to that analysis.

9.5.2 ANALYSIS OF PFS AND OS

A table will be presented indicating the proportions of composite outcomes in terms of disease progression or death by randomised group. For some of the early intermediate analyses, there may be a limited number of events relative to the number of minimisation factors and, to improve model stability, a propensity score method will be used to ensure balance beween the randomised groups. A logistic regression model with randomised group as the outcome will be used to derive a propensity score for each patient based upon the minimisation factors (and possibly on other important prognostic factors). This propensity score will be used as a single adjustment variable in the subsequent survival models. As more events arise, the propensity score will become less necessary and a more standard adjustment method will be applied to the survival models. A test of proportional hazards (PH) will be performed to determine whether there is significant deviation from the PH assumption by regressing scaled Schoenfeld residuals against the log of time[11]. If there is not statistically significant violation of the PH assumption, a Cox proportional-hazards model will be fitted, adjusted for all factors used in the minimisation procedure (or propensity score as described above) as well as any other pre-specified factors felt to be important. If the PH assumption does not hold, the primary emphasis will be given to a suitable alternative model, such as restricted mean survival time[12] or a Flexible Parametric Model[13]. The point estimate of the unadjusted and adjusted hazard ratios will be presented with the relevant confidence interval, and Kaplan-Meier curves will be plotted between the randomised groups. However, for the purposes of determining whether or not to continue recruitment to a trial at each analysis stage, the adjusted HR point estimate will be compared to the relevant “critical HR” generated (in advance) by the nstage program.

For the final efficacy analysis of a trial, in addition to the Cox proportional-hazards model being fitted, a test of statistical significance will be carried out using a log-rank test. This is a more efficient test of significance when the PH assumption holds.

9.5.3 ANALYSES OF SAFETY AND TOXICITY

Given that patients will have recently completed a 16 week regimen of standard chemotherapy prior to randomisation into their biomarker trial, baseline levels of toxicity at randomisation will be collected so that changes in toxicity can be investigated from the time of randomisation adjusted for baseline. These results may also be required at the interim analysis stages if they are felt to be relevant to the decision on whether to terminate or continue a trial.

Safety outcomes (AE, AR, SAE, SAR, SUSAR etc.) as described in Section 7 for each trial protocol will be tabulated by randomised group at each of the interim analysis stages. If a novel agent progresses to the final analysis, a logistic regression model may be fitted to compare safety outcomes.

10 ANCILLARY STUDIES

10.1 BIOMARKER DEVELOPMENT STUDIES FOR MRNA BASED STRATIFICATION IN THE ALL WILD TYPE COHORT

In the all-wild type cohort, treatment approaches which block epidermal growth factor signalling are being investigated. Initial research investigating predictive markers of responsiveness to the EGFR monoclonal antibody cetuximab identified a novel group of potential biomarkers[14]. This work showed that high expression of messenger rna (mRNA) for the EGFR ligands epiregulin (EREG) and amphiregulin (AREG) were most closely associated with response to cetuximab therapy. These ligands EREG and AREG bind the EGFR encouraging the formation of receptor dimers and potent down-stream signalling. High levels of expression suggest the tumour is dependant on this pathway for tumour growth so such tumours are more likely to be responsive to EGFR inhibition. In addition, the dual-specific phosphatases (DUSP 4 and 6) were identified. Increased expression of these enzymes occurs when the MAPKinase pathway is activated and these phosphatases operate as a negative feedback mechanism damping down pathway activity. Elevated DUSP gene expression is best understood as a biomarker for the MAPK pathway being activated. Thus, the combination of these four genes provides information on how much the cancer is using the EGFR-RAS-MAPK pathway to sustain the tumour proliferation, in the absense of KRAS or BRAF mutation.

In FOCUS4-D, the quadruple wildtype cohort, it is planned to stratify randomisation by gene expression levels. This preliminary work will attempt to address the following questions in our analysis of the efficacy of agents used in this comparison:

- In the best-defined cetuximab responsive cohort, with high ligands above the defined mRNA cutpoint, does AZD8931 (which inhibits not only EGFR (HER1) but the alternate human EGFR receptors (HERs) 2 and 3 result in improved PFS compared to placebo? If so, the later stages of comparison may be against cetuximab, rather than placebo, if advised by the IDMC and approved by the TMG and funders.
- In those with ligand expression below the cut-point, in whom preliminary evidence suggests there is little or no benefit from cetuximab, does AZD8931 have a broader spectrum of activity as shown by improved efficacy compared to placebo?

The preparatory laboratory work to establish the criteria for stratification of this cohort will be performed in the reference laboratories prior to randomisation of the first patients.

10.2 FRESH TUMOUR BIOPSIES BEFORE RANDOMISATION AND AT PROGRESSION

Every cancer is the product of an independent somatic evolutionary process within an individual, in which successive genetic and epigenetic changes are selected for and drive the progression of the disease. It is these changes that define the biology of the cancer, in the context of its microenvironment, and so its clinical progress in the face of available therapies.

In a proportion of patients on FOCUS4, biopsy samples will be obtained after initial chemotherapy but prior to randomisation and, if possible, on progression also. This would be limited to those patients giving informed consent to extra biopsies for research purposes having read the appropriate PIS and having accessible tissue for biopsy from a metastatic or unresected primary site. The large majority of investigators recognise the importance of this and are committed to requesting permission for such biopsies. These biopsies will be analysed using high throughput genomic techniques to identify changes in the genetic make up and gene expression of the tumour in response to therapy. The first question to be asked is: Does detailed molecular analysis of biopsies from metastases following initial chemotherapy (prior to interval therapy) result in better selection of therapy than the limited biomarker analysis on archival material taken (often a long time) before initial chemotherapy?

In addition, FOCUS4 will request repeat biopsy of metastatic disease at the time of progression of the disease to investigate mechanisms of resistance to therapy. At any given time during tumour progression, there are bound to be different, possibly competing, clones present. Under the selective pressure of targeted therapies, resistant subclones will demonstrate a survival advantage and will emerge as the dominant clone. On this basis, Vogelstein recently concluded that resistance is therefore a *fait accompli*—the time to recurrence is simply the interval required for the subclone to repopulate the lesion[15]. Therefore, wherever possible, biopsies of metastatic disease will be collected on progression to investigate the mechanism of progression following the novel therapy using high throughput genomic analyses in comparison with the biopsy at randomisation.

