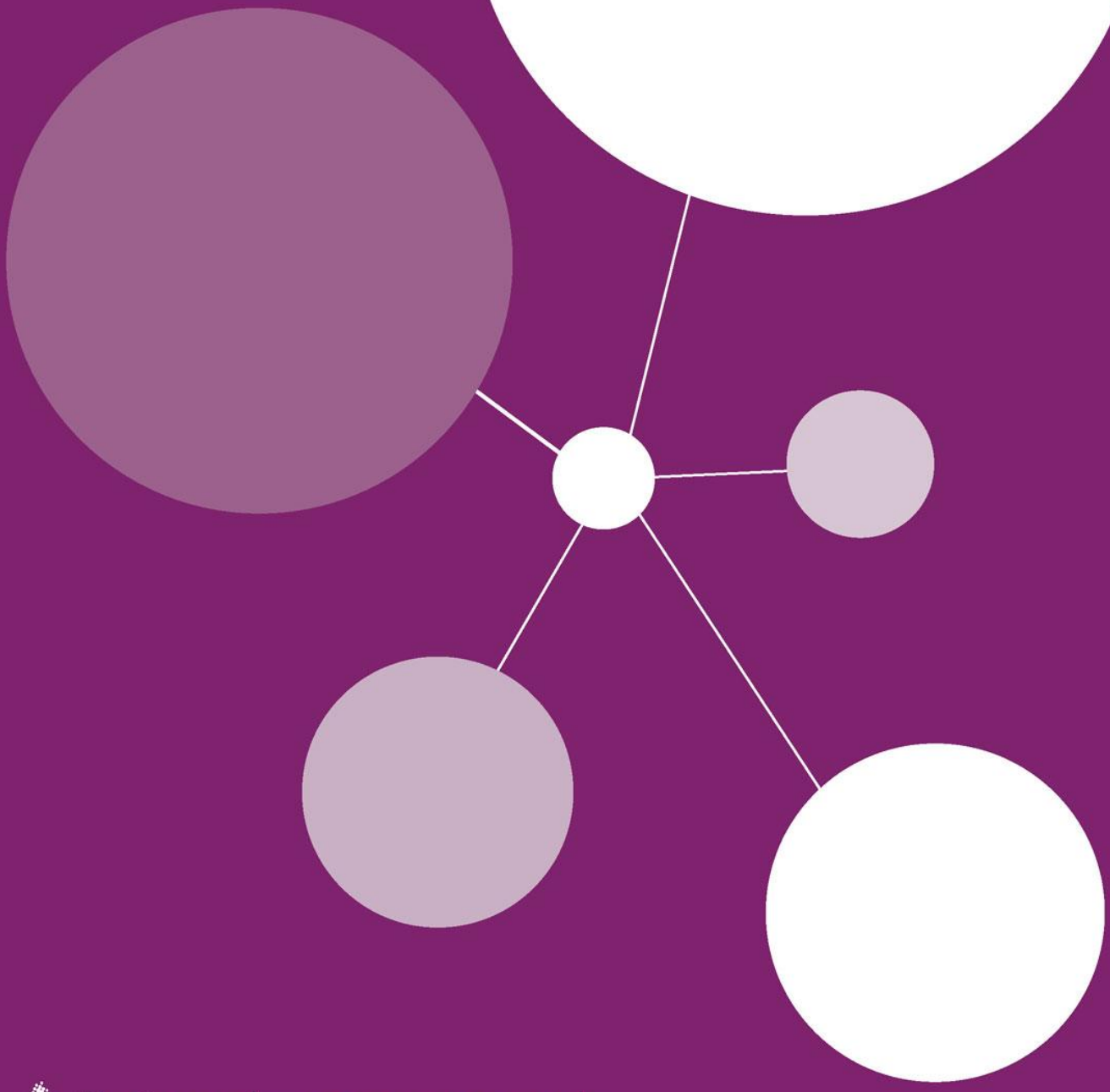
NCRI
National
Cancer
Research
Institute

NCRI Colorectal Cancer Clinical Studies Group

Annual Report 2014/2015



Partners in cancer research

NCRI Colorectal Cancer CSG Annual Report 2014/15

1. Executive Summary (including top 3 achievements in the year)

Over the past year, the Colorectal CSG has refined its strategy, grown its portfolio, extended its interactions with other CSGs and prepared for its progress review by an international panel. Preparation for this review, which follows on from the last and very successful review in 2011, has been very helpful for us in our discussions around strategy, further internationalization of our research, and how best to work within evolving NCRI rules around subgroups and increasing our collaborations.

