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

Master Protocol

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

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Date: 17th April 2018
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 comparison protocols for each of the randomised comparisons, encompasses the protocol for the FOCUS4 Trial Programme. FOCUS4 is coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College Hospital (UCL) (referred to in the protocol as MRC CTU), and these documents provide information about procedures for entering patients into FOCUS4.

The FOCUS4 Trial 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 Trial 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: Z6364106), 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 Trial Programme. Queries relating to MRC sponsorship should be addressed to the Director, Professor Max Parmar, Institute of Clinical Trials & Methodology, MRC CTU at UCL, 90 High Holborn, 2nd Floor, London, WC1V 6LJ, or via the FOCUS4 Trial Team.

FUNDING

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

AUTHORIZATIONS AND APPROVALS

This FOCUS4 Trial Programme and all current comparisons within it were approved by the NRES South Central Oxford – Panel C ethics committee and the Medicines and Healthcare products Regulatory Agency. Subsequent comparisons will all be submitted for approvals. FOCUS4 is part of the NIHR Clinical Research Network (NIHR CRN) portfolio.

TRIAL REGISTRATION

The FOCUS4 Trial Programme has been registered with the ISRCTN Clinical Trials Register, where it is identified as 90061546.
TRIAL ADMINISTRATION

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

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

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FOCUS4 STRUCTURE AND SCHEMA

FOCUS4 is a molecularly stratified, multi-arm, multi-stage (MAMS) design, multi-site randomised trial programme for patients with colorectal cancer (CRC). During the initial registration period, all patients are treated with standard first-line treatment and considered for a standard treatment break if they have responding or stable disease after first-line treatment. 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 first-line treatment after approximately 16 weeks. The patient will then be offered entry into a specific comparison on the basis of their molecular cohort(s). Each of these comparisons (which are each identified by a unique letter) may be double blind and placebo controlled for oral agents but may be modified for intravenously administered agents as a double blind placebo design may not be appropriate or acceptable to patients. A separate specific comparison protocol will describe the procedures for each comparison. See Figure 1 for the original FOCUS4 Trial Programme Schema. As new agents are tested within each molecular cohort of the FOCUS4 Trial Programme a new letter is assigned to that comparison. The Trial schema adapts as new comparisons are opened and the trial schema in each comparison protocol will be updated whilst the original in the Master Protocol remains unchanged. For the current status of the comparisons within the FOCUS4 Trial Programme please refer to each comparison protocol and the FOCUS4 website, www.focus4trial.org.
**Figure 1: Original FOCUS4 Trial Programme Schema - registration, randomisation and treatment**

For the current trial schema, please see comparison-specific protocols and the website.

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 first-line treatment. It will also cover aspects such as trial governance generic to all comparisons within the FOCUS4 Trial Programme.

- **FOCUS4 Comparison Protocols**: Following the biomarker panel results, patients are allocated into a series of individual randomised comparisons. Initially these are effectively randomised phase 2 comparisons but, within the multi-stage statistical design, each can independently roll forward into a randomised phase 3 comparison 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 the molecularly stratified cohorts to which patients may be randomised. The

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*Patients with more than one mutation can be offered entry into whichever molecular comparisons for which they are eligible or FOCUS4-N, in discussion with their clinician. The exception is BRAF mutant, where patients can only be offered FOCUS4-A (when it is open) and FOCUS4-N.
comparisons listed below are the original ones (no longer current) that were planned for each corresponding cohort:

- Patients with **BRAF**-mutation: **FOCUS4-A**
- Patients with **PIK3CA** mutation: **FOCUS4-B**
- Patients with either **KRAS** or **NRAS** mutation: **FOCUS4-C**
- Patients with PTEN expression and wild type for **BRAF**, **PIK3CA**, **KRAS**, **NRAS** mutations: **FOCUS4-D**
- Patients unclassified or unable/unwilling to enter a molecular comparison: **FOCUS4-N**

For a small group of patients with multiple mutations, e.g. a patient with **PIK3CA** mutation and **KRAS** mutation, they may be offered entry into both the FOCUS4-B and FOCUS4-C comparisons. Clinicians should discuss all the possible comparisons with the patient (including FOCUS4-N), before confirming with the MRC CTU the molecular cohort they will be randomised into. The exception is patients with **BRAF** mutation for which there is no current available FOCUS4-A comparison. Therefore, if a patient has **BRAF** mutation and **PIK3CA** mutation they will only be eligible for FOCUS4-N (that is, they would not be eligible for FOCUS4-B). This is due to the poor prognosis of patients with **BRAF** mutations.

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 comparisons within the FOCUS4 Trial Programme please refer to the FOCUS4 website, [www.focus4trial.org](http://www.focus4trial.org).

The comparisons 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 Trial Programme

<table>
<thead>
<tr>
<th>TERM</th>
<th>MEANING</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOCUS4</td>
<td>The whole FOCUS4 Trial Programme</td>
</tr>
<tr>
<td>Master Protocol</td>
<td>The FOCUS4 Master Protocol describes the procedures for patient identification, registration, biomarker testing and initial standard therapy procedures. It also contains generic information relating to all comparisons in the FOCUS4 Trial Programme.</td>
</tr>
<tr>
<td>FOCUS4-A</td>
<td>The name for a specific comparison (letter A onwards)</td>
</tr>
<tr>
<td>Comparison Protocol</td>
<td>The protocol for a specific comparison (letter A onwards)</td>
</tr>
<tr>
<td>Molecular cohort</td>
<td>The molecular sub-group determined from the biomarker tests performed on the tumour sample sent off at registration.</td>
</tr>
<tr>
<td></td>
<td>The original molecular cohort classification within FOCUS4 is:</td>
</tr>
<tr>
<td></td>
<td>• <em>BRAF</em> mutation</td>
</tr>
<tr>
<td></td>
<td>• <em>PIK3CA</em> mutation</td>
</tr>
<tr>
<td></td>
<td>• <em>KRAS</em> or <em>NRAS</em> mutations</td>
</tr>
<tr>
<td></td>
<td>• wild type for all mutations above and with <em>PTEN</em> expression</td>
</tr>
<tr>
<td>Biomarker defined cohort</td>
<td>Same as molecular cohort</td>
</tr>
<tr>
<td>Stage I, II, III or IV</td>
<td>The interim analysis stages in the MAMS design.</td>
</tr>
<tr>
<td>Phase 2 or 3</td>
<td>The phases of the trial:</td>
</tr>
<tr>
<td></td>
<td>Phase 2 includes stages I and II</td>
</tr>
<tr>
<td></td>
<td>Phase 3 includes stages III and IV</td>
</tr>
<tr>
<td>Step 1 or 2</td>
<td>The patient information and consent steps for registration (Step 1) and randomisation (Step 2)</td>
</tr>
<tr>
<td>Period</td>
<td>Registration or trial period</td>
</tr>
<tr>
<td>Level</td>
<td>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.</td>
</tr>
</tbody>
</table>
FOCUS4 DETAILED SUMMARY TABLE

<table>
<thead>
<tr>
<th>SUMMARY INFORMATION TYPE</th>
<th>SUMMARY DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACRONYM</td>
<td>FOCUS4</td>
</tr>
<tr>
<td>Long Title of Trial Programme</td>
<td>Molecular selection of therapy in colorectal cancer: a molecularly stratified randomised controlled trial programme</td>
</tr>
<tr>
<td>Note</td>
<td>This protocol is the FOCUS4 Master Protocol. Patients will be registered into the FOCUS4 Trial Programme and subsequently randomised into a comparison available for their molecular cohort. These comparison protocols will have the acronyms of FOCUS4-A, FOCUS4-B etc., and are provided as separate protocol documents.</td>
</tr>
<tr>
<td>Version</td>
<td>6.0</td>
</tr>
<tr>
<td>Date</td>
<td>5th April 2018</td>
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<tr>
<td>MRC CTU ID</td>
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<td>ISRCTN #</td>
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<td>00316/0245/001-0001</td>
</tr>
<tr>
<td>REC #</td>
<td>13/SC/0111</td>
</tr>
<tr>
<td>Type of Participants to be Studied</td>
<td>Adult patients with inoperable advanced or metastatic colorectal cancer (CRC) who are suitable for intermittent chemotherapy.</td>
</tr>
<tr>
<td>Study Design</td>
<td>The FOCUS4 Master Protocol describes the registration period - identification of patients, biomarker testing and initial standard first-line therapy prior to randomisation into FOCUS4. Patients undergoing first-line treatment 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 patients into one of several possible molecular cohorts. Patients are offered entry into the comparison(s) available for their molecular cohorts following discussion with their clinician. Each comparison within these patient molecular cohorts will aim to be double blind and compare an intervention with a placebo control and have its own dedicated comparison protocol. FOCUS4-N will run concurrently for patients whose biomarker panel results are unclassifiable; for those whose molecular cohort comparison is temporarily not open for recruitment, and for any patients unable or unwilling to travel. (For safety reasons, agents for some cohorts...</td>
</tr>
</tbody>
</table>
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 active monitoring; unlike the other trials, this chemotherapy comparison will not be blinded or placebo controlled.