10.3 CIRCULATING TUMOUR DNA ANALYSIS

The recognition of the importance of the tumour's genetic make-up in determining response to therapy and the fact that this changes over time is fundamental to current understanding of cancer. In haematological cancers, it is routine to access bone marrow or circulating tumour cells from the blood to assess these changes. In solid cancers, repeat biopsies as described above are the only established technique. However, it is becoming increasingly clear that tumour DNA is detectable using highly sensitive assays in the plasma of patients with advanced cancer. Further mutations in tumours can be found in this circulating free DNA[16]. Within this study therefore it is planned to collect blood for circulating free DNA in order to provide the resource to investigators to analyse the change in mutation pattern during therapy. This will require 10ml EDTA samples at registration, on randomisation into any of the FOCUS4 trials, and every 8 weeks until progression. This will attempt to address the question: Does sequential assessment of circulating tumour DNA from plasma for the presence of somatic mutation provide early information on resistance and/or document specific mechansims of resistance to the investigational therapies?

10.4 SEQUENCING OF GENES IN CANDIDATE PATHWAYS FROM FFPE

FOCUS4 aims to undertake a relatively limited biomarker analysis in order to allocate patients to the differing trials. In addition, funding will be sought to perform exome sequencing of a large (>400)

panel of cancer genes. This will give a much fuller picture of the genetic abnormalities in each patient. These data will not be used to guide treatment allocation in the trial certainly in the first instance. It will be used to attempt to find new biomakers which may be able to predict more precisely which patients are responding to which novel therapies. The samples used for this will be the same diagnostic samples used for the biomarker panel in FOCUS4, so no extra samples will be required for this purpose.

10.5 PHARMACOGENOMIC SUB-STUDIES

A sample of 20ml of EDTA blood at registration will be collected to provide a germline DNA resource. All next generation cancer sequencing research requires access to germline DNA to establish the individual patient's genotype for comparison with the tumour genotype. In addition, predisposition genes for colorectal cancer are still being discovered from studies such as this. Further germline changes may influence response and toxicity to novel therapies and the investigation of these factors may enable further individualisation of therapeutic decisions if single nucleotide polymorphisms (SNPs) associated with tumour response or toxicity can be identified.

10.6 PHARMACODYNAMIC SUB-STUDIES (FOR GIVEN COHORTS)

Within the individual FOCUS4 Trials, studies examining the effect of the specific novel therapies being tested in the trial will be included. These will be defined in the relevant FOCUS4 Trial Protocol.

These studies are dependant on further research funding. Further studies will be considered by the TMG and TSC and if approved be added to the above.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The FOCUS4 Trials Programme complies with the 1996 version of the principles of the Declaration of Helsinki. It will be conducted in compliance with the approved protocols, the principles of Good Clinical Practice (GCP), EU Directives 2001/20/EC Article 2 and 2005/28/EC and subsequent amendments, their implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

11.1.2 PARTICIPATING SITE COMPLIANCE

The participating sites will comply with the above. An agreement will be in place between the sites and the MRC CTU, setting out respective roles and responsibilities (see Section 13 - Finance).

The participating sites will inform the MRC CTU as soon as they are aware of a possible serious breach of compliance, so that the MRC CTU can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects

or

- The scientific value of the registration period or subsequent FOCUS4 trials

11.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 10 years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor, with suitable notice. The data may be subject to an audit by the competent authorities.

11.2 ETHICAL CONDUCT OF THE STUDY

11.2.1 ETHICAL CONSIDERATIONS

The provision of information for the FOCUS4 Trials Programme will follow the successful model used in FOCUS 3 which was developed with patient and carer input. This divides the information into a staged approach to reduce information overload and this proved to be successful in FOCUS 3. PIS1 (trial registration and consent for biomarker analysis) is a simple non-technical sheet explaining what will be done with the tumour tissue in the biomarker analysis. A separate PIS2 has been written for

each trial and follows the more usual RCT consent requirements explaining the trial design, randomisation, placebo control, unwanted side-effects and toxicity of the novel agents, advantages and disadvantages of participating and all other issues related to RCT consent. Patients will be provided with PIS2 as early as possible during the registration period to allow as much time as possible for them to consider participation in one of the trials. A patient may of course request all information sheets at any time if they so wish. The information sheets will also be available on the trial website (www.focus4trial.org). The TMG includes two patient representatives and both have contributed substantially to the development of the patient consent process.

Ethical issues that arise from this study:

The use of double-blind, placebo-controlled design:

It is common practice in the UK and elsewhere to advise a break from chemotherapy after an initial period of at least 3 months and the issue has been carefully studied in the COIN and MRC CR06B trials[4,17] which demonstrated that overall survival is not adversely affected, except in the patient group with elevated platelets at baseline (as yet unconfirmed); pending confirmation, patients with elevated platelets will be excluded from this study. In FOCUS4, placebos will be used rather than no treatment in the control arms to minimise conscious and subconscious bias in assessing the PFS endpoint (disease progression clinically or on CT scan), which is essential in the initial stages of the trial. Also, as the agents being tested are relatively new and unlicensed, blinded patient and investigator assessment of toxicity will be helpful in ensuring unbiased and robust reporting of toxicity and symptoms.

Referral of patients to other sites for experimental treatments:

All novel agents being tested in the molecular trials will be unlicensed. Although there will be phase 2 clinical experience with each of them, this usually will have been only in major cancer centre settings. To assure optimal patient safety, most regimens in FOCUS4 will initially be administered and monitored in major centres with special expertise and facilities for managing any serious adverse events. Patients in some participating sites will be asked, if they are inclined toward the molecularly stratified approach, to accept the inconvenience of travelling to other centres, at least for the first several cycles of trial treatment. However, in all cases, the FOCUS4-N Trial is an available alternative to all patients who do not with to travel.

Release of results at the end of Stage II:

FOCUS4 employs the MAMS design[9 10], which includes the capability for an encouraging phase 2 outcome to lead directly into a phase 3 trial. Conventionally, phase 2 activity results for a new unlicensed agent would be released to investigators before a phase 3 trial is initiated. A similar approach may be employed within FOCUS4, which may necessitate an amendment to the relevant protocol (FOCUS4-A to D) and revision to the PIS.

