Study Title: Prognostic value of ploidy and digital tumour-stromal morphometric analyses for guiding chemotherapy treatment for Stage II / III Colon Cancer Patients

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Potential Conflicts of Interest

David Kerr is a founder (and shareholder) of Oxford Cancer Biomarkers Limited, the company that has developed the digital pathology test (OncoProg®) test to assess risk of cancer recurrence in early stage colon cancer patients.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Contents

1. ABBREVIATIONS

CI	Chief Investigator
eCRF	electronic Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SoC	Standard of Care
SOP	Standard Operating Procedure

2. BACKGROUND AND RATIONALE

BACKGROUND

It has become clear that the traditional pathological biomarkers of T, N, V and L status do not adequately stratify the stage II and stage III colon cancer patients and therefore cannot give detailed enough information to allow clinicians to make coherent decisions about the type and duration of adjuvant

chemotherapy, or even whether such chemotherapy should be administered at all. There are frequent unresolved discussions about whether individual patients with stage II disease should have any chemotherapy at all; and whether 'lower risk' stage III patients should be treated in a way more like stage II patients and not receive oxaliplatin. This has led to quite different patterns of clinical treatment between countries, between different cancer centres in the same country, and in some cases, divergence between different clinicians practising in the same cancer centre [1,2].

In addition to the patients demographics (age, general fitness, tumour stage and grade, there are a number of tools used in standard of care ("SoC") to help the Oncologist recommend the most appropriate post-surgical treatment for individual patients, including microsatellite instability (MSI) Microsatellite instability status is currently used as a prognostic marker in patients with stage II/III colon cancer, with MSI tumours reported to have a better prognosis than those that are microsatellite stable (MSS). Specifically, stage II MSI tumours may not benefit from 5-fluorouracil-based adjuvant chemotherapy. The prognostic value of MSI status has important clinical implications, and usually supports the decision not to offer adjuvant chemotherapy to stage II colon cancer patients that have a MSI result.

Additional prognostic tools could improve the treatment decision making progress for those high-risk patients where MSI status may not be sufficient for this process.

ONCOPROG BACKGROUND

We have previously reported the prognostic value of ploidy and digital tumour-stromal morphometric analyses using material from 2,624 patients with early-stage colorectal cancer (CRC). The combination of the analyses of tumour cell DNA content as a measure of genomic instability (DNA ploidy) and an evaluation of the impact of the tumour microenvironment (tumour stroma content) were estimated using automated digital imaging systems and were analysed for prognostic impact using 5-year cancer-specific survival (CSS) as the clinical end point. Ploidy and stroma-tumour fraction were significantly prognostic in a multivariate model adjusted for age, adjuvant treatment, and pathological T/N-stage in stage II and III (T3N1) patients, and the combination of ploidy and stroma-tumour fraction was found to stratify these patients into three clinically useful groups.

Analyses demonstrated 5-year CSS of 90%, 83% and 73% respectively for low - intermediate- and high-risk groups, with a statistically significant ($P<0.001$) hazard ratio (HR) for the intermediate versus low-risk group [HR 1.77 (95% CI: 1.13–2.77)] and for the high versus low-risk group [HR (2.95 (95%CI:1.73–5.03)] (Figure 1). In an expanded assessment of stage II and early stage III (pT3pN1) the combined ploidy and stroma marker were also shown to be have prognostic value in this patient cohort, with a hazard ratio (HR) for the intermediate - versus low-risk group [HR 1.9 (95% CI: 1.4–2.6)] and for the for the high-versus low-risk group, [HR (2.9 (95%CI:2.0–4.3)]. In addition, the combined ploidy and stroma biomarker outperformed MSI status as a prognostic marker in this study, where MSI did not have a significant impact on risk of prognosis, [MSI versus MSS HR = 0.73 (95% CI: 0.40–1.35), P= 0.32)] in stage II patients [3].