FOCUS4 is a rolling trial programme that utilises the MAMS design. A maximum of 4 staged interim analyses are proposed for each comparison: 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.

Specific agent(s) are detailed separately in each of the comparison protocols. The comparisons listed below were the original comparisons planned for each molecular cohort:

**Cohort: BRAF mutant tumours**

Comparison 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: Active Monitoring (treatment break)

**Cohort: PIK3CA mutant tumours**

Comparison name: FOCUS4-B  
Intervention(s): Aspirin  
Control: Placebo

**Cohort: KRAS or NRAS mutant tumours**

Comparison name: FOCUS4-C  
Intervention(s): Dual pathway inhibition using an AKT inhibitor and MEK inhibitor  
Control: Dual Placebo
### Cohort: All wild type (no BRAF, PIK3CA, KRAS, NRAS mutations) with PTEN expression
- Comparison 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 comparison available in their molecular cohort or the comparison for their molecular cohort is not open to recruitment at that time).
- Comparison 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 treatment, 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 comparisons 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 v1.1 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 comparisons that progress to Stage III.

### Secondary Outcome Measure(s)
1) Safety, toxicity and tumour response.
2) Quality of life (QL) may be assessed in any molecularly stratified comparison where the release of interim results at the end of stage II leads to a decision to continue the comparison to stage III. However, QL data may be collected at other stages if it is deemed to be important for that specific comparison. QL will be assessed throughout FOCUS4-N from randomisation onwards.

### Randomisation
Randomisation into the trial will not occur until the completion of
first-line treatment/end of the registration period. Minimisation with a random element will be used for patient allocation and the randomisation ratio will be defined within each comparison 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 trial programme that utilises the MAMS design. The following numbers are generic and indicate the cumulative number of patients required to evaluate an intervention up to the end of each interim analysis stage. **Actual sample sizes will vary for each comparison within these cohorts and are detailed in the specific comparison protocols:**

- **BRAF mutant** = 61 (stage I), 97 (II), 139 (III), 301 (IV)
- **PIK3CA mutant/PTEN loss** = 170 (I), 264 (II), 373 (III), 546 (IV)
- **KRAS/NRAS mutant** = 177 (I), 273 (II), 378 (III), 574 (IV)
- All wild type = 180 (I), 275 (II), 381 (III), 547 (IV)
- **FOCUS4-N**: Target up to 643 patients.

**Duration**

7 years (4 to 5 years recruitment)

**Ancillary Studies/Substudies**

1) Biomarker development programme for the all wild type cohort
2) Fresh tumour biopsies at randomisation and on progression from patients giving consent and with accessible tumour
3) Circulating Free 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**

MRC/NIHR EME programme and CR-UK

**Chief Investigators**

Overall: Professor Tim Maughan and Professor Richard Wilson

Each individual comparison:
- **FOCUS4-A**: Professor Gary Middleton
- **FOCUS4-B**: Professor Richard Wilson & Dr David Church
- **FOCUS4-C**: Professors Tim Maughan, Matt Seymour and Dr Jenny Seligmann
- **FOCUS4-D**: Dr Richard Adams
- **FOCUS4-N**: Professor Tim Maughan

**Current Status of FOCUS4 Trial**

Please refer to FOCUS4 website at:

[http://www.focus4trial.org/](http://www.focus4trial.org/)
**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). The chart is presented for a patient who has had exactly 16 weeks of uninterrupted first line treatment. (This is also provided in Section 6.1 on page 35)

| WEEK | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| First-line treatment# |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Check registration eligibility criteria Δ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PIS1Δ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Registration Δ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tumour block sent Δ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CT scan § |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| RECIST v1.1 response |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PIS2 ∞ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Check specific comparison eligibility criteria |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Baseline assessment † |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Wash out from first-line chemo ‡ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Randomisation ¥ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Start trial treatment £ |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Optional Assessments * |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Blood (Genomic DNA) * |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Blood (Circulating DNA) * |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tumour biopsy * |             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

**Key to symbols**

# Regime determined locally for approximately 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 comparisons.

Δ PIS1, registration and tumour block can be completed at any time up to week 12 of first-line treatment

§ Mandatory CT scan within 6 weeks (see section 3.3) prior to the start of standard first-line treatment, recommended interim CT scan after 8 weeks of treatment; mandatory CT scan after last dose of first-line treatment

∞ PIS2 can be given when biomarker panel results are known and interim CT scan shows SD, PR or CR

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

‡ Wash out period of 3 weeks between end of first-line treatment and start of allocated trial therapy (NB this is not applicable for FOCUS4-N, please refer to specific comparison protocols for full details)

¥ Randomisation must be within 28 days of pre-randomisation CT scan

£ Trial Treatment should be commenced as soon as possible after randomisation

* Not required if patient has withheld consent for molecular research tumour biopsy or there is no tumour accessible for percutaneous biopsy. Genomic DNA sample only required once, i.e. it is only required at randomisation if not already taken during the registration period.
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### ABBREVIATIONS AND GLOSSARY