Optional consent:

The consent process separates out some parts of the research as optional and additional consent is requested for:

1) Permission for the investigators to search for longer term data from central registries such as Office of National Statistics (ONS) or the NHS Strategic Tracing Service.

2) Their pathological tissue to be used for bowel cancer research and for a blood sample for DNA and other analyses. 91% of patients in COIN agreed to this.

3) Additional biopsies to be collected at randomisation and on progression.

11.2.2 ETHICAL APPROVALS

The Master and all trial protocols will be submitted, reviewed and approved by the Oxford Multicentre Research Ethics Committee prior to study launch. Any changes to the protocols including adaptive design changes such as addition of new trials or treatment arms within trials will be submitted as substantial amendments to this ethics committee as they arise.

Before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective participant will be submitted to each appropriate local/regional research ethics committee for approval. Any further amendments will be submitted and approved by each ethics committee.

The rights of the participant to refuse to participate in the trial without giving a reason will be respected. After the participant has entered into the trial, the clinician will remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interests of the participant. The reason for doing so and the alternative treatments chosen should be reported to the trials unit. The participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the participant is free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

11.3 COMPETENT AUTHORITY APPROVALS

The Master and all trial protocols will be submitted, reviewed and approved by the MHRA prior to study launch.

This is a programme of trials of Investigational Medicinal Products (IMP) as defined by the EU Directive 2001/20/EC. Therefore, CTA **is** required in the UK.

A EudraCT number has been obtained for the entire FOCUS4 Trials Programme.

The progress of each trial and safety issues will be reported to the MHRA in accordance with their requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the MHRA in accordance with their requirements in a timely manner.

11.4 OTHER APPROVALS

The Master and Trial Protocols will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval. A copy of the local R&D approval (or other relevant approval as above) and of the PIS and Consent Forms (CF) on local headed paper should be forwarded to the MRC CTU before patients are entered.

12 INDEMNITY

The sponsor of the trial is the Medical Research Council (MRC).

The Medical Research Council ("the MRC") is not insured but it has indemnity arrangements in place such that public funding is provided to meet claims.

The likely scenarios in which the MRC might face claims for damages are set out below. The MRC also sets out below instances where it might make *ex gratia* payments without any admission of liability.

1. The MRC accepts that it might face claims for damages in cases where:

a) it sponsors the research: (that is it has responsibility for securing the arrangements for initiating, managing and financing the study including any research carried out by its Units); **and**

b) the MRC, or any of its employees, or any person formally acting with the MRC's authority, have been negligent or have failed to adhere to the relevant guidelines/guidance, legislation or procedure on good practice in relation to medical research; **and**

c) That negligence or failure to adhere to legislation, etc has caused or has materially contributed to the personal injury suffered by the individual making the claim.

2. In relation to instances where the MRC is the sponsor of research the MRC may consider making an *ex gratia* payment when a significant adverse reaction in the form of a personal injury has occurred which is likely to have been caused by, or materially contributed to, by participation in a research study. In deciding whether to make such a payment, the MRC will not require the research participant to demonstrate that the personal injury has been caused by a breach of any duty of care that may have been owed by the MRC.

13 FINANCE

The entire FOCUS4 Trials Programme will be sponsored by the MRC and co-ordinated by the MRC CTU in London. The grant holder is the University of Oxford. Funding will be jointly provided by the NIHR/MRC Efficacy and Mechanism Evaluation (EME) Programme and Cancer Research UK (CRUK). There may be some contribution and support from pharmaceutical companies for drug provision and distribution in their individual trials. This will be stated in each trial protocol.

The MRC CTU will have in place an agreement with the participating clinical organisations, which will include NHS Trusts or Boards in the UK that are willing and able to provide clinical research facilities. This agreement will set out the obligations of the parties to the agreement, their respective roles and responsibilities and cover arrangements for budgets and financial transfers and reporting.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in Figure 14.1.

14.1 TRIAL MANAGEMENT GROUP (TMG)

The Trial Management Group (TMG) comprises the Chief Investigators, all trial chief investigators, other co-investigators (clinical and non-clinical), members with specific interests (e.g. pharmacist, nurse, user representative) and members of the MRC CTU. The TMG will be responsible for the day-to-day running and management of the trial. It will hold regular teleconferences and face-to-face meetings where required. The full details can be found in the TMG Charter.

14.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the senior members of the TMG and representatives of the funder plus independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

14.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial up to end of stage II. Reports to the IDMC will be produced by the MRC CTU statisticians. The frequency of IDMC meetings will be dictated in the IDMC charter. The IDMC will consider data using the statistical analysis plan (see Section 9.5 - Analysis Plan (Brief)) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trials or discontinuation of recruitment to any research arm.

Further details of IDMC functioning, and the procedures for interim analysis and monitoring are provided in the IDMC Charter.