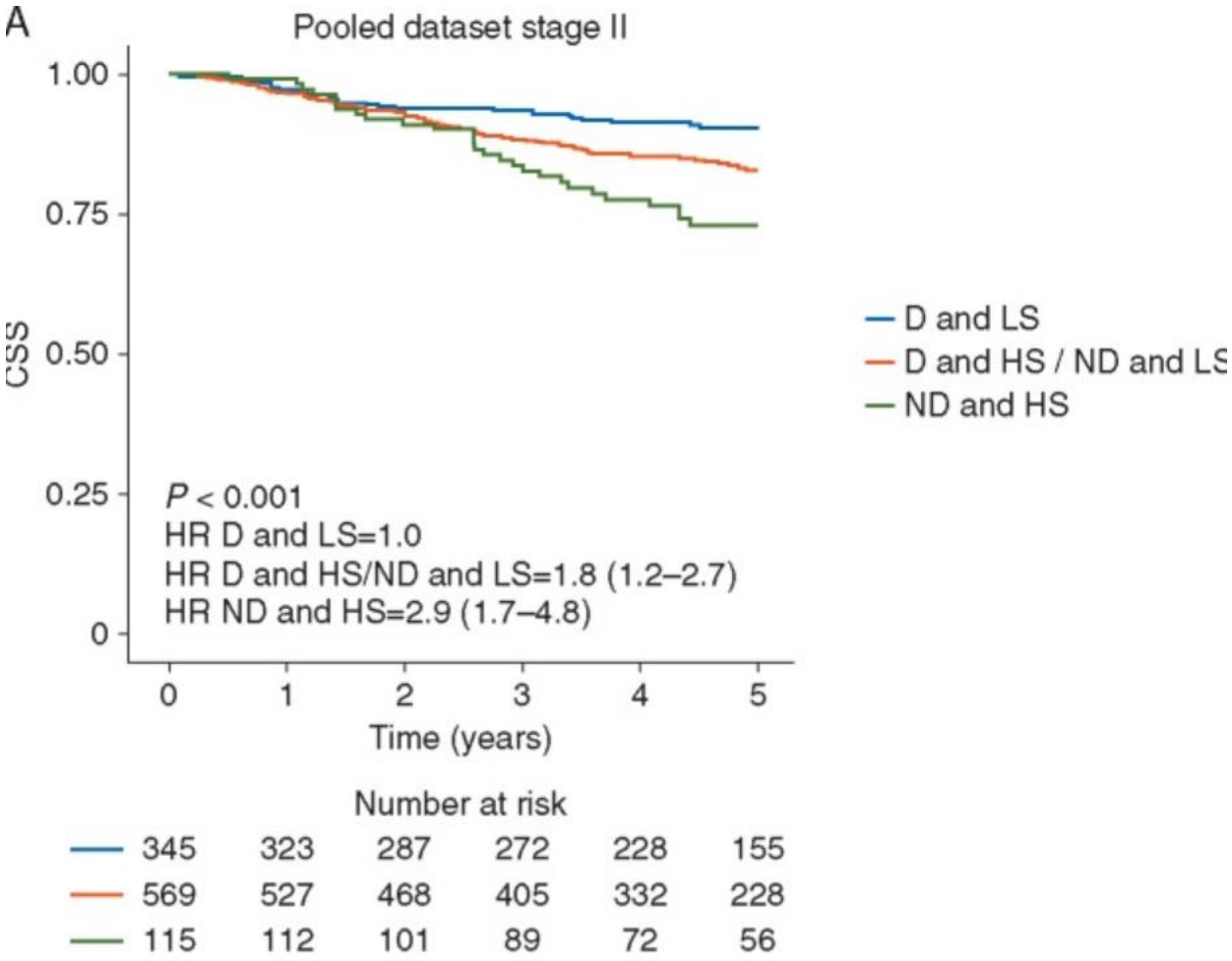

Figure 1. Kaplan–Meier plots illustrating cancer-specific survival (CSS) for patients with tumours that were diploid and low stroma (D and LS), diploid and high stroma or non-diploid and low stroma (D and HS/ND and LS), and non-diploid and high stroma (ND and HS) among (A) patients with stage II tumours.