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<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase (also known as ALKP)</td>
</tr>
<tr>
<td>All Wild Type</td>
<td>Wild type for BRAF, KRAS, NRAS, PIK3CA mutations and PTEN</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Transaminase</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>AREG</td>
<td>Amphiregulin</td>
</tr>
<tr>
<td>APC gene</td>
<td>Adenomatous Polyposis Coli Gene</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate Transaminase</td>
</tr>
<tr>
<td>AZ</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>BD or BID</td>
<td>Twice Daily</td>
</tr>
</tbody>
</table>
| Biomarker    | The molecular sub-group determined from the biomarker tests performed on the defined cohort tumor sample sent off at registration. The original molecular cohort classification in FOCUS4 is:  
  - BRAF mutation  
  - PIK3CA mutation  
  - KRAS or NRAS mutations  
  - Wild type for all mutations above and with PTEN expression |
| BRAF         | B-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                                     |
<p>| 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 |
| Comparison   | The protocol for a specific comparison (letter A onwards)                   |
| Protocol     |                                                                           |
| CRC          | Colorectal Cancer                                                          |
| CRF          | Case Report Form                                                           |
| CRN          | Clinical Research Network                                                  |</p>
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CR-UK</td>
<td>Cancer Research UK</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trials Authorisation</td>
</tr>
<tr>
<td>CTAAC</td>
<td>Clinical Trials Awards and Advisory Committee</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTIMP</td>
<td>Clinical trial of an investigational medicinal product</td>
</tr>
<tr>
<td>CTU</td>
<td>Clinical Trials Unit</td>
</tr>
<tr>
<td>DH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DM</td>
<td>Data Manager</td>
</tr>
<tr>
<td>DMC</td>
<td>Data Monitoring Committee</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DPA</td>
<td>(UK) Data Protection Act</td>
</tr>
<tr>
<td>DUSP4 &amp; 6</td>
<td>Dual Specific Phosphatases 4 &amp; 6</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECMC</td>
<td>Experimental Cancer Medicine Centre</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>eDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylene Diamine Tetraacetic Acid</td>
</tr>
<tr>
<td>EGFR</td>
<td>Epidermal Growth Factor Receptor (also HER-1 and Erb1)</td>
</tr>
<tr>
<td>EGFR Dependent</td>
<td>Wild type for BRAF, PIK3CA, KRAS, NRAS, mutations and PTENWithin this comparison the term “EGFR dependent” is sometimes used synonymously with the term “All wild type”</td>
</tr>
<tr>
<td>EME</td>
<td>Efficacy Mechanism Evaluation</td>
</tr>
<tr>
<td>EREG</td>
<td>Epiregulin</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EudraCT</td>
<td>European Union Drug Regulatory Agency Clinical Trial</td>
</tr>
<tr>
<td>FBC</td>
<td>Full Blood Count</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin Fixed Paraffin Embedded</td>
</tr>
<tr>
<td>FOCUS4</td>
<td>The whole FOCUS4 Trial Programme</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>5FU, folinic acid and Irinotecan</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>5FU, folinic acid and Oxaliplatin</td>
</tr>
<tr>
<td>5FU</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>HER</td>
<td>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</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for...</td>
</tr>
</tbody>
</table>
**Term** | **Definition**
---|---
Registration of Pharmaceuticals for Human Use | Registration of Pharmaceuticals for Human Use
Independent Data Monitoring Committee | IDMC
Immunohistochemistry | IHC
Investigational Medicinal Product | IMP
Integrated Research Application System | IRAS
International Standard Randomised Controlled Trial Number | ISRCTN
Interactive Web Response System | IWRS
Intention-to-Treat | ITT
Lactate Dehydrogenase | LDH
Level | Refers to the categorisation of sites into Levels 1, 2 or 3
Liver Function Tests | LFTs
Lower Limit of Normal | LLN
Lack of Sufficient Activity | LSA
Left Ventricular Ejection Fraction | LVEF
v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog | KRAS
Metre-squared | m²
Multi Arm Multi Stage | MAMS
The FOCUS4 Master Protocol describes the procedures for patient identification, registration, biomarker testing and initial standard therapy procedures. It also contains generic information relating to all comparisons in the FOCUS4 Trial Programme.
Metastatic Colorectal Cancer | mCRC
Multidisciplinary Team | MDT
Magnesium | Mg
Milligrams | mg
Medicines and Healthcare products Regulatory Agency | MHRA
Millilitre | ml
Millimetres of Mercury | mmHg
Mis-matched Repair | MMR
The molecular sub-group determined from the biomarker tests performed on the tumour sample sent off at registration.
The original molecular cohort classification in FOCUS4 is:
- **BRAF** mutation
- **PIK3CA** mutation
- **KRAS or NRAS** mutations
- Wild type for all mutations above and with PTEN expression
Medical Research Council | MRC
Medical Research Council Clinical Trials Unit at UCL | MRC CTU
Main Research Ethics Committee | MREC
Messenger Ribonucleic Acid | mRNA
Millisecond | mSec
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD</td>
<td>Maximum Tolerated Dose</td>
</tr>
<tr>
<td>MUGA</td>
<td>Multi Gated Acquisition Scan</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NCRI</td>
<td>National Cancer Research Institute</td>
</tr>
<tr>
<td>NCRN</td>
<td>National Cancer Research Network</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>NIHR CRN</td>
<td>National Institute for Health Research Clinical Research Network</td>
</tr>
<tr>
<td>NIHR CSP</td>
<td>National Institute for Health Research Co-ordinated System for gaining NHS Permission</td>
</tr>
<tr>
<td>NIMP</td>
<td>Non-Investigational-Medicinal Product</td>
</tr>
<tr>
<td>NRAS</td>
<td>Neuroblastoma RAS viral (v-ras) oncogene homolog</td>
</tr>
<tr>
<td>ONS</td>
<td>Office of National Statistics</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival (an additional potential primary outcome)</td>
</tr>
<tr>
<td>OxMdG</td>
<td>Oxaliplatin , 5FU and Folinic acid</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive Disease (RECIST)</td>
</tr>
<tr>
<td>Period</td>
<td>Registration or trial period</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-Free Survival (the primary outcome)</td>
</tr>
<tr>
<td>PH</td>
<td>Proportional Hazards</td>
</tr>
<tr>
<td>Phase 2 or 3</td>
<td>Phases of the trial:  Phase 2 includes Stages I and II</td>
</tr>
<tr>
<td></td>
<td>Phase 3 includes Stages III and IV</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha</td>
</tr>
<tr>
<td>PIS</td>
<td>Patient Information Sheet:</td>
</tr>
<tr>
<td></td>
<td>- PIS1 = for registration</td>
</tr>
<tr>
<td></td>
<td>- PIS2 = for randomisation</td>
</tr>
<tr>
<td></td>
<td>- PIS3 = for optional biopsy sub-study</td>
</tr>
<tr>
<td>PR</td>
<td>Partial Response (RECIST)</td>
</tr>
<tr>
<td>PS</td>
<td>Performance Status</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and Tensin homolog</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>QL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors (V1.1)</td>
</tr>
<tr>
<td>RGC</td>
<td>Research Governance Committee</td>
</tr>
<tr>
<td>RGF</td>
<td>Research Governance Framework (for Health and Social Care)</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>SD</td>
<td>Stable Disease (RECIST)</td>
</tr>
<tr>
<td>SNP</td>
<td>Single-Nucleotide Polymorphism</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>Stage I, II, III or IV</td>
<td>Interim analysis stages in the MAMs design</td>
</tr>
<tr>
<td>Step 1 or 2</td>
<td>The patient information and consent steps for registration (step 1) and randomisation (step 2)</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>TCGA</td>
<td>The Cancer Genome Atlas</td>
</tr>
<tr>
<td>TGF</td>
<td>Transforming Growth Factor</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine Kinase Inhibitor</td>
</tr>
<tr>
<td>TM</td>
<td>Trial Manager</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
</tr>
<tr>
<td>UAR</td>
<td>Unexpected Adverse Reaction</td>
</tr>
<tr>
<td>U&amp;Es</td>
<td>Urea and Electrolytes</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WT</td>
<td>Wild type</td>
</tr>
<tr>
<td>XELOX</td>
<td>Xeloda (Capecitabine) plus Oxaliplatin</td>
</tr>
</tbody>
</table>
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. The use of EGFR-targeted therapy has led to the discovery of the importance of \( \textit{BRAF}, \textit{PIK3CA}, \textit{KRAS} \) and \( \textit{NRAS} \) mutations in prediction of lack of response to EGFR-targeted therapy. 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 comparison 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 \( \textit{BRAF} \) mutation who only comprise 8% of the metastatic CRC population.

This trial programme 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 in-depth molecular characterisation of colon and rectal cancer. A key driver of CRC is the \( \textit{wnt} \) pathway which is affected in nearly every case of CRC, and can be deregulated at many points but most commonly at the \( \textit{APC} \) gene. The TGF-\( \beta \) 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 \( \textit{myc} \) 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 comparisons 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 MRC CoNtinuous or INtermittent (COIN) trial 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.

**Prevalence:** COIN trial, 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, 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 expression**

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 expression by various mechanisms including mutation, methylation silencing of the promoter and microRNA inhibition. The TGCA report has identified increased signalling through the IGF receptor due to amplification of IGF2 as an important additional driver within this pathway.

**Prevalence:** 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 expression 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\(^7\).

**Prevalence:** 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.

**Wild type for all the above mutations (EGFR dependent)**

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.