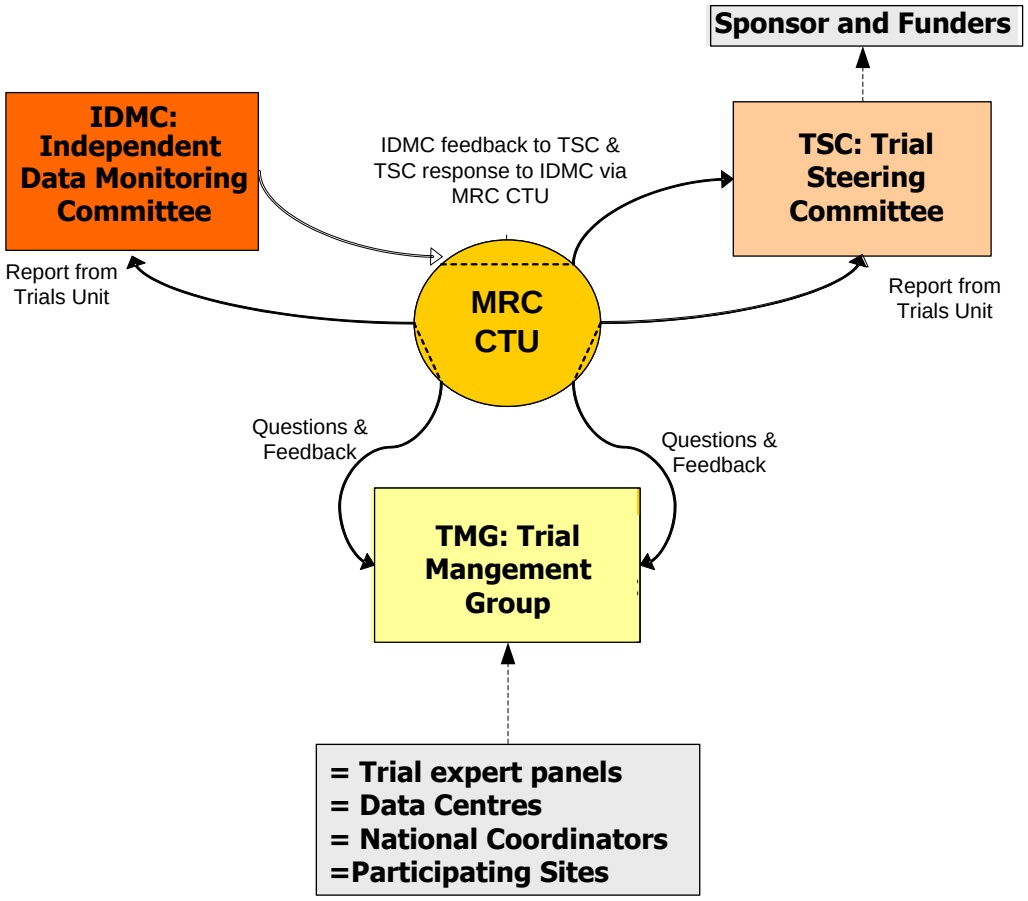
14.4 OTHER COMMITTEES

A Site Evaluation committee will be convened under the chairmanship of Professor Will Steward. All interested sites will submit a site evaluation form which will be reviewed by members of this committee with site visits performed if necessary. On the basis of their findings, they will classify each site with Level 1, 2 or 3 status (see section 2).

14.5 ROLE OF STUDY SPONSOR

FOCUS4 is sponsored by the MRC. The MRC CTU will have overall responsibility for the study design; obtaining and complying with the requirements of the relevant regulatory bodies; collection, management, analysis, and interpretation of data; writing of any reports; the decision to submit reports for publication, including who will have ultimate authority over each of these activities. It will work closely with the Chief Investigators, Grant holder (University of Oxford), all members of the Trial Management Group (TMG) and Industrial collaborators.

Figure 14.1: Relationship between Trial Committees



15 PUBLICATIONS

The results for each trial within the FOCUS4 Trials Programme will be analysed separately when appropriate and according to pre-defined criteria developed from the MAMS design. The results from FOCUS4 analyses will be published when appropriate and possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions being addressed in FOCUS4 until the TMG has published its final report. The TMG will form the basis of the writing committee and decide on the nature of the publications.

All publications shall include a list of investigators (participating clinicians, nurses, pathologists etc) and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least.

The ISRCTN **[*Insert Info*]** that has been allocated to this trial should be attached to any publications resulting from this trial. Acknowledgement of funding along with any disclaimers required by the funding bodies must also be added to any publications.

The members of the TSC and IDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

16 PROTOCOL AMENDMENTS

Please check with the MRC CTU FOCUS4 Trial Manager or the FOCUS4 website to confirm the most recent version of the FOCUS4 protocols and associated documents. This is the first signed agreed draft of the Master Protocol so no amendments have been made to date.

Please note this section will only refer to the FOCUS4 Master Protocol and the registration documents. Each separate trial protocol will document trial protocol amendments separately.

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Appendices for the FOCUS4 Master Protocol

FOCUS4 – Molecular selection of therapy in colorectal cancer: a molecularly-stratified randomised controlled trials programme

Master Protocol

Registration of patients and generic trial governance issues related to the FOCUS4 Trials Programme

Version: 1.0

DATE: 01 February 2013

MRC CTU ID: CR13

ISRCTN #:

NCT #:

EUDRACT #: 2012-005111-12

CTA #:

REC #: 13/SC/0111

CONTENTS

APPENDIX I – PATIENT INFORMATION SHEET 1

<Print on hospital headed paper>

Patient Information Sheet 1 (PIS1)

(Consent step 1)

Date: February 2013, version 1.0

Information for patients eligible for registration into the FOCUS4 Trials Programme in colorectal cancer

1. Why am I being given this patient information sheet?

- You are being invited to take part in a research study called FOCUS4, because your oncology doctors are recommending or have already started you on a course of chemotherapy for colorectal (bowel) cancer.

- Participation in the research is entirely voluntary. If after considering it, you decide not to participate, this will not affect your care in any way and your oncology doctor will explain the best alternative standard treatment available.

2. Why am I being asked to participate in this research?

- When cancer of the bowel is not completely removable by surgery or when it has spread to elsewhere in your body, chemotherapy may be given. This is a form of drug treatment which aims to kill cancer cells. Your oncology doctor is recommending that you have 16 weeks of chemotherapy to try and stabilise or reduce the size of your tumour.

- Usually, the type of chemotherapy that is offered to a patient depends on how well it works on average in patients with bowel cancer.

- However, there are now some specific tests that can be done on the tumour which may help us to choose more accurately which sort of treatment might be best for you when you reach the end of your 16 weeks of chemotherapy.

- After the first 16 weeks we will offer you entry into a trial of a new form of treatment for your type of bowel cancer.

3. What am I being asked to consent to?

- To take part in this research study you will be asked to consent to two separate steps. We have provided a flow chart at the end of this information sheet to show the steps more clearly. The first step is explained here and step 2 is described in section 5 of this

information sheet. Step 1 asks for your permission to send a piece of your tumour (already stored in the local hospital pathology department where your cancer was diagnosed) to a central laboratory. A copy of your consent form will be sent to your local hospital pathology department (where it will be kept in a secure location), to authorise the release of your pathology block to the central laboratory.

- This central laboratory will run specific tests (known as 'molecular markers') on the tumour sample. These tests will identify your cancer as one of four 'types'. This process will take several weeks. In a few patients (about 2%), the tests do not work properly and the tumour is considered as a fifth type (unclassified). These test results will be made available to your oncology doctor for this research study. However they may help determine whether there are other future studies that you should consider following your participation in FOCUS4.