Our main challenges have been around declining recruitment, gaps in our trials portfolio and increasing capacity blocks and obstacles to clinical research in the NHS. Recruitment to our studies peaked in 2012 and has declined since. Maintaining high levels of recruitment has proved challenging not only because of the restructuring of the NIHR and funding committees, but because of the move to more personalised medicine and the consequent changes to the Group's portfolio. FOCUS4, highlighted as a significant strength at the last review, had taken longer to roll out than had been anticipated for a number of reasons, although two cohorts are now open and three more expected to open in the next six months. We still need to have simple pragmatic trials, which can be undertaken at all hospitals, in addition to the complex personalised medicine ones. Add-Aspirin is one such study, which will fill the gap from the closure of the adjuvant SCOT trial. However, despite successful funding and study set-up, there have been long delays around drug distribution and contracting. The lack of a large adjuvant trial had been the main reason for the drop in recruitment since 2012. There are other gaps in the portfolio and the Group is actively seeking to address these.

The top 3 achievements of the Colorectal CSG in 2014-15 were:

- The opening of FOCUS4 to over half of the planned UK centres and the agreements with Novartis, Bayer and AstraZeneca for support and supply drug for 3 more cohorts.
- Very positive interactions with the leadership of the Supportive & Palliative Care, Psychosocial Oncology & Survivorship and Primary Care CSGs and with SPED and the new UK Therapeutic Cancer Prevention Network.
- Successful funding achieved from the MRC and CRUK for S-CORT, our flagship stratified medicine programme across all stages of colorectal cancer which uses clinical, pathological and trial data and tissues from many of our CSG portfolio of randomised trials.

2. Structure of the Group

The Colorectal CSG has not changed its structure and continues with 4 subgroups. Chairmanship of the Adjuvant & Advanced Disease Subgroup moved from Professor Richard Wilson to Professor Anne Thomas in March 2014. Later that year, Professor Mark Hull replaced Professor Bob Steele as Chair of the Screening & Prevention Subgroup. There are currently 28 members on the Colorectal CSG, with wide ranging specialisms and representing all four devolved nations (see Appendix 1). There is a policy of regular rotation of membership, and the choice of new members is based on their track record of involvement with research in colorectal cancer and on the need to maintain a balance of expertise and broad geographic representation. There has been a very considerable change since March 2014 both in membership of the main CSG and of its 4 subgroups. Some very distinguished and longstanding members have rotated off the CSG (Professors Richard Gray, Phil Quirke and Bob Steele), with the latter duo remaining involved through membership of subgroups. Professor Steward had been Chair of the CSG from 2010 and was replaced by Professor Wilson through a competitive process in spring 2014. Mrs Lindy Berkman, one of our very successful consumer representatives, rotated off the CSG, but has remained involved with one of our subgroups. Mr Alf Oliver has also rotated off the CSG after many years of distinguished service, and will continue as a subgroup member. We welcomed a dynamic new consumer member, Mrs Alison Allam, in late 2014. Mrs Ann Russell will also leave our CSG at the end of this 2014-15 year, with a replacement to be appointed soon afterwards.

3. CSG & Subgroup strategies

Main CSG

Our 2014-19 strategy was developed at a 2 day meeting in November 2013, and has since been refined following significant changes in our CSG/subgroup leadership, through discussions at the CSG and subgroup meetings in 2014 and during our discussions prior to our International Progress Review in April 2015.

Our aims are to:

- Extend and formalise our interactions and collaborations with the ECMC Network, cross-cutting CSGs, NCRI Advisory Groups, CTRad, the Upper GI CSG and international collaborators.
- Maintain excellent imaging, surgery, pathology and radiotherapy QA in all our clinical trials
- Move forward a stratified medicine approach to research across prevention, adjuvant and advanced disease settings.
- Systematically collect germline and tumour DNA, normal and tumour tissue throughout the disease pathway.
- Develop comprehensive tissue access and data access policies for both historical and prospective portfolio studies.
- Regularly review our membership to ensure appropriate statistical, GI and molecular pathology, imaging and other specialist expertise on the main group and appropriate subgroup membership and equitable rotation.
- Develop and promote large pragmatic studies to maintain high levels of recruitment and trial access to all recruiting sites.
- Expand our research activities in screening, prevention, early diagnosis and survivorship

- Expand the range and number of funding bodies to which our funding submissions are made and improve their likelihood of funding success
- Develop a research programme on colorectal cancer biology using our current and historical portfolio clinical trials and translational studies to improve our understanding of the molecular subtypes within CRC, develop biomarker stratifications that predict outcomes from current and novel therapies and enable personalised therapy to improve outcomes in early and late stage CRC.