**Prevalence:** 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 comparisons which are suspended between novel therapy evaluations or patients who chose not to participate in their specific molecular comparison due to reasons such as distance to an experimental therapy centre. Once a patient enters a particular comparison, they would not be able to enter another FOCUS4 comparison 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 of 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 comparisons for each molecular cohort, the novel therapy comparisons will be double blind and placebo controlled where possible. FOCUS4-N will allocate patients to either capecitabine or active monitoring and thus will be an open, unblinded trial. Standard objective measurements of tumour response and toxicity grading will be used. Tumour responses will be documented on CT scans and disease response will be evaluated according to RECIST v1.1 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 TREATMENT

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

1) The COIN Trial, which randomised 1630 patients, tested whether intermittent chemotherapy is non-inferior to continuous chemotherapy. 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 (>400x10⁹/L in 28% patients, n=271) was the only variable associated with a significant overall 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). Thus, when FOCUS4 first opened, it was agreed that these patients would be excluded. However, this finding that patients with high platelets (>400x10⁹/L) fare less well with a treatment break had not been validated or tested in a new patient group. Subsequently, a meta-analysis was undertaken of all available trials testing continuous versus intermittent therapies in whom baseline platelet data has been collected. The results did not validate the finding seen in COIN and although they confirmed that high platelets are predictive of poor prognosis overall, there was little evidence to suggest an interaction with continuous versus intermittent therapies in terms of overall survival. Therefore, following discussion and approval by the IDMC and TSC, the Master protocol has been amended (from version 3.0 to 4.0) to allow patients with high platelets (>400x10⁹/L) to be registered into the FOCUS4 Trial Programme. Future randomisations will be stratified by high or low platelet status.

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 first-line treatment 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 \(\text{KRAS}\) 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 treatment.

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, 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 comparisons and the intervention is given in the
specific comparison protocols. The specific agents and the biomarker definition of the molecular
cohorts may change as subsequent FOCUS4 comparisons are introduced. This master protocol will
continue to apply as the over-arching trial protocol.
1.3.2 TRIAL DESIGN IMPROVEMENT

In the FOCUS4 Trial Programme, patients will be registered with newly-diagnosed advanced or metastatic disease from colorectal cancer, undertake a centralised biomarker panel test and allocate patients into the most appropriate cohort based on the results of the biomarker analysis. Some comparisons 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 comparison 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 Trial Programme, there will be times when not all comparisons will be open in the molecular cohorts but a current list of open comparisons will be available on the FOCUS4 website. Patients who are classified into any cohort for which a comparison is not currently open will be offered entry into FOCUS4-N or, if appropriate, entry into one of the other molecular cohort comparisons where they are selected for that mutation (e.g. 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 (All wild type) cohort:**

   What is the optimal algorithm for stratification of the EGFR dependent (All wild type) 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 starting trial treatment 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 mechanisms 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 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, e.g. 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 FOCUS4-N, 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 Comparison 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 FOCUS4-N; referral of patients to Level 2 and 3 sites for randomisation to the other FOCUS4 comparisons; 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 Trial Programme
- Identification of an FFPE block containing tumour by the pathologist and sending the block for biomarker analysis to their allocated central laboratory
- If the site can deliver standard chemotherapy, then the first-line treatment (prior to randomisation) can be delivered at the site
- CT scans to be performed prior to start of standard first-line treatment, at an interim time point (8 weeks recommended) and at the end of first-line treatment, with ability for electronic transfer of scans to other sites

IMPORTANT NOTE: The FOCUS4 trial is 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 obtained by the Level 2 or 3 site.
- Randomisation of patients into FOCUS4-N
- Treatment and follow-up of patients randomised into 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 into FOCUS4 comparisons of novel agents against placebo when these have been approved for use at Level 1 sites
- **24 hour access** to a clinician for patients including notification of SAEs that occur out of hours.

### 2.1.2 LEVEL 2 SITES

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

- Assessing patients for eligibility for randomisation into the specific FOCUS4 comparisons open at Level 2 sites
- Obtaining informed consent for randomisation, including for additional research biopsies
- Randomisation of patients into the specific FOCUS4 comparisons open at Level 2 sites
- Obtaining consent, performing, 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 obtained by the Level 3 site
- Administration of trial treatments that have been approved for use at Level 2 sites
- **24 hour access** to a clinician for patients including notification of SAEs that occur out of hours. 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 comparisons only open at Level 3 sites
• Randomisation of patients into the specific FOCUS4 comparisons 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 assessment. Once this has been completed and level of site determined, the FOCUS4 team will provide the site with the FOCUS4 Trial 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 comparisons 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 treatment, 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 first-line treatment during the registration period. 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 Trial Programme protocol

i. All staff assisting with FOCUS4 are adequately informed and trained about the FOCUS4 Trial Programme protocols, the investigational products and their FOCUS4 related duties. Staff will participate in mandatory initial and ongoing training for the FOCUS4 Trial Programme

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 Trial 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 Trial 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 onward to a Level 3 site for consideration in comparisons involving more experimental agents, until the therapy is deemed to be sufficiently safe and appropriate for patients 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 biological therapies
b. Readiness and resource to attend additional monitoring and Investigator teleconferences as required when the first patients are being dosed
c. Willingness to accept referrals from Level 1 and 2 sites.

To participate in the FOCUS4 Trial 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 comparison 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 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. The investigator will ensure all onward training will be recorded and documented.

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 facilities 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 comparison 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 comparison which requires Level 2 or 3 responsibility, randomisation into FOCUS4-N 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 confirming eligibility, obtaining informed consent, randomisation and administration of trial therapy. Full details and assessment schedules can be found in the FOCUS4 comparison protocol.

Once a patient has been randomised, 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, treatment and follow up should be continued at that site until the therapy is deemed to be sufficiently safe and appropriate for that patient to be returned to the registration site. At this point, their surveillance may revert back to the original Level
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 comparison protocol. Information on the current status of FOCUS4 comparisons 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 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 UCL 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 HRA approval for the trial.
- CV of Principal Investigator and co-investigators (or confirmation that these are held on site) and show evidence of GCP training.
- 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, a signature and delegation log and training log for all FOCUS4 personnel at the site, (see section 2.5.2 for more information on required site training). 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 a 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. Once site training has been completed, the members of staff who have completed the training should be added to the training log and signed off by the PI. The log should then be stored in the FOCUS4 Local Investigator Site File and a copy of the up-to-date log should also be sent to the MRC CTU.

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 comparisons. If applicable, this will be explained in further detail in the individual comparison protocol. If a substantial amendment or new comparison is started, the FOCUS4 TMG will determine if further training is required for any new procedures and will notify the applicable sites.

At least one member of staff personnel who will be carrying out data entry on the FOCUS4 MACRO4 databases will also need to attend an eDC training session (carried out via WebEx by the FOCUS4 Data Managers) and complete a dummy data exercise in order to gain access to the databases prior to site activation. On completion of the eDC training/dummy data exercise, the attendee will receive a certificate of completion and access to the live FOCUS4 databases.

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 comparisons 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 comparisons they are activated and be sent the pharmacy pack containing required relevant information in regards to initial and subsequent drug orders.

Following substantial amendments and future comparisons opening, sites will be notified 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. If a violation or deviation from the approved protocol is found, the PI or delegate should notify the trial team at the MRC CTU as soon as they become aware. A Corrective Action Plan (CAP) should then be completed to document the deviation and action taken (this can be found in the Investigator’s Area of the FOCUS4 website: http://www.focus4trial.org).
3 SELECTION OF PATIENTS FOR REGISTRATION

3.1 NUMBER OF PATIENTS

FOCUS4 aims to randomise 1536 patients across all molecular cohorts over five 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 and ~2400 of these will be registered. For sample size calculations, please refer to Section 9.3 or the statistical sections in each comparison 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 with plenty of time for consideration.

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 first-line treatment, ideally within 8-10 weeks but no later than 12 weeks into the treatment regimen, providing the patient meets all the registration eligibility criteria prior to starting their first-line treatment. Registration during these first 12 weeks allows an absolute minimum of 4 weeks for biomarker assessment before the end of first-line treatment 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 eEDC guidelines) and a unique registration number is allocated to that patient.

3.2.2 PATIENT INFORMATION SHEET 2 (PIS2)

PIS2 is specific to each comparison 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 cohort(s) the patient belongs to and thus which molecular comparison(s) they can be considered for.

ii) An interim CT scan (recommended 8 weeks after the start of first-line treatment) indicating that the patient has stable or responding disease and is therefore more likely to be stable and responding at the end of first-line treatment.

Once both these results are known, the information and consent procedure for the relevant comparison(s) can commence and the specific PIS2 for that comparison 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 comparison(s), then the alternative options (including FOCUS4-N) must be discussed with the patient and they must be provided with PIS2 for FOCUS4-N (PIS2-N).