ONCOPROG TECHNOLOGY

The combination of DNA content (ploidy) and stroma-tumour fraction biomarkers was developed into the OncoProg® test by Oxford Cancer Biomarkers Ltd. OncoProg® is a UKCA and CE marked Software as a Medical Device (SaMD). OncoProg® is a digital pathology tool which assesses the two biomarkers from a sample of the patients resected tumour after surgery.

The OncoProg® test uses image processing software algorithms to analyse the whole slide images of the biological tissues resected from the patient to determine the risk of relapse based on the combined biomarkers to stratify stage II/IIIA CRC patients into categories indicative of the risk of disease relapse ("low", "intermediate" or "high risk"). A report is produced for use by clinicians as a decision-making tool advising on the degree of adjuvant chemotherapy (Figure 2).

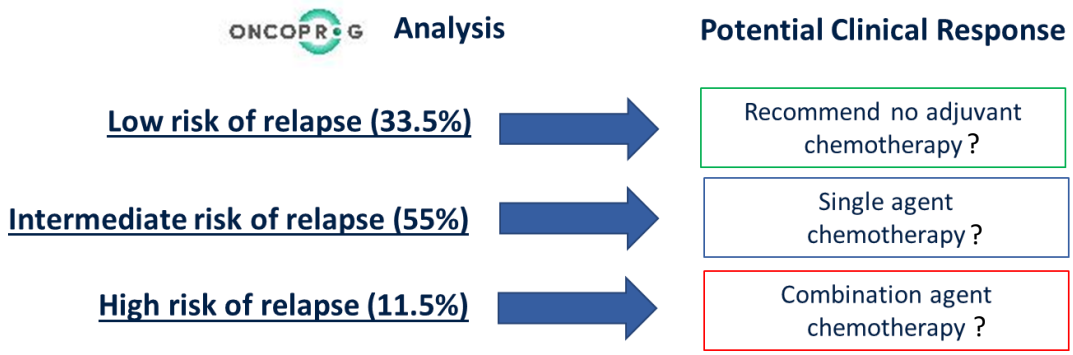

Figure 2. Stratification of stage II/III CRC patients using the OncoProg assay to assess the relative risk of relapse.

ONCOPROG CLINICAL VALUE

OncoProg is a decision making tool to guide Oncologists on the optimal treatment for an individual following surgical removal of a CRC.

3. STUDY DESIGN

This is an Interventional Prospective study.

Duration of study:

- Months 0-18 : trial start up and patient recruitment
- Months 18-24 : statistical analysis and preparation of final report

The patients' involvement in the study is from the time of consent until the post-surgical treatment appointment with the Oncologist to agree post-surgical treatment.

4. STUDY OBJECTIVES

1. Assess the differences, if any, in treatment recommendation for CRC Stage II and Stage IIIA patients, before and after the provision of OncoProg results

2. Demonstrate the health economic benefit of adopting OncoProg as a tool for guiding chemotherapy treatment for CRC Stage II and Stage IIIA

PARTICIPANT IDENTIFICATION

4.1. Study Participants

The participants will be patients with stage II and stage IIIA colorectal cancer (CRC) who have been referred for consideration of adjuvant therapy.

4.2. Inclusion Criteria

1. Stage II (T3 / T4) or stage IIIA (T1-3N1) colorectal carcinoma (histological diagnosis).

2. Age >18 years.

3. The patient is considered fit enough to be considered for fluoropyrimidine (FP) based systemic chemotherapy as treatment for colorectal cancer, in the adjuvant setting.

4. In the Investigator's opinion, is able and willing to comply with all trial requirements and give clearly documented consent.

5. Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

4.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

1. Any known contraindications to 5FU based chemotherapy.

2. Pregnancy or breast-feeding.

3. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

4. Rectal tumours that have been treated with chemo-radiotherapy prior to surgery

5. Patients that have been treated with chemotherapy prior to surgery

5. STUDY PROCEDURES

5.1. Recruitment

Patients agreeing to take part in the study will be consented and will receive a unique identifier code (UIC) number.