Surgical Subgroup (Chair, Mr Simon Bach)

Aim: The Surgical Subgroup aims to improve outcomes for patients with colorectal cancer through surgical trials and translational research, to build international networks and to promote trial participation to consultant and trainee colorectal surgeons across the UK.

Strategy: Our strategy is to ensure that the Surgical Subgroup trial portfolio increases in size and breadth, is of an international standard, embraces organ preservation and improves survival and quality of life of patients with colorectal cancer.

Achievements: The Subgroup has had significant achievements over the past year including successful recruitment ahead of target to various trials, and increasing involvement of both surgical trainees and now medical students across the UK in clinical trials. We have increased our collaborative working, particularly with the Anorectal Subgroup on anorectal trials within the UK, and with European and other international partners.

Challenges: Surgical studies in advanced disease have continued to be a challenge in terms of accrual and in successfully obtaining funding (eg failure to enable UK involvement in the Dutch ORCHESTRA trial).

Anorectal Subgroup (Chair, Dr Richard Adams)

Aim: The Anorectal Subgroup aims to improve outcomes for patients with all stages of anorectal cancer through a platform of clinical trials backed by translational and correlative scientific research.

Strategy: Our strategy is to ensure that the Anorectal Subgroup trial portfolio is of an international standard across the spectrum of early to late phase studies to improve the outcomes of patients with anorectal cancer and to promote organ preservation with less toxicity and better functional outcomes.

Achievements: The Subgroup has had significant achievements over the past year, including increasing recruitment to ARISTOTLE and attainment of outline and full approval for key future trials such as the umbrella design phase II/III trial PLATO in anal cancer and SAILOR in low rectal cancer. International collaboration has been agreed for PLATO and also for the CREATE trial which is in development. The ARISTOTLE phase III locally advanced rectal cancer trial sample collection will collect FFPE tumour blocks and serial plasma samples and was funded by CTAAC in November and will include around 600 patients. An anal cancer translational research collaboration using retrospective FFPE sample collection was funded by BDRF in December 2014 and will interrogate approximately 600 samples.

Challenges: We continue to strive to develop a seamless portfolio of trials that allow timely follow-on with no significant gaps between trials, but failures at funding bodies and other reasons for delay continue to thwart this aim. Innovative trials such as BACCHUS are challenging to deliver in the constrained NHS. We have linked with other CSGs on development of a multi-tumour setting trial in HPV-driven cancers, but have so far been unsuccessful in getting this funded.

Screening & Prevention Subgroup (Chair, Professor Mark Hull)

Aim: The Screening & Prevention Subgroup aims to lower invasive cancer incidence and significantly improve survival rates through a suite of clinical trials in screening, prevention and early diagnosis including behavioural and lifestyle modification.

Strategy: Our strategy is to ensure that the Screening & Prevention Subgroup trial portfolio is of an international standard with strong accrual across the diverse settings that we work in and linked with a large group of UK and international partners.

Achievements: The Subgroup has had significant achievements over the past year, including a refreshed and vibrant subgroup membership, a successful funding application for the EMT2 maintenance study using Eicosapentaenoic Acid in patients as a secondary prevention/maintenance strategy for patients who have undergone potentially curative resection of colorectal liver metastases and the opening of the CAPP3 trial in patients with Lynch Syndrome. We have made considerable progress in enhancing our research links with the 4 UK national bowel cancer screening programmes, the Screening Subgroup of the Primary Care CSG, the ECMC UK Therapeutic Cancer Prevention Network, the National Awareness and Early Diagnosis Initiative and with the UK Screening, Prevention and Early Diagnosis Advisory Group.

Challenges: The sheer breadth of the portfolio engenders a significant challenge in working with a diverse group of constituencies. Much of the UK's therapeutic cancer prevention comes out of the ECMC network and we need much closer collaboration with these centres. In addition, the subgroup needs to work more closely with both the British Society of Gastroenterology and Public Health England, neither of which the CSG has had a history of working with before.

Adjuvant & Advanced Disease Subgroup (Chair, Professor Anne Thomas)

Aim: The Adjuvant & Advanced Disease Subgroup aims to improve outcomes for patients with colorectal cancer through rationally designed clinical trials based on cutting edge translational research.

Strategy: Our strategy is to ensure that the Adjuvant & Advanced Disease Subgroup trial portfolio is of an international standard from early phase studies to large biomarker-driven phase III studies encompassing qualitative research where appropriate to improve the lives of patients with colorectal cancer.