Once the end of first-line treatment CT scan has been performed, if this confirms the patient still has stable or responding disease, the patient can be offered entry into their relevant molecular comparison(s) 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 end of registration CT scan can be used for patients entering the molecular cohort comparisons 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 performed in all sites providing there are adequate facilities.

Patients wishing to receive all information about all the available comparisons 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 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.
Figure 3.1: Patient Consent Process for Level 3 and Level 2 sites where the patients’ molecular cohort comparison(s) is available

Clinician and research nurse discusses FOCUS4 with patients using PIS1

Patient consents to registration?

Yes

Register patient with MRC CTU

Patient allocated Trial number

Research nurse contacts pathologist for rapid release of block to Cardiff/Leeds

Research nurse confirms with MRC CTU when request submitted to pathologist

Research nurse books interim and end of registration (16 week) CT scans

Patient has interim CT scan (recommended at 8 weeks)

Stable/responding disease?

Yes

Investigator informed of Biomarker Panel results, molecular cohort and which FOCUS4 comparison they can be considered for

Treatment Consultation with more detailed overview of specific trial to which the patient is eligible using the applicable PIS2

PIS2-A PIS2-B PIS2-C PIS2-D PIS2-N

Patient has end of registration (16 week) CT scan

No

Stable or responding disease?

Yes

Is the patient eligible and consents to their molecular cohort trial?

Yes

Randomise to FOCUS4 Trial for their molecular cohort

No

Is the patient eligible & consents to enter FOCUS4-N?

Yes

Randomise to FOCUS4-N

No

Patient not eligible for FOCUS4

Patient offered standard therapy off-trial

No

Patient begins/continues 16 weeks of standard first-line chemotherapy

Block received at reference laboratory

Receipt of block logged with MRC CTU

Biomarker panel performed at reference lab

Results sent to MRC CTU

Patient offered standard therapy off-trial

Register patient with MRC CTU

Patient allocated Trial number

Research nurse contacts pathologist for rapid release of block to Cardiff/Leeds

Research nurse confirms with MRC CTU when request submitted to pathologist

Research nurse books interim and end of registration (16 week) CT scans

Patient has interim CT scan (recommended at 8 weeks)

Stable/responding disease?

Yes

Investigator informed of Biomarker Panel results, molecular cohort and which FOCUS4 comparison they can be considered for

Treatment Consultation with more detailed overview of specific trial to which the patient is eligible using the applicable PIS2

PIS2-A PIS2-B PIS2-C PIS2-D PIS2-N

Patient has end of registration (16 week) CT scan

No

Stable or responding disease?

Yes

Is the patient eligible and consents to their molecular cohort trial?

Yes

Randomise to FOCUS4 Trial for their molecular cohort

No

Is the patient eligible & consents to enter FOCUS4-N?

Yes

Randomise to FOCUS4-N

No

Patient not eligible for FOCUS4

Patient offered standard therapy off-trial
Figure 3.2: Patient Consent Process for Level 1 and Level 2 sites where the patients’ molecular cohort comparison is NOT available

Clinicin and research nurse discusses FOCUS4 with patients using PIS1

Patient consents to registration?

Yes

Register patient with MRC CTU

No

Patient offered standard therapy off-trial

Block received at reference laboratory

Research nurse contacts pathologist for rapid release of block to Cardiff/Leeds

Research nurse confirms with MRC CTU when request submitted to pathologist

Research nurse books interim and 16 week CT scans

Patient has interim CT scan (recommended at 8 weeks)

Stable/responding disease?

Yes

Investigator informed of Biomarker Panel results, molecular cohort and which FOCUS4 comparison they can be considered for

PIS2-A PIS2-B PIS2-C PIS2-D PIS2-N

Patient has end of registration (16 week) CT scan

Stable/responding disease?

No

Patient not eligible for FOCUS4

No

Yes

Patient agrees referral to level 2 or 3 site?

Yes

At level 2/3 site: Is the patient eligible & consents to their molecular cohort trial?

Randomise to FOCUS4 Trial for their molecular cohort

No

Is the patient eligible & consents to enter FOCUS4-N?

Yes

Randomise to FOCUS4-N

No

Patient offered standard therapy off-trial

No

Yes

Stable/responding disease?

Patient offered standard therapy off-trial
3.3 PATIENT INCLUSION AND EXCLUSION CRITERIA FOR REGISTRATION

As MHRA inspections allow for no 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 Trial 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 Eligibility Checklist should be completed to confirm eligibility and signed by the registering investigator listed on the delegation log. A copy of the signed form must be submitted to the Trial Team at the MRC CTU.

Please note for each comparison, 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 comparison 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 first-line treatment and available for biomarker analysis
3. Histologically confirmed adenocarcinoma of the small bowel or 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 v1.1 classification (see Appendix IV)
7. Have had an electronically accessible CT scan performed. This scan should ideally be performed just before but no more than six weeks prior to commencement of standard first-line treatment.
   - Unavoidable delays of a few days for scheduling reasons may be approvable, but sites must contact the MRC CTU prior to registering the patient.
   - CT scans performed a few days after the start date of standard first-line treatment may also be approvable, but only after discussion with the MRC CTU team and prior to registering the patient.
8. For women of child-bearing potential, a negative pregnancy test and acceptable contraceptive precautions (see Appendix V)
9. Effective contraception for male patients if the risk of conception exists (see Appendix V)
10. Consent for screening of an archival FFPE tumour block for biomarker analysis
11. Patients who have already commenced on standard first-line treatment must be registered for the trial during the first 12 weeks of first-line treatment (this allows approximately 4 weeks for return of their biomarker results prior to the end of first-line treatment) providing they fulfilled the other registration eligibility criteria listed above prior to starting their standard chemotherapy.

12. Patients should have sufficient capacity for informed consent.

13. 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.
5. Patients with known HIV, hepatitis B or hepatitis C infection.

Patients with previous cancers may be considered for the trial providing they meet the above eligibility criteria. It is up to clinician discretion whether a patient with dual/previous cancers is approached dependent on stage of their other cancer and likely prognosis. Please contact the trial team at MRC CTU for further guidance.

Neo-adjuvant capecitabine given as a radiosensitiser for non-metastatic disease is permissible.
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 is 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 Data Provision Guidelines)
- Tumour samples need to be sent for testing as early as possible following registration to avoid delays in obtaining biomarker results. This is a rate limiting step in starting FOCUS4 treatment.
- Contact pathologist to arrange for the fast-track release of the patient’s tumour sample blocks to the laboratory which was assigned at site activation (Cardiff or Leeds), and complete Biomarker Panel Request Form
- If patient consents to blood sample collection, obtain the required samples as per described in section 4.6 and the Sample Collection and Handling SOP.

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 unambiguously 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 via the FOCUS4 MACRO Registration Database, a trial number will be issued. This trial 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 trial 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 and relevant data items have been collected.

### 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) and PTEN immunohistochemistry (IHC) of their primary tumour to determine their eligibility for randomisation within the FOCUS4 Trial Programme. Tumour Samples need to be sent for testing as early as possible following registration to avoid delays in obtaining biomarker results. This is a rate limiting step in starting FOCUS4 treatment.

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. Tumour blocks will therefore be tracked from time of patient registration to the time of patient randomisation or refusal/ineligibility to enter a trial.

The sample handling and tracking process is documented in the Sample Collection and Handling SOP and below 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 via MACRO, 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 first section of the Biomarker Panel 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 7670 4653) the partially completed Biomarker Panel Request Form. A copy of the patient registration consent form must also be sent via post or fax 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 trial number and patient’s 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 anonymised histology report (with trial number added) 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 Request Form and a copy of the anonymised histology report 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 the Biomarker Panel Request Form for their records.

Central Laboratory

• When the block arrives at the central laboratory, their staff will inform the MRC CTU of receipt.
  o If the block has not arrived at the central laboratory within two weeks 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 molecular cohort(s) the patient belongs to and which comparison(s) the patient can be considered for. A notification of the results will also be sent to the patient’s clinician and the pathologist that release the block for their information.

Please note the MRC CTU will enter the details of the Biomarker Panel Request Form into the registration database.
Figure 4.1: Tumour Sample Block Request Process

All blocks will be returned upon completion of translational research requirements but the central laboratories will undertake to return the blocks at short notice if these are required for patient management.