- Following the specific tests, we would like your permission to store the piece of your tumour that was used to perform these tests. It will be stored at a central laboratory to be used for other studies for future bowel cancer research. This research will help us understand more about bowel cancer and the type of treatment that might be more effective for other patients in the future. It will involve extracting DNA or other material from the piece of your tumour. This research is based in UK Universities but may involve collaboration with commercial companies or other institutions.

  All such work is anonymous: your specimens will be identified by your unique trial number, not your name. These additional studies will not affect your treatment in any way, and you are free to withhold this permission without affecting your participation in FOCUS4 or your relationship with your doctor.

- In addition to the blood samples that will be taken as part of your standard care, we would also like your permission to take some further blood for other bowel cancer research purposes. This will help us find substances in your blood which might help us understand more about bowel cancer and the type of treatment that might be more effective for other patients in the future. It will not help us with your own treatment. There are two types of blood sample collection required for two different areas of bowel cancer research. One area of research just requires one blood sample. The other requires a sample at the start and some additional samples later during the study. Your consent form will ask whether you are happy to provide the initial blood samples for these areas of research. We will ask you in the second stage of the trial about the later samples.

- A copy of your consent form will also be sent to the Medical Research Council Clinical Trials Unit (MRC CTU) who are responsible for running this trial. They will destroy their copy of the consent form once they have checked it.

- We are also asking if we may collect future routine information about your health status after participation in the trial. This will be collected by adding your name to government national registers such as the Office for National Statistics (ONS) and the NHS Strategic Tracing Service. The MRC CTU is registered to store this information according to the requirements of the UK Data Protection Act (DPA). There is a question about this on the consent form that we will ask you to sign before you agree to be registered into FOCUS4.

4. What will happen to me during my initial chemotherapy treatment?

- Your initial treatment will include a 16 week standard course of chemotherapy as recommended by your oncology doctor. It is routine practice to see how the tumour is responding by having a CT scan and this will be arranged about half way through, and again at the end of your 16 weeks of chemotherapy. CT stands for computerised tomography. The CT scanner uses X-rays to take a series of very detailed pictures of the body and is a painless procedure. The pictures are taken while you lie on a couch, which moves backwards and forwards through the hole of the machine. This procedure involves some exposure to ionising radiation. Like all medical procedures, this does entail some risk, but in this case the benefits outweigh any such risk.

- If the CT scan half-way through your chemotherapy shows that you are responding to treatment (your cancer has not grown or even shrunk), you will continue on treatment to the 16 week scan. If your tumour has got bigger at this half-way scan, your oncology doctor will discuss with you about other treatment options at that time.

5. What will happen to me at the end of my initial chemotherapy?

- The second step of this research study will start at the end of your 16 weeks of chemotherapy when we will have the results of your specific tests back from the central laboratory. If at the end of your 16 weeks of chemotherapy your cancer has shrunk or at least not grown, for many people this would be a time when they might take a break from the chemotherapy. In our last trial called The COIN Trial we showed that having a break from chemotherapy after this initial course of chemotherapy, is a safe thing to do for most patients.

- The aim of the FOCUS4 is to find a good treatment for your particular type of cancer after you have finished your first 16 weeks of chemotherapy. We will be doing it by comparing how patients get on with either a new treatment tablet or a dummy tablet.

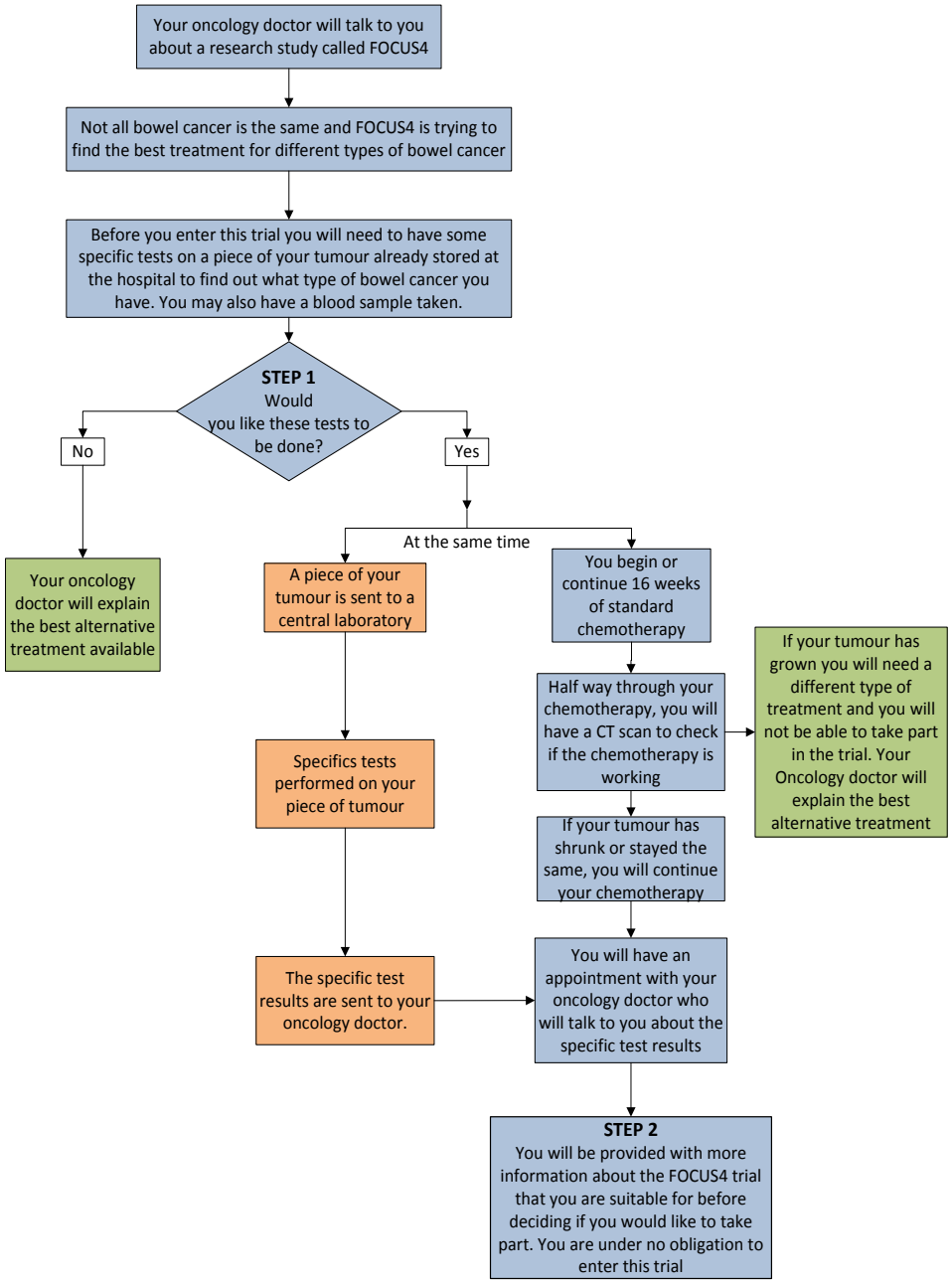
- The new treatments that we will be testing will be selected because they may offer a possibility of benefit for patients with the type of bowel cancer that we will identify by your specific tests. When we know the results of your specific tests, we will provide you with more detailed information on the trials that will be available to you at that time. Please look at the flow chart at the end of this information sheet to see where step 1 ends and step 2 starts.