It is envisaged that the majority of patients shall be consented post-surgery, at an appointment with their Oncologist to discuss chemotherapy options (WORKFLOW A).

Eligible individuals i.e., those patients with suspected stage II or IIIa CRC, will be identified during the MDT based on presumptive staging (CT).

The Research Nurse (RN) will periodically check those patients notes that have gone for surgery with suspected CRC to see if the pathology report is present. The RN will consult with the Oncologist and check the pathology report to identify those patients that have been diagnosed with Stage II or IIIa cancer who may be suitable for recruitment.

Once the pathology report has been made available (Workflow A Process 9), The RN shall consult with the Oncologist and check the pathology report to verify eligibility (confirmed stage II/IIIa diagnosis). At

this stage of the treatment pathway the study will be discussed with the patient. Eligible patients shall be provided with the PIS for review. At the first suitable post-surgical appointment, Colorectal Nurse Specialist or RN will consult with the Oncologist and confirm the patient has reviewed the PIS. The patient may consent by calling or emailing the Colorectal Nurse Specialist or RN or at the next appointment with the Oncologist. The Oncologist will be provided with the Clinician Information sheet and will be asked to complete a pre-study questionnaire to assess their opinions of the OncoProg test before engaging with the consented patient (Workflow A Process 10-11).

Once the patient has consented to enrolment in the study, the Colorectal Nurse Specialist or RN will send a request to the pathology department to locate the tissue and request that the tissue is processed to allow assessment using the OncoProg test (Workflow A Process 12).

NOTE 1: if the patient is being treated at a primary study site (HUB) (QEUH Birmingham) tissue processing and OncoProg testing will occur on site. If the patient is being treated at a satellite study site, a request must be made to send to the patient tissue to the relevant HUB site for processing and OncoProg testing. (Workflow A Process 13).

The OncoProg test is conducted on the processed tissue and the results of the test are recorded. The OncoProg results are then send to the Oncologist for review alongside other SoC test results (Workflow A Process 14).

NOTE 2: as SoC patients will have a set of standard baseline blood tests to measure their full blood cell counts, blood clotting, and kidney and liver function. At this point, clinicians will be asked to record what adjuvant treatment they would aim to prescribe, based on the conventional information made available to them, *e.g.,* standard morphological pathology data, mismatch repair status, performance status and comorbidities (other medical history).

The oncologist will consider the OncoProg results alongside SoC test results and record whether OncoProg test results affect their chemotherapy recommendations and if so what changes to recommendations would be made (Workflow A Process 15-17).

During the clinical appointment where the Oncologist and patient discuss treatment options the treatment will be agreed based on evidence of SoC data. The OncoProg result will then subsequently be discussed by the patient and Oncologist and the Oncologist shall record if any change in treatment is agreed with the patient and record the nature of that change (Workflow A Process 18-19). The Oncologist and the patient will then be asked to complete an acceptability questionnaire to record their views on the use of OncoProg for treatment decision making (Workflow A Process 20).

NOTE 3: if the OncoProg results are not available prior to initiation of chemotherapy (usually within 2 months from the time of surgery), then treatment will proceed as planned *i.e.,* treatment will NOT be delayed. It is standard for chemotherapy treatment to start approximately 2-3 weeks after the oncology consultation.

5.2. Informed Consent

The patient participants must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. Written and verbal versions of the Participant Information and Informed Consent will have been made available to the participants detailing no less than:

- The exact nature of the study.
- What it will involve for the participant.
- The implications and constraints of the protocol.
- The known side effects and any risks involved in taking part.
- Details of the OncoProg test

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

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

5.3. Data Collection

A CRF will be completed, by the RN at each study site and pathologists sending tissue for OncoProg testing and performing OncoProg to capture all information relevant for the study including patient demographics, performance status, comorbidities, and other clinical and pathological tumour characteristics, any genetic tests undertaken, standard pathology results, OncoProg results, Oncologist decisions, Oncologist + patient decision.