The Sample Collection and Handling SOP will be sent to sites as instructions for this and other translational sub-studies. A detailed laboratory manual has been prepared by the Cardiff and Leeds laboratories which details the methods used for biomarker panel assessment. 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 for patient in the all wild type cohort
- IHC for PTEN and MMR proteins

The results of these tests will be returned to the MRC CTU who will determine which molecular cohort the patient belongs to and which comparison(s) the patient can be considered for. The site will be informed of this information and the individual patients will be offered entry into the relevant comparison(s) 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), further blocks will be requested by the MRC CTU. However where further tissue is not available, these patients will be offered entry into FOCUS4-N. If one or more biomarker tests fail but sufficient data have been obtained for the other biomarker tests, the MRC CTU will allocate a cohort(s) and specific comparison(s) 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 should include the chest, abdomen and pelvis
- CT scans must be performed:
  1. Have had an electronically accessible CT scan performed. This scan should ideally be performed just before but no more than six weeks prior to commencement of standard first-line treatment.
     - Unavoidable delays of a few days for scheduling reasons may be approvable, but sites must contact the MRC CTU prior to registering the patient.
     - CT scans performed a few days after the start date of standard first-line treatment may also be approvable, but only after discussion with the MRC CTU team and prior to registering the patient.
  2. At an interim time during first-line treatment (recommended 8 weeks into chemotherapy) to see if the patient is responding to treatment. This scan is recommended but not mandatory.
  3. At the end of first-line treatment (after last dose of first-line treatment) to evaluate the progress of the patient’s response to first-line treatment. It is recommended that this scan is performed during the washout period (within the 3 weeks following the end of first-line treatment).

For those patients registered during the first 12 weeks of their first-line treatment, it is a requirement that CT scanning had been undertaken (refer to point 1 above) and the scan is accessible for review.

- For a patient to be eligible for randomisation they must have documented measurable disease (RECIST v1.1 criteria, Appendix IV) stating SD, PR or CR after first-line treatment. This scan must be within 28 days prior to randomisation.

IMPORTANT NOTE: The FOCUS4 trial is 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 v1.1 criteria.

4.5 PRIOR TO RANDOMISATION

- The specific comparison(s) for which the patient can be considered for will be known when the biomarker panel results have been obtained. Once the end of first-line treatment CT scan has confirmed stable or responding disease, the inclusion and exclusion criteria must be checked for randomisation into the comparison(s) for which they are eligible (please refer to the specific comparison protocol for the criteria).

- If not already given earlier (for example following receipt of the biomarker panel results and interim CT scan RECIST v1.1 assessment), the patient must be provided with PIS2 for the comparison(s) for which they are eligible. An explanation of the aims, methods, benefits and potential hazards of the specific comparison(s) must be discussed with the patient by the responsible treating clinician. FOCUS4-N can be discussed as a backup or alternative 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 comparison at any given time may be obtained from the Trial Managers or will be available on the FOCUS4 website. This referral must be arranged promptly to facilitate a smooth transition between the end of first-line treatment 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 comparison protocol which describes the specifics that are required.

- For patients who did not consent to the collection of blood samples 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 comparison (CF2)).

- At randomisation, patients are also asked for consent for further samples for circulating free DNA. Please refer to section 4.6 for further information.

- An End of Registration eCRF must be completed for all registered patients and submitted to the MRC CTU regardless of whether they are randomised or not.

Please note there is a wash out period of 3 weeks between the end of standard first-line treatment and commencement of randomised protocol treatment. Please note that this does not apply to patients in FOCUS4-N. This is a mandatory safety issue prior to use of novel investigational agents. Please refer to each comparison protocol for specific comparison 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 comparison 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 10mL EDTA tube, labelled with the date and patient’s 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. The Genomic Blood Sample Submission CRF should also be sent with the sample. 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 Trial Programme
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 time points 1), 2) and 4) below and for as many 8 week time points as possible during the course of a patient’s involvement with FOCUS4:

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

In sites where rapid centrifuge, plasma extraction and freezing are possible 2 x 10ml blood samples will be taken directly into EDTA tubes. 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). Samples must be frozen at -80°C and stored until courier delivery is organised for collection.

The protocol for handling these samples is included in the Sample Collection and Handling SOP.

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 starting trial treatment 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 CT scan taken at the end of first-line treatment 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 into a molecular cohort comparison 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 into a molecular cohort comparison. 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. Ideally this should be performed once eligibility has been confirmed and the patient has been randomised into a molecular cohort comparison. 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. Details on sample handling and curation can be found in the Sample Collection and Handling SOP.

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 initial first-line treatment, which do not interfere with the FOCUS4 Trial 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 treatment is likely to be incompatible with FOCUS4 as they may require longer durations of therapy than 16 weeks.
- Patients whose disease progressed during first-line treatment are not eligible for randomisation into FOCUS4, 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 eCRFs.

4.8 REGISTERED PATIENTS WHO DO NOT CONSENT TO RANDOMISATION

Patients may register into FOCUS4 but then decide not to consent for randomisation into FOCUS4. 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 eCRF. 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 FIRST-LINE TREATMENT

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

During the registration period, the choice of standard first-line treatment 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 patient is eligible for any of the comparisons.

Standard chemotherapy regimens that are acceptable during first-line treatment include the following:

- FOLFOX (OxMdG)
- XELOX
- FOLFIRI (IrMdG)
- Irinotecan plus capecitabine
- Infusional 5FU plus folinic acid (MdG)
- Capecitabine
- Oxaliplatin/Raltitrexed
- Raltitrexed
- Biological agents that are acceptable in addition to any of the chemotherapy regimens above include the following:
  - Bevacizumab
  - Cetuximab
  - Panitumumab

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

It is recommended that patients with liver only metastases are discussed at a hepato-biliary MDT to determine resection of all metastases is possible.

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 a resection, radioembolisation or other liver-directed therapy of liver predominant disease in which 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 is 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 first-line chemotherapy and start of allocated FOCUS4 trial therapies. Please note that this does not apply to patients recruited to FOCUS4-N.

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 eCRF 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 eCRF and for those patients randomised, on the Randomisation eCRF.

5.4 REGISTRATION DATA COLLECTION

Minimal data will be collected at trial registration. Data on the type of systemic therapy used during first-line treatment will be collected and used as a stratification variable in the minimisation procedure for any subsequent comparison. This will be recorded on the End of Registration eCRF or the relevant Randomisation eCRF where applicable, along with CT assessment according to RECIST v1.1 criteria of the end of first-line treatment scan, prior to randomisation into one of the available comparisons.

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 Comparison Protocols as specific to each comparison and the comparison therapies.
5.6 UNBLINDING

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

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 comparisons is provided in the relevant comparison 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). The chart is presented for a patient who has had exactly 16 weeks of uninterrupted first line treatment. (This is also provided in the Summary on page xiv)

<table>
<thead>
<tr>
<th>Week</th>
<th>Registration period</th>
<th>Trial period</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>First-line treatment#</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Check registration eligibility criteria Δ</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>PIS1 Δ Registration Δ</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Tumour block sent Δ</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>CT scan §</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>RECIST v1.1 response</td>
<td></td>
</tr>
<tr>
<td>8-12</td>
<td>PIS2  ∞ Check specific comparison eligibility criteria</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Baseline assessment †</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Wash out from first-line chemo ‡</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Randomisation ¥</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Start trial treatment £</td>
<td></td>
</tr>
<tr>
<td>17-19</td>
<td>Optional Assessments *</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Blood (Genomic DNA) *</td>
<td></td>
</tr>
<tr>
<td>21-22</td>
<td>Blood (Circulating DNA) *</td>
<td></td>
</tr>
<tr>
<td>23-24</td>
<td>Tumour biopsy *</td>
<td></td>
</tr>
</tbody>
</table>

Key to symbols

# Regime determined locally for approximately 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 comparisons.

Δ PIS1, registration and tumour block can be completed at any time up to week 12 of first-line treatment

§ Mandatory CT scan within 6 weeks prior to the start of standard first-line treatment (see section 3.3), recommended interim CT scan after 8 weeks of treatment; mandatory CT scan after last dose of first-line treatment

∞ PIS2 can be given when biomarker panel results are known and interim CT scan shows SD, PR or CR

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

‡ Wash out period of 3 weeks between end of first-line treatment and start of allocated trial therapy (NB this is not applicable for FOCUS4-N, please refer to specific comparison protocols for full details)

¥ Randomisation must be within 28 days of pre-randomisation CT scan

£ Trial Treatment should be commenced as soon as possible after randomisation
**Not required if patient has withheld consent for molecular research tumour biopsy or there is no tumour accessible for percutaneous biopsy. Genomic DNA sample only required once, i.e. it is only required at randomisation if not already taken during the registration period.**

### 6.1.1 CASE REPORT FORM (CRF) RETURN TIMELINES

- **Registration eCRF** should be completed prior to registration and used to register the patient with the MRC CTU via the MACRO Registration database (please refer to FOCUS4 MACRO eEDC guidelines). Please note the Eligibility Checklist must be completed and signed by the registering investigator and a copy submitted the Trial Team at the MRC CTU.