- If you want to get information on all the trials that we will be conducting, we can provide you with patient information sheets for all of them now, but we feel it would be easier for you to wait until we know the results of your specific tests and give you the relevant information at that time.

6. What if I do not want to participate in one of these trials at 16 weeks?

- By consenting to sending your piece of tumour for specific testing, you are under no obligation to consent to participate in any of these trials. If you decide not to consent into these trials, we would hope to be able to use the results from your specific tests from the central laboratory for other research. However, you can ask for the results not be given to anyone else or used in any way.

Flow chart for FOCUS4



Please use this space below to record any questions you might have for your oncology doctor at your next visit.

Contact Details for further information:

Local Investigator: Dr …….. Telephone no: ……

Research Nurse: …….. Telephone no: ……..

APPENDIX II – PATIENT CONSENT FORM 1

REGISTRATION CONSENT FORM

For the FOCUS4 Trials Programme in colorectal cancer

Date: February 2013, version 1.0

Centre name and number: ……

Patient Registration ID number: ……

Please initial boxes:

1. I confirm that I have read and understand the Patient Information Sheet 1 - consent step 1 (Version 1.0, February 2013) for the above research study and have been given a copy to keep. I have had the opportunity to ask questions and am satified with the answers to my questions. ☐
2. I understand that sections of any of my medical notes may be looked at by individuals from organisations involved in developing and running the trial (e.g. MRC CTU), or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records, but understand my confidentiality will be maintained. ☐
3. I give permission for a sample of my stored tumour to be sent for specific tests at the central laboratory as required for FOCUS4 . ☐
4. I give permission for a copy of my consent form to be sent to the local pathology department (where it will be kept in a secure location), to authorise the release of my pathology block and to the MRC CTU where once checked, the consent form will be destroyed. ☐
5. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
6. I agree to take part in the above research study. ☐

For the following questions (7- 9)if you do not wish to give this permission, please tick the "No"box – you can still participate in the main research.

	Yes	No
7. I give permission for my name to be registered with the Office of National Statistics (ONS) or traced via the NHS Strategic Tracing Service should I lose contact with my hospital doctor. I give permission for information about my health status to be obtained from the ONS and/or the NHS Strategic Tracing Service by the Medical Research Council if necessary.	☐	☐
8. I give permission to take blood samples including the DNA to be used for future bowel cancer research.	☐	☐
9. I give permission for my stored pathological material to be used for future bowel cancer research.	☐	☐

Name of Patient	Date	Signature
Researcher	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature

APPENDIX III – WHO STATUS CRITERIA

Clinical Performance Status:

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable only of limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

APPENDIX IV – RECIST RESPONSE DEFINITIONS (V1.1)[1]

RECIST (Response Evaluation Criteria In Solid Tumours) v1.1[1] has now superseded RECIST v1.0. The key amendments are:

- A maximum of **five** measurable non-nodal lesions should be measured, with a maximum of **two** per organ.
- Lymph node measurement rules have changed.
- The definition of progressive disease has changed.

MEASURABLE DISEASE:

- Disease is measurable if there is at least one measurable target lesion. Target lesions should be selected on the basis of size and suitability for repeat measurement, up to a maximum of two measurable lesions per organ, and up to a maximum of five lesions in total. These should be representative of all involved organs.
- Target lesion (non-nodal) must be accurately measurable in at least 1 dimension, with the longest diameter ≥10 mm (assuming CT slice thickness is no greater than 5mm). If the lesion is smaller than this then it is classed as non-measurable.
- Measurements must be taken as close as possible to the beginning of treatment and never more than 5 weeks before the start of treatment. Target lesions should be assessed by CT, MRI or CXR, not by clinical assessment alone. The same imaging modality should be used throughout for any given patient.
    - When intra-venous contrast agents are given with CT, it is important to measure hepatic lesions in the same vascular phase on subsequent examinations.
    - If MRI is used then the same sequence (e.g. T1 or T2 weighted images) in the same anatomical plane should be used.
- Add the longest diameters of the target lesions and report this as the baseline sum longest diameter. This will be used as a reference by which the tumour response will be measured.

LYMPH NODE MEASUREMENT RULES

- Measure short axis
    - Target lesion if short axis ≥ 15mm
    - Non-target lesion is short axis 10 to < 15mm
    - Normal if short axis < 10mm
- Add ACTUAL short axis measurements to sum of longest diameters of non-nodal lesions.
- When considered normal if < 10mm, for CR the sum may not be zero if nodes are included as target lesions.
- The implication of this is that patients previously considered PR because of residual nodes <10mm may now be considered CR.