At the time of patient registration, the medical oncologist will complete a baseline pre-OncoProg questionnaire, recording the planned treatments as observation, fluoropyrimidine monotherapy (5-FU [infusional or bolus] or capecitabine), or combination chemotherapy with oxaliplatin and duration of treatment (3 *vs* 6 months).

Additionally, upon completion of the the study each patient and clinician shall be asked to complete acceptability questionnaires.

After the OncoProg results have been made available the medical oncologist will discuss the results and treatment options with the patient, and agree the treatment regimen. A post OncoProg CRF will be completed.

5.4. Sample Handling

Tissue that is taken from a consented patient will be sent to the pathology lab as per standard practice for those sites conducting the full OncoProg workflow ("Hub site"). Tissue will be stored or disposed of as per standard practice.

For Satellite sites (sites that are sending tissue to a Hub site for OncoProg processing), FFPE tissue blocks will be added to "transfer tubes", placed in a SAE and sent to a Hub site. Samples will be shipped and stored at ambient temperature. Tissue will be stored or disposed of as per standard practice at the Hub site or returned to the Satellite site that sent the tissue.

Pathology will be advised to store all CRC tissue in FFPE blocks so that they can be accessed at a later date and processed through the OncoProg workflow. Tissue will be stored for a minimum of 4 weeks.

The tissue will be prepared for OncoProg; a 50 micron thick tissue section to create the nuclear monolayer slide for ploidy analysis plus a H&E-stained tissue slide for the stroma analysis.

Slides will be scanned on the scanner, the digital images generated will then be processed through the OncoProg® software to generate a clinical risk report. The report will then be added to the CRF.

The maximum turnaround time from sending samples to receiving the OncoProg report will be within 10 working days.

5.5. Discontinuation/Withdrawal of Patient Participants from Study

Each participant has the right to withdraw from the study at any time.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility
- Significant protocol deviation
- Withdrawal of Consent

5.6. Definition of End of Study

The end of the study for a specific patient is after the patient has decided with the Oncologist on the treatment that the patient will receive.

The definition of end of the study will be the date that the eCRF is completed for the last consented patient of if the study is stopped due to safety concerns. The study team will then require up to 6 months to analyse all the data.

6. SAFETY REPORTING

No new medicinal product is being administered and no new diagnosis method is being made in this study. The product under evaluation adds to the portfolio of established tools, used by Oncologists, for aiding decision making for adjuvant chemotherapy treatment for patients that have had a colorectal tumour surgically removed.

7. STATISTICS AND ANALYSIS

7.1. Analysis

According to the clinical workflow (see section 14.1) Oncologists will be asked to recommend chemotherapy treatment based on SoC alone plus SoC + OncoProg results:

1. Oncologist and patient shared treatment decision based on SOC

2. (after #1) Oncologist and patient shared treatment decision, following knowledge of SoC and OncoProg results, this measures the actual impact of OncoProg

Oncologists will be asked to record:

1. Whether the treatment recommendations based on SoC were the same as recommendations suggested by SoC plus OncoProg report

2. Changes in <u>treatment recommendation (if made)</u>:

    - from chemotherapy to observation
    - changes from observation to chemotherapy
    - changes in the chemotherapy regimen to exclude or include oxaliplatin
    - changes in the duration of chemotherapy (3 vs 6 months)

3. Whether the confidence of the Oncologists treatment recommendation was altered with the inclusion of OncoProg report; this will be recorded on a Likert scale of 1-5.

For qualitative data such as questionnaire responses, data shall be collated and tabulated into datasets.

Summary statistics shall be generated from qualitative datasets exposing trends in acceptability for both patients and clinicians.

7.2. Description of Statistical Methods

This decision impact study aims to evaluate the therapeutic impact of OncoProg and provide data for a health economic model as per the primary objectives of the study. The clinical study protocol was reviewed by the York Health Economics Consortium (YHEC) who provided advice on the clinical study protocol and on the outcomes.