- **Biomarker Panel Request Form** will be used to facilitate the sending of the FFPE block as described in section 4.2. This will be entered onto the MACRO Registration database by the MRC CTU.

- An **End of Registration eCRF** must be completed for all patients at the end of their registration period regardless of whether they are entered into a subsequent randomised comparison. This must be completed as soon as the decision has been made on whether the patient wishes to enter a specific FOCUS4 comparison. This should be completed prior to any randomisation.

- For patients being randomised into a specific FOCUS4 comparison, the **Randomisation CRF** should be completed before the patient is randomised. Forms must be submitted immediately afterwards using the MACRO Randomisation Database. These specific procedures are documented in the specific comparison protocols and in the FOCUS4 Data Provisions Guidelines.

### 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 comparison, they will have a CT scan every 8 weeks until their cancer progresses. However this is comparison-specific and therefore please refer to the specific comparison protocol for further details.

**IMPORTANT NOTE:** The FOCUS4 trial is 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 v1.1 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 comparison and details are provided in each comparison 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 comparison are provided in the specific comparison protocol.

6.5 EARLY STOPPING OF FOLLOW UP DURING THE REGISTRATION PERIOD

During the registration period patients may choose 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 eCRF.

However, their decision must be respected and the patient may stop follow up early from FOCUS4 as requested. The MRC CTU should be informed of this in writing.

Patients will be followed up in the long-term through usual mechanisms, which may include flagging with the NHS Information Centre, or similar approaches unless consent is withdrawn to this.

6.6 PATIENT REFERRAL FOR RANDOMISATION

If a site is not open to a specific FOCUS4 comparison due to their level of site categorisation, patients may be referred to another participating site to allow them to be treated on that specific comparison. 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 comparison at the site where they will receive treatment.

After randomisation, when it is deemed safe or following completion of treatment, the patient may be transferred back from the treatment site to the original site. If the patient is still receiving treatment, it must be a suitable level site. Permission must be obtained from both sites and all outstanding data and queries resolved. The patient will need to sign a new consent form with the original hospital headed paper. Only once all this has been done, the MRC CTU will transfer access to the patient’s eCRFs to the new sites. Then 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 of the appropriate level. The patient will need to sign a new consent form with the new hospital headed paper and all outstanding data and queries must be resolved. 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. The MRC CTU will then transfer over access to the patient’s eCRFs.

### 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 eCRF 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 Trial 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 comparison, full safety reporting is required.

The principles of 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 comparison 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 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, Safety and Monitoring Plans, which will be kept separately. Please see each comparison protocol for any specific details of its risk assessment.

8.2 CENTRAL MONITORING AT MRC CTU

Essential FOCUS4 Trial Programme issues, events and outputs will be detailed in the Data Management, Safety 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 comparison 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 biomarker-defined cohort(s) and offered entry into the comparison for that cohort. Within each molecular comparison, patients will be randomised either to a placebo (where possible) or to a new targeted agent (or targeted combination) specific to their biomarker cohort. The specific ratio to be used in each comparison will be defined and justified within each comparison 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 FOCUS4-N, patients will be randomised to either capecitabine or active monitoring 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 comparison 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 28 days of the CT scan confirming (at least) stable disease at the end of first-line treatment.

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 first-line treatment. A global list of minimisation factors will be agreed for all comparisons and some comparison-specific factors will be added as necessary, e.g. FOCUS4-N will stratify on the biomarker profile of patients for those who choose not to go into their selected molecular comparison(s). The agreed list of minimisation factors will be clearly specified in the statistical analysis plan. At the amendment from version 3.0 to 4.0 that removed the exclusion criterion of high platelets, future randomisations will be stratified by low vs high platelets.

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 enrolled 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 FOCUS4 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 comparison 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 comparison will either stop recruitment or progress to continued recruitment to assess efficacy for PFS (Stage III) and, possibly, efficacy for overall survival (OS) (Stage IV) a potential additional primary outcome. Continuation to further recruitment 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 comparison (depending on the 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 comparison to comparison. 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 comparison separately.

Quality of Life (QL) data, measured by EuroQol-5D, will only be assessed in any novel agent comparison 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 comparison. 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 recruitment 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 after first-line treatment → 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.

**Table 9.1: Anticipated recruitment for screening and randomisation across cohorts**

<table>
<thead>
<tr>
<th>Molecular cohort</th>
<th>Prevalence</th>
<th>Randomised patients/mth</th>
<th>Total over 4 years</th>
<th>Total over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100%</td>
<td>32</td>
<td>1536</td>
<td>1920</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>8%</td>
<td>2.6</td>
<td>125</td>
<td>156</td>
</tr>
<tr>
<td>PIK3CA mutation and/or PTEN loss</td>
<td>30%</td>
<td>9.6</td>
<td>461</td>
<td>576</td>
</tr>
<tr>
<td>KRAS or NRAS mutation</td>
<td>33%</td>
<td>10.6</td>
<td>509</td>
<td>636</td>
</tr>
<tr>
<td>All wild type</td>
<td>27%</td>
<td>8.6</td>
<td>413</td>
<td>516</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2%</td>
<td>0.6</td>
<td>28</td>
<td>36</td>
</tr>
</tbody>
</table>

### 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 $\alpha=0.30$) 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 comparison (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 comparison. 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 comparison will be transparent to patients, clinicians and providers of the novel agent under scrutiny.

For each comparison, 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 comparison successfully opened to randomisation are given within the relevant comparison 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: Recruitment, PFS and Overall Survival (OS) from date of randomisation for the control group assumed for the generic sample size calculations for each cohort**

<table>
<thead>
<tr>
<th>Molecular cohort (Prevalence)†</th>
<th>Monthly randomisation*</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF mutation (8%)</td>
<td>3</td>
<td>3.1</td>
<td>15</td>
</tr>
<tr>
<td>PIK3CA mutation and/or PTEN loss (30%)</td>
<td>10</td>
<td>3.6</td>
<td>17</td>
</tr>
<tr>
<td>KRAS or NRAS mutation (33%)</td>
<td>11</td>
<td>3.6</td>
<td>18</td>
</tr>
<tr>
<td>All wild type (27%)</td>
<td>9</td>
<td>4.6</td>
<td>19</td>
</tr>
</tbody>
</table>

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

* Uniform recruitment assumed
Table 9.3: Summary of generic operating characteristics and timelines for each cohort. (Please refer to specific comparison protocol for actual operating characteristics)