Achievements: The Subgroup has had significant achievements over the past year, including successful recruitment to some challenging studies such as FOXFIRE. We are particularly proud of the opening of FOCUS4 which demonstrates our ability to establish logistics of sample collection and builds adaptability and sustainability into a pivotal study. We believe it is this track record that has helped secure £5.1M MRC/CRUK funding for the S-CORT Stratification in colorectal cancer

programme. In the last year there have been some major publications for AADSG trials including COIN, AVEX, and New EPOC.

Challenges: The complexity of understanding the molecular genetics in CRC and then appropriately targeting signalling pathways effectively has been especially difficult in the advanced disease setting; this has led to the delay in opening arms of FOCUS-4. For two large proposals CHALLENGE and ORCHESTRA, the unsuccessful funding applications were perplexing. While the 70 day target has improved study opening timelines, a delay still exists especially around contracts. Consequently we have had gaps in the portfolio e.g. closure of SCOT and opening of Add-Aspirin.

4. Task groups/Working parties

The Colorectal CSG had no Task Groups or Working Parties operational or planned during 2014-15.

5. Patient recruitment summary for last 5 years

In the Colorectal CSG portfolio, 17 trials closed to recruitment and 26 opened during 2014-15. There are currently 43 interventional and 41 non-interventional studies spread across adjuvant and advanced disease, surgery, anorectal and screening and prevention categories. The Group thus feels its portfolio is broad and can potentially include the majority of patients seen with colorectal cancer, although there are still significant gaps that we are trying to fill. Since 2011-12, there has been a continuing fall in recruitment to interventional studies and this is almost entirely explained by large trials closing in screening and in first and second-line and beyond in the metastatic setting, by the lack of a large first or second- line trial in advanced colorectal cancer and the closure of the adjuvant trial SCOT in late 2013. While the figures for trials opening are encouraging, many of the trials opening will recruit relatively small numbers and only from a small selection of our centres, and there is an increasing excess of observational over interventional trials. We are trying very hard to develop and obtain funding for several large, pragmatic interventional trials in both the early and later disease settings. The ongoing roll-out of opening centres and new cohorts in FOCUS4 and the imminent opening of Add-Aspirin will significantly improve accrual to interventional trials.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2010/2011	4734	2696	4317	2696	12.6	7.8
2011/2012	8855	2560	7767	2560	22.6	7.4

Table 2 Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2012/2013	4690	6416	3433	3151	8.5	7.8
2013/2014	3276	4432	1908	1924	4.7	4.8

2014/2015	4825	1081	4728	1020	11.7	2.5

6. Links to other CSGs, international groups and network subspecialty leads

We have made significant steps with the Supportive & Palliative Care, Psychosocial Oncology & Survivorship and Primary Care CSGs on increasing awareness of each other's portfolios and on closer collaborative working. This has included invitations to both our CSG and Annual Trials meetings, but also dedicated teleconferences. We anticipate significant outputs from the much more mutually informed and collegiate working relationships that we now have. Professor Hull has joined SPED alongside Mrs Russell, our consumer representative. The close working of our Anorectal Subgroup with CTRaD continues, with Anorectal Subgroup members taking on new co-chair roles in 2015 (Dr Adams in Workstream 2 for Phase I/II trials and Professor Sebag-Montefiore in Workstream 3 for Phase III trials and methodology).

Our CSG has always undertaken joint trials in the management of colorectal liver metastases with the Upper GI CSG. In the past, liaison and flow of information between the CSGs around trial development has been suboptimal but this has now been addressed by both parties, and there is cross-representation on the appropriate subgroups.

We have had very good joint working around the International Rare Cancers Initiative (IRCI) with colleagues from NCI, NCI Canada, EORTC, INCA, Australia and Japan. CSG members are in leadership positions in the Anal Cancer and the Small Bowel Adenocarcinoma Working Groups and in development of the InterAACT relapsed/metastatic anal cancer trial which is open and the adjuvant BALLAD trial which will open in summer 2015.

We had a very successful first meeting jointly between the leadership of the Colorectal and Upper GI CSGs and the GI cancer NIHR Cancer network subspecialty leads this spring. We are exploring how most efficiently to run joint meetings in future, and to involve leads for lower GI cancer from the other three UK devolved nations.

7. Funding applications in last year

In the last year, significant funding has been obtained for both clinical trials and translational studies. We are working to diversify the bodies to which we apply for funding, as we perceive that we have become overly dependent on CRUK through CTAAC and FSC. Professor Sebag-Montefiore has prepared an excellent discussion document on the clinical trials application process for the next Colorectal CSG meeting.