YHEC calculated a sample size for their current study aligned to the indications received and provided a description of the statistical methods to be included in the protocol. The results of these analyses were provided in a report. (YHEC-Primary outcome analysis and sample size-OCB_v1.0). A summary of the analyses and the statistical methods is provided here.

7.2.1. Statistical Methods: Primary Objective

The possible treatment options that can be influenced by the OncoProg results are:

- observation

- chemotherapy regimen to exclude oxaliplatin (chemotherapy)

- chemotherapy regimen to include oxaliplatin (adjuvant therapy)

Thus, the possible treatment changes to be included in the analysis are:

- from observation to chemotherapy

- from observation to adjuvant chemotherapy

- from chemotherapy to observation

- from chemotherapy to adjuvant chemotherapy

- from adjuvant chemotherapy to observation

- from adjuvant chemotherapy to chemotherapy

The number and proportion of these changes will be reported.

The rate of treatment change will be presented as a percentage with a 95% confidence interval (CI) and will be compared to a minimum rate of 15% treatment change using a one-arm binomial test."

A McNemar's test may also be used to determine if there are changes in treatment recommendations before and after sight of the OncoProg results.

7.2.2. Health Economic Methods: Secondary Objective

A previously developed economic model provided by YHEC will be updated using data generated from this study. The model is a cost-utility model comparing OncoProg with standard care, allocating patients in each arm to either combination, monotherapy or observation only and tracks lifetime outcomes as informed by the retrospective trial [3]. The current trial will provide the model inputs for the proportions of people who used either combination, monotherapy or observation only. Since no long-term outcomes will be available from the current trial, they will be informed as in the original model. The model will also be updated with the most recent cost data [4, 5].

The health economic analysis will be done in Excel. The model structure, assumptions and the input sources will be predefined in a health economic analysis plan (HEAP).

Specifically, we will:

- Review any new, relevant evidence available.
- Review the current comparators and sources, supported by a pragmatic review of relevant literature.
- Review the original model alongside the data collection plan to ensure congruence.
- Develop a summary report in Microsoft Word:
    - This will outline our findings from the review stage.

- Describe any structural changes that we recommend and detail justification, if structural changes are deemed necessary.
- Describe any additional data to be collected and detail justification and proposed use in the economic model.
- Detail which model parameters will need to be updated at a later stage and propose the most appropriate source.

The economic model will not be amended at this stage as a number of the inputs are potentially time-sensitive such as, background mortality, national health service costs and drug costs which are typically updated annually. The proposed source will be identified at this stage, with the update proposed to happen at the latest possible time to ensure the most recent and relevant inputs are used.

7.3. The Number of Participants

We are aiming to approach 450 patients to ensure recruitment of 270 patients with a final enrolled cohort target of 246 CRC Stage II and Stage IIIA patients to be able to achieve a target half width of <5% for the two-sided 95% confidence interval (CI). This is based on the assessment that with an expected change in treatment recommendations of 20%, an expected consent rate of 60%, and an additional drop-out rate of ~10%.

7.4. Analysis of Outcome Measures

Analysis of Objective 1, is described above in the statistical methods section.

The health-economic study (Objective 2) will incorporate the findings of Objective 1 into an algorithm developed by York Health Economic Consortium.

This will result in a publication that describes the impact of the use of OncoProg on the costs to the NHS of treating patients following resection of colon cancer.

8. DATA MANAGEMENT

8.1. Access to Data

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

8.2. Data Recording and Record Keeping

All documentation and materials used for the study will by anonymised. Patients agreeing to take part in the study will be consented and will receive a unique identifier code (UIC) number.

FFPE tissue blocks corresponding to the patients resected tumour will be labelled with the patient UIC and sent for OncoProg® analysis. Slides generated from the tissue, digital images produced from the slides and reports produced by OncoProg will contain the UIC.

Anonymised data will be added to an electronic Case Report Form (“eCRF”).

Read and / or write access to the eCRF will be monitored and restricted to only those staff that are required to add and view data.