RESPONSE DEFINITIONS:

- **Complete response (CR):** disappearance of all lesions (i.e. all evidence of disease, not just the target lesions) determined by 2 observations not less than 4 weeks apart. All lymph nodes must be non-pathological in size (<10mm short axis).
- **Partial response (PR):** ≥30% decrease in the sum of longest diameters of target lesions compared to baseline, with response or stable disease observed in non-target lesions, and no new lesions.
- **Stable disease (SD):** neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, with response or stable disease observed in non-target lesions, and no new lesions.
- **Progressive disease (PD):** ≥20% increase in the sum of longest diameters of target lesions compared to smallest sum longest diameter recorded. In addition, the sum must also demonstrate an absolute increase of at least 5mm. Unequivocal progression of non-target lesions, or the appearance of new lesions is also considered progression. Unequivocal progression means the patient has overall status of progressive disease at that time point. Modest increases in the size of one or more non-target lesions is usually not sufficient.

REMINDERS:

- New lesions must be unequivocal and not attributable to a different scanning technique or non-tumour (e.g. “new” bone lesions may be flare). When in doubt continue treatment and repeat evaluation.
- If a scan shows a new lesion in anatomical region which was not included in the baseline scans, this is still PD.
- Response is judged against baseline, but progression is judged against the smallest recorded score.

EXAMPLES:

Month	0	3	6	9	12
Measurement (mm)	100	90	50	55	≥60
Classification	Baseline	SD	PR	PR	PD

TIME POINT RESPONSE: PATIENTS WITH TARGET (+/- NON-TARGET) DISEASE

Target Lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD **or** not all evaluated	No	PR
SD	Non-PD **or** not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD

REFERENCES:

1. Eisenhauer EA, Therasse, P *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009, 45, 228-247.
2. Gehan EA and Tefft MC. Will there be resistance to the RECIST (Response Evaluation Criteria in Solid Tumours)? J Natl Cancer Inst 2000, 92, 179-181.

APPENDIX V – EFFECTIVE METHODS OF BIRTH CONTROL

For particpation in the FOCUS4 Trials Programme, women of child-bearing potential and men must be using acceptable contraceptive precautions if the risk of conception exists. The acceptable contraception precautions that should and should not be used within FOCUS4 are listed below:

ACCEPTABLE HIGHLY EFFECTIVE METHODS

- True heterosexual abstinence (i.e. not just stopping intercourse for the duration of the trial)
- Vasectomised or vasectomised sexual partner (with appropriate post-vasectomy documentation of the absence of sperm in ejaculate)
- Implanon (Etonogestrel slow-release subcutaneous implant)
- Female sterilisation by tubal occlusion
- IUD/IUS provided coils are copper-banded. Steel and copper wire devices are not acceptable
- Mirena—levonorgestrel containing intra-uterine system (IUS)
- Depo Provera injections (medroxyprogesterone)
- Normal and low dose combined oral contraceptive (COC) - only if used in TriCycle regime Please note: This means instead of taking a single 3-week course of COC pills followed by one week off COC, the patient takes 3 or 4 courses together (i.e. 9-12 weeks of daily COC) with, between each prolonged cycle, a shortened 4-day pill free interval (PFI) rather than the usual 7-day PFI. Note: the less commonly used Triphasic pills, which have different strength pills in the same pack, are not considered highly effective and are therefore excluded from this instruction
- Evra Patch: norelgestromin/ethinyl estradiol transdermal system - only if used in above Tricycle regime with 4-day patch-free intervals after each long cycle
- Nuvaring (intravaginal device containing ethinyl estradiol and etonogestrel (3-ketodesogestrel) - only if used in above Tricycle regime with 4-day ring-free intervals after each long cycle
- Cerazette ™ (desogestrel-releasing progestogen-only pill with established failure rate of <1 per 100 women in first year)

Although the failure rate for combined hormonal contraception (pills, Evra patch and Nuvaring) when used consistently and correctly is <1.0%, in reality the failure rates are closer to 8% (www.who.int/reproductive-heath) and the main cause of failure is due to omitting pills or devices around the “7-day treatment free interval”. Therefore the recommendation to “Tricycle” reduces the risks associated with the treatment free interval and makes these hormonal methods acceptable.

UNACCEPTABLE CONTRACEPTION THEREFORE INCLUDES:

- Triphasic COCs
- All progesterone only pills except Cerazette™
- All barrier methods
- Non Tricycle Combined hormonal pills/patches/rings plus barrier methods (subject to the same failure rate due to poor compliance)
- Non copper containing IUDs
- Fertility awareness methods
- Coitus interruptus

OTHER CONSIDERATIONS

- Women should have been stable on their chosen method of birth control for a minimum of 3 months before entering the trial.
- Pregnancy testing is recommended at registration and if felt required at randomisation at clinician discretion. There is no general requirement to conduct additional pregnancy testing throughout the trial unless there is a history of late injections of parenteral contraceptives or an extended "treatment free interval" or is otherwise clinically indicated. Within trial/post trial pregnancy testing may be considered where there is strong evidence that the clinical trial agent is developmentally toxic.
- Contraceptive history should however be rechecked throughout the trial and patients should be made aware of the availability of emergency "post-coital" contraception if there is an indication for it (for example missing IUD threads or a late injection).
- Gastro-intestinal side effects: diarrhoea is unlikely to affect oral contraceptive absorption unless cholera-like. Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill and volunteers/patients should follow the guidelines for a missed pill or missed Cerazette™. Neither diarrhoea nor vomiting will affect non-oral routes for hormones.

APPENDIX VI – TRIAL MANAGEMENT GROUP

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APPENDIX VII – PATIENT INFORMATION SHEET FOR OPTIONAL BIOPSY SUB-STUDY

<Print on hospital headed paper> Date: February 2013, version 1.0

Patient Information Sheet 3 (PIS3)
Patient information sheet for the Additional Biopsies Sub-Study in FOCUS4

1. Introduction

You will already have received information (Patient Information Sheet 1) which explains the FOCUS4 trial. This document explains why we would like to ask for your further help with our research study and what would be involved. Taking part in this study will not affect your routine care.

At the time your bowel cancer was diagnosed, you will already have had at least one biopsy or removal of tissue performed. This may have been the initial tumour itself, in the large bowel, or it may have been a biopsy (a small piece) taken from the bowel or somewhere else. It is widely believed that each cancer contains specific information that should make it possible to select the most effective available treatment for each individual patient; this is called stratified (or "personalised") medicine. You have already given permission for your previously stored tumour sample to be examined with molecular tests, in order to better understand the different types of bowel cancer and to guide your treatment within the FOCUS4 trial.