<table>
<thead>
<tr>
<th>Molecular cohort</th>
<th>Randomised allocation ratio</th>
<th>Phase</th>
<th>Outcome and stage</th>
<th>Target HR</th>
<th>Max number of events required: total (control arm)</th>
<th>Estimated cumulative analysis time (months)</th>
<th>Max number of pts required</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF mutation</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.5</td>
<td>41 (16)</td>
<td>20.4</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.5</td>
<td>76 (28)</td>
<td>32.5</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.5</td>
<td>118 (42)</td>
<td>46.5</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.65</td>
<td>217 (79)</td>
<td>100.4</td>
<td>301</td>
</tr>
<tr>
<td><strong>PIK3CA mutation and/or PTEN loss</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.65</td>
<td>107 (40)</td>
<td>17.0</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.65</td>
<td>197 (71)</td>
<td>26.5</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.65</td>
<td>303 (107)</td>
<td>37.2</td>
<td>373</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.7</td>
<td>289 (109)</td>
<td>54.6</td>
<td>546</td>
</tr>
<tr>
<td><strong>KRAS or NRAS mutation</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.65</td>
<td>109 (41)</td>
<td>16.1</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.65</td>
<td>198 (72)</td>
<td>22.8</td>
<td>273</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.65</td>
<td>302 (107)</td>
<td>31.4</td>
<td>378</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.7</td>
<td>287 (109)</td>
<td>50.6</td>
<td>574</td>
</tr>
<tr>
<td><strong>All wild type</strong></td>
<td>2:1</td>
<td>2</td>
<td>PFS - I</td>
<td>0.65</td>
<td>109 (41)</td>
<td>20.0</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS - II</td>
<td>0.65</td>
<td>198 (72)</td>
<td>30.6</td>
<td>275</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>PFS - III</td>
<td>0.65</td>
<td>301 (107)</td>
<td>42.3</td>
<td>381</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS - IV (potential)</td>
<td>0.7</td>
<td>289 (109)</td>
<td>60.8</td>
<td>547</td>
</tr>
</tbody>
</table>
Table 9.4: Provided as an example of the detailed generic operating characteristics for a possible comparison in the All wild type cohort. (Please refer to comparison protocol FOCUS4-D for actual operating characteristics in this cohort)

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

* 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 comparison. Where possible, each molecularly stratified comparison will be double blind but it will be 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 comparison will be analysed entirely independently of other comparisons. Therefore, any analysis details specific to a cohort can be found in the relevant comparison protocol. Additionally, a formal Statistical Analysis Plan for each comparison 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, inverse probability weighting (IPW) will be used to ensure balance between the randomised groups. As more events arise, the use of IPW 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. 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 IPW 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 or a Flexible Parametric Model.

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 comparison 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 first-line treatment 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 comparison 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\(^\text{14}\). 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 downstream signalling. High levels of expression suggest the tumour is dependent 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 absence of KRAS or BRAF mutation.

In FOCUS4-D, the analysis of the quadruple wild type cohort will be adjusted for gene expression levels such as EREG. 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?

10.2 FRESH TUMOUR BIOPSIES BEFORE TRIAL TREATMENT 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 first-line treatment but prior to starting trial treatment and, if possible, on progression also. This would be limited to those patients giving informed consent to extra biopsies for research purposes having read
PIS3 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 first-line treatment (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 first-line treatment?

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 \textit{fait accompli}—the time to recurrence is simply the interval required for the subclone to repopulate the lesion\textsuperscript{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\textsuperscript{15}. 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 2 x 10ml EDTA samples at registration, on randomisation into FOCUS4, 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 mechanisms 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 comparisons. 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 comparison certainly in the first instance. It will be used to attempt to find new biomarkers 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 10ml 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 Comparisons, studies examining the effect of the specific novel therapies being tested in the comparison will be included. These will be defined in the relevant FOCUS4 comparison protocol.

These studies are dependent 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 Trial 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: Z6364106), 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
- The scientific value of the registration period or subsequent FOCUS4 comparisons

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 at least 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 Trial 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 comparison 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 comparisons. 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 trials4,16 which demonstrated that overall survival is not adversely affected, except in the patient group with elevated platelets at baseline. Subsequent meta-analysis has not confirmed this platelet interaction and therefore, we amended protocol version 3.0 to allow previously excluded high platelet patients to be registered into FOCUS4. In FOCUS4, placebos will be used wherever possible 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 comparisons that require referral 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, FOCUS4-N is an available alternative to all patients who do not wish to travel.

Release of results at the end of Stage II:
FOCUS4 employs the MAMS design9,10, 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 blood samples 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 comparison protocols have been submitted, reviewed and approved by the Oxford South Central Research Ethics Committee prior to study launch (REC# 13/SC/0111). Any changes to the protocols including adaptive design changes such as addition of new comparisons or treatment arms within comparisons will be submitted as substantial amendments to this ethics committee as they arise.

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 comparison protocols have been submitted, reviewed and approved by the MHRA prior to study launch (CTA# 00316/0245/001-0001).

This is a trial programme 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 Trial Programme (2012-005111-12).

The progress of each comparison 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 Comparison 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 as per local requirements. A
copy of the HRA 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). FOCUS4 is co-ordinated by the MRC CTU at University College London (UCL).

University College London holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial.

University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the University College London’s Insurers, via the University College London’s office.

Hospitals selected to participate in FOCUS4 must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.
13 FINANCE

The entire FOCUS4 Trial Programme will be sponsored by the MRC and co-ordinated by the MRC CTU at UCL in London. The grant holder is the University of Oxford. Funding will be jointly provided by the MRC/NIHR 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 comparisons. This will be stated in each comparison 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, 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) has been 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 comparisons or discontinuation of recruitment to any research arm.

Further details of IDMC functioning, 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 Chris Twelves. 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 at UCL 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 comparison within the FOCUS4 Trial 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 number (90061546) 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 FOCUS4 Trial Managers or the FOCUS4 website to confirm the most recent version of the FOCUS4 protocols and associated documents. This is the fifth signed agreed version of the Master Protocol and sixth version of its appendices.

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

1) Appendices change from version 1.0 to version 2.0 – this was a minor amendment to remove the unapproved versions of the patient information sheets, consent forms and GP letters from the appendices. These were replaced with the following statement:
   “Patient information sheets and consent forms are provided to participating sites as separate documents. Current copies can be downloaded from the trial website www.focus4trial.org or requested from the FOCUS4 Trial Team.”

2) Master Protocol version 1.0 to version 2.0 and appendices version 2.0 to version 3.0
   a) Change of study title to be FOCUS4 Trial Programme rather than Trials Programme to highlight that all the sub-trials are under one trial
   b) Typographical and formatting changes
   c) Addition of ethics and MHRA approval numbers
   d) Updating indemnity, insurance and sponsor sections to reflect that the MRC CTU is now part of University College London although the MRC remain sponsor for FOCUS4
   e) Clarification on procedures such as CRF completion and assessment schedule
   f) Updated contact details following the joining of the MRC CTU to UCL

3) Master protocol Version 2.0 to Version 3.0 and appendices Version 3.0 to Version 4.0
   a) Updates to the Trial Management Group membership
   b) Change in inclusion criteria to allow CT scan to be performed up to 6 weeks prior to starting first-line treatment
   c) Clarification that the end of registration CT scan should be performed after first-line treatment
   d) Clarification on timing of the optional additional biopsy
   e) Typographical and formatting changes
   f) Updates to terminology used throughout the protocol
   g) Addition of the UCL logo

4) Master protocol Version 3.0 to Version 4.0 and appendices Version 4.0 to Version 5.0
   a) Updates to the Trial Management Group membership
b) Removal of inclusion criterion for platelets <400x10^9/L within 14 days of starting first-line treatment

c) Addition of exclusion criteria to exclude patients with known HIV, hepatitis B or hepatitis C infection

d) Updates made to Required site training

e) Further guidance added concerning protocol violations and deviations in section 2.5.3

f) Typographical and formatting changes

g) Updates to terminology used throughout the protocol including clarification of some terms in the statistical analysis section 9.5.2

5) **Master protocol Version 4.0 to Version 5.0 and appendices Version 5.0 to Version 6.0**

a) Updates to the Trial Management Group membership

b) Inclusion of small bowel patients

c) Clarification to the timing of the registration period CT scan

d) Clarification of raltitrexed as a permissible regimen during first line therapy

e) Typographical and formatting changes

6) **Master protocol Version 5.0 to Version 6.0 and appendices Version 6.0 to Version 7.0**

a) Removal of the biomarker hierarchy that determines which cohort a patient can be offered limiting it to only one comparison (when multiple mutations present) and FOCUS4-N (the exception being the BRAF mutation)

b) Changes to MRC CTU staff telephone numbers

c) Typographical and formatting corrections
REFERENCES