The eCRF will be hosted on the Cloud and have security built into the infrastructure and platform to ensure the security of the data.

9. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures of the host and sponsor.

Oxford Cancer Biomarkers has a BS EN ISO 13485:2016 accredited Quality Management System.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

10.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

10.3. Approvals

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

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

10.4. Reporting

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

10.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant UIC number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and

only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

10.6. Expenses and Benefits

As no visits are expected beyond the scheduled standard treatment visits, then no expenses will be offered.

10.7. Other Ethical Considerations

We do not expect to include patients who cannot consent for themselves.

11. FINANCE AND INSURANCE

11.1. Funding

NIHR AI Award # 02659. The Secretary Of State For Health And Social Care

11.2. Insurance

Oxford Cancer Biomarkers has professional indemnity, product liability, public liability cover to £5 million, plus employers liability to £10 million.

12. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by Oxford Cancer Biomarkers. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

13. REFERENCES

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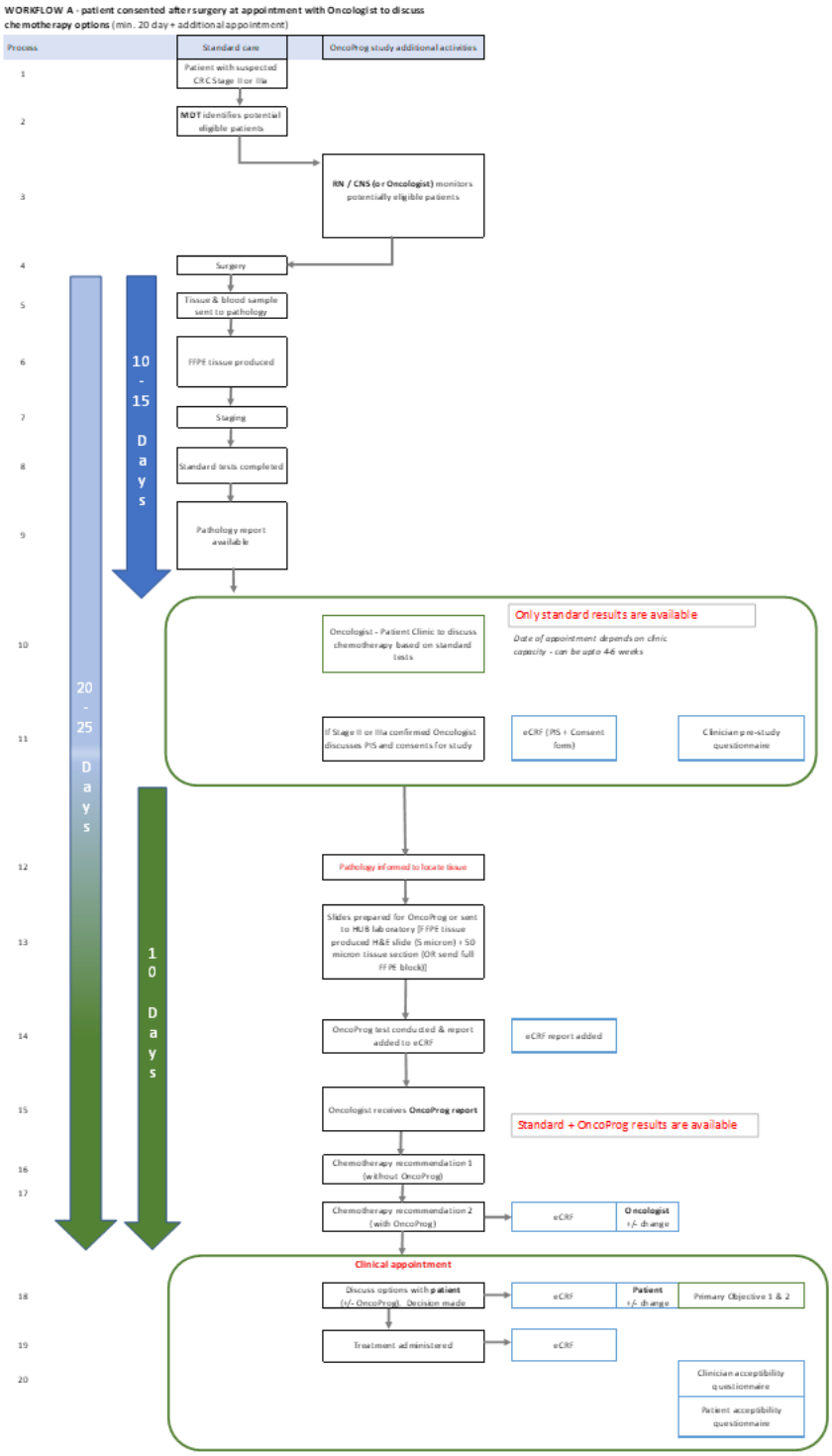
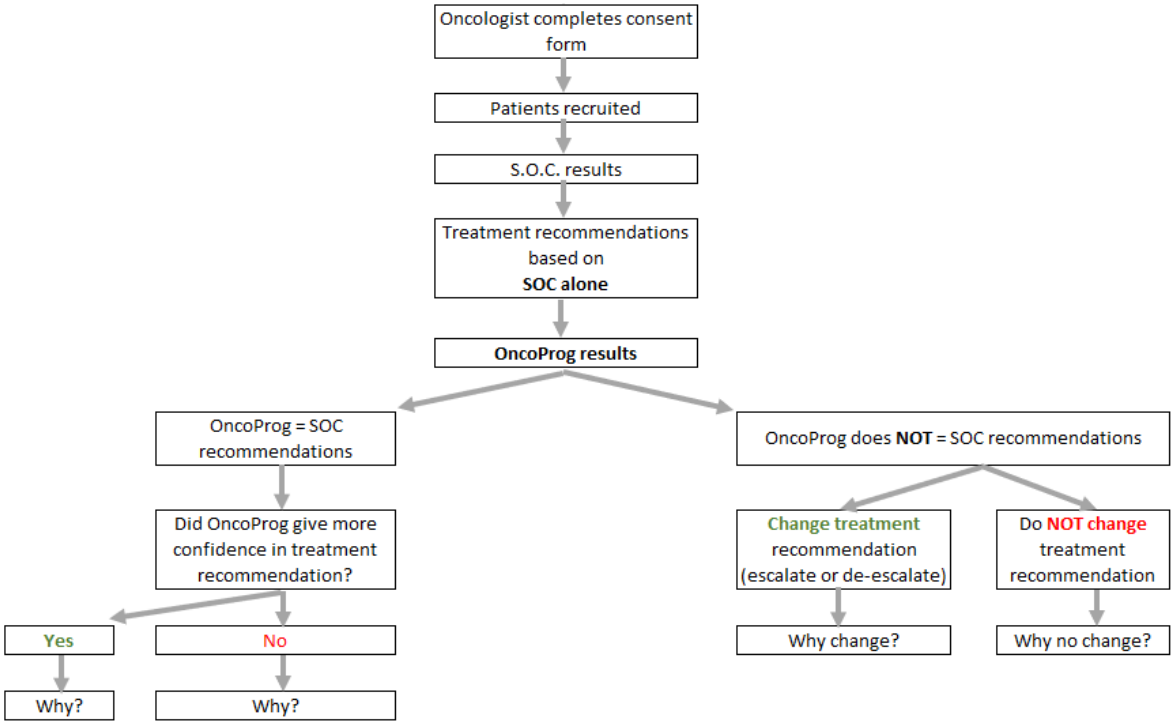
14. APPENDICES

14.1. Study Workflow



14.2. Clinical decision workflow



14.3. Sponsor's quality documents

PR.08 - Procedure for Customer Communication, Feedback and Complaints
PR.14 - Procedure for Control of Non-Conformities
PR.15 - Procedure for Adverse Event Investigation and Reporting
PR.18 - Procedure for Corrective and Preventive Action