What we are now asking is for you to consider having a minor procedure (a biopsy) to provide tumour tissue that can be compared with the first specimen. This will allow us to learn how cancers change over time or differ from one place in the body to another, and that information should eventually improve the way different treatments are selected for different patients.

2. Why are additional biopsies required if one has already been taken?

It is not routine to repeat a biopsy except when an oncology doctor is not sure whether something is or is not cancerous. This is not the reason we are requesting the additional biopsy or biopsies. We know that in some cases the molecules or genes that are present in the original bowel cancer change with time, or are found to be different when cancers spread to another part of the body. Also, cancer treatment itself can sometimes alter the patterns of molecules and genes.

Therefore these samples will be used for bowel cancer research including genetic analyses. By examining a sequence or series of samples before and after treatment, we think we can find

valuable information to help improve our matching of treatments to individual tumours in the future. The information from these 'extra' samples will not be routinely passed on to you or be used to help to select a treatment for you as we need to collect enough samples from a number of patients before we can learn how best to use this information. However, they should help future patients by improving our understanding of why these drugs work in some people but not others and how a treatment that works initially may then stop working. As per the trial overall your personal information will be anonymised and confidential.

3. Do I have to have a biopsy taken?

Additional biopsies are not compulsory; you may still take part in the trial without taking part in this sub-study. However, we hope you will consider it for the reasons above. You will be asked to have a biopsy only if your oncology doctors feel that this can be done in your case with minimal risk or discomfort.

4. How are the biopsies taken?

You will have blood tests before the biopsy to check how well your blood will clot. This is to make sure that bleeding following the biopsy will not be a problem. You may be advised to stop medicines that affect blood clotting, such as aspirin and clopidogrel, for one week before the biopsy. (You may need to discuss your medication with your oncology doctor if you take such medicines for other conditions). Please inform your oncology doctor if you are taking warfarin.

The technique for obtaining an additional biopsy from your cancer will vary depending upon which part or parts of your body the cancer is affecting. Usually a CT or MRI scan will have already given us this information which is specific to you. We will usually choose the easiest place to access this sample. The commonest place for a biopsy to be taken from is the liver but other places will include the lung or skin or the abdomen or a lymph gland.

The biopsy would only be taken after your full consent has been obtained by your oncology doctor. Your oncology doctor or a surgeon or a radiologist will perform the procedure. First the area is sterilised to make sure it is clean and no infection is introduced. Often a local anaesthetic is used to numb the skin and an ultrasound or CT scan is used to guide a needle into exactly the right place where the biopsies are to be taken from. A special hollow needle is pushed through the skin into the area. Because of the local anaesthetic, you should not feel much discomfort. However, you may feel some pressure as the doctor pushes on the needle.

You may be asked to hold your breath for 5 - 10 seconds when the needle is quickly pushed in and out (you will be told exactly when). This is because the body moves slightly when you breathe in and out. As the needle comes out it brings with it a small sample of tissue. To ensure enough tissue is obtained containing cancer cells, a second sample will be taken at the same time.

5. What are the risks of having a biopsy?

The risks from the biopsy depend on from where the biopsy is to be taken and these risks will commonly consist of mild local bleeding/bruising and discomfort. In the case of a liver biopsy, there is a very small risk of bleeding which would require an operation to control. In the case of a lung biopsy, there is a small risk of causing the collapse of one lung requiring the insertion of a tube to allow the lung to re-inflate. The specific risks will be discussed with you depending on which biopsy is to be performed and you will need to sign a separate consent form in relation to this, after talking to the team that will actually perform the procedure.

6. What happens after a biopsy has been taken?

After a liver biopsy:

You will need to lie on a bed and be observed for several hours to check that you have no bleeding. Therefore, you may wish to bring in a book or an mp3 player for this time.

You can drink fluids immediately after returning to the ward and will be allowed food a few hours later. If the biopsy was done early in the morning, you should be able to go home later in the day. If the biopsy is done later in the day, you may need to stay overnight. You may have some discomfort which is usually eased with painkillers.

Your oncology doctor will advise you not to take part in contact sports such as rugby for a certain length of time after the procedure. This is to make sure the liver has a chance to heal properly.

After a lung biopsy:

A chest X-ray will be performed shortly after the procedure and will be reviewed prior to your discharge, which will usually be on the same day as the biopsy is taken. If there is a small collapse of the lung further x-rays may be required to ensure that this is improving itself. A larger collapse of the lung may require a tube called a chest drain to be inserted between the ribs in order to re-inflate the lung. This would require you to be admitted overnight and possibly for a few days.

After any biopsy:

You will receive specific advice, but in general should seek medical advice if:

- You become short of breath
- Develop chest pain
- Become dizzy or faint
- The biopsy site becomes red or angry looking
- You develop a fever or temperature
- The biopsy site is still painful three days later and painkillers do not help

If you experience any side effects or if you have any questions about this research during this study you may contact:

Local Investigator: Dr …….. Telephone no: ……
Research Nurse: ……. Telephone no: ……..

Thank you for taking the time to read this information sheet and for considering taking part in FOCUS4 Additional Biopsy sub-study. Please feel free to keep this information sheet. You may wish to discuss this option with friends or family before agreeing to take part. Please use this space below to record any questions you might have for your oncology doctor at your next visit.

APPENDIX VIII – PATIENT CONSENT FORM FOR OPTIONAL BIOPSY SUB-STUDY

<PRINT ON HOSPITAL HEADED PAPER>

CONSENT FORM 3 (CF3)

FOCUS4 Additional Biopsies Sub-Study:

Date: Version 1.0, February 2013

Centre name and number: ……..
Patient Registration ID number: ……..

Please initial boxes:

1. I confirm that I have read and understand the Patient Information Sheet 3 (Version 1.0, February 2013) for the above research study and have been given a copy to keep. I have had the opportunity to ask questions and am satified with the answers to my questions. ☐
2. I give permission for an additional biopsy to be taken and for the sample to be sent to the central laboratory for bowel cancer research including genetic analyses. ☐
3. I give permission for a copy of my consent form to be sent to the MRC CTU where once checked, the consent form will be destroyed. ☐
4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
5. I agree to take part in the above research study. ☐

Name of Patient	Date	Signature
Name of person providing consent (if different from patient)	Date	Signature
Researcher	Date	Signature