Table 3 Funding submissions in the reporting year

Clinical Trials Advisory and Awards Committee (CTAAC)			
Study	**Application type**	**CI**	**Outcome**
July 2014			
SAILOR: Multicentre randomised phase II feasibility study evaluating neoadjuvant chemoradiotherapy plus surgery with surgery alone in low rectal cancer	Feasibility application	Professor Dean Harris	Not funded

Phase IB/II study of VX-970 in combination with irinotecan in irinotecan-refractory colorectal cancer	Feasibility application	Dr David Church	Not funded
SIRIUS: Phase I-II trial of selective internal radiotherapy to the liver combined with irinotecan-fluorouracil chemotherapy in patients with metastases from colorectal cancer	Feasibility application *Endorsement*	Dr Ricky Sharma	Not endorsed
ARISTOTLE sample collection	Sample collection application	Drs Richard Adams and Nicholas West	Decision deferred (fundable but insufficient funds at this meeting)
November 2014			
Pulmonary metastasectomy in colorectal cancer (PulMiCC). Continuation of a multicentre international randomised controlled trial to test the clinical effectiveness of surgical resection of lung metastases in disseminated colorectal cancer	Full Application	Professor Tom Treasure	Funded
ORCHESTRA: A randomised multicentre clinical trial for patients with multi-organ, colorectal cancer metastases comparing the combination of chemotherapy and maximal tumor debulking versus chemotherapy alone	Full Application	Professor John Primrose	Not funded
STAR-TREC: Single port TransAnal surgery and Radiotherapy versus Total mesorectal excision for early Rectal Cancer	Feasibility Application	Mr Simon Bach/Professor David Sebag-Montefiore	Funded
Single arm feasibility study of Cediranib plus standard chemotherapy and IMRT for stage III/IV HPV induced squamous carcinomas in cervix, anus and vulva	Feasibility Application	Dr Marcia Hall	Not funded
PLATO: PersonaLising Anal cancer radioTherapy dOse – incorporating ACT3, 4 and 5	Outline Application	Professor David Sebag-Montefiore	Full application invited
March 2015			
PLATO: PersonaLising Anal cancer radioTherapy dOse – incorporating ACT3, 4 and 5	Full Application	Professor David Sebag-Montefiore	Funded
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
REALM: randomised controlled trial of resection vs. ablation of solitary and small volume CRCLM	HTA Commisioned Call May 2014 (Full application)	Drs Gina Brown and David Breen	Not funded
S-CORT: Stratification in COloRectal cancer: from	MRC Stratified	Professor Tim	Funded

biology to Treatment prediction	Medicine Programme and CRUK November 2014 (Full application)	Maughan	
EASI-SWITCH: Early switch to oral antibiotic therapy in patients with low risk neutropenic sepsis: a randomised, controlled, non-inferiority trial with allocation concealment.	HTA January 2015 (Full application)	Dr Vicky Coyle	Funded
MEDI3039 phase I/II trial with an expansion cohort in biomarker-selected metastatic CRC	CRUK New Agents Committee February 2015 (Full application)	Professor Richard Wilson	Funded
CHALLENGE UK: A UK arm of the Colon Health And LifeLong Exercise chaNGE trial	CRUK Population Research Committee April 2015 (Full application)	Dr Vicky Coyle	Pending
Lilly LY3177833 Cdc7 inhibitor phase I/II trial with an expansion cohort in metastatic CRC	CRUK New Agents Committee May 2015 (Full application)	Professor Richard Wilson	Pending
RIT Study: phase I trial of a radiolabelled anti-CEA therapy.	MRC EME May 2015 (Outline application)	Dr John Bridgewater	Pending
An adaptive randomised factorial phase III trial of FOLFOX +/- Irinotecan +/- Bevacizumab in patients with liver only metastases from colorectal cancer (OCTOPUS)	CTAAC July 2015 (Full application)	Professor John Primrose	Pending

8. Collaborative partnership studies with industry

We have an increasing number of industry trials (9 in 2014-15) entering our portfolio this year that have been adopted by the NIHR. These studies are still problematic because of competition with our academic studies and poor information flows to the CSG about the conduct and progress of these trials.

The FOCUS4 trial has involved very close working with a large number of pharmaceutical companies. Often the agents have only been used in relatively small numbers of patients and a recommended phase II dose only recently determined. The processes of partnership for these agents are very intensive and time-consuming.

A very challenging feature of collaboration with industry is late withdrawal from studies by companies with no warning or compensation. A stark example of this has been with Sanofi Oncology. Four studies that were in the pending and set-up parts of our portfolio investigating aflibercept (a phase III RCT in advanced small bowel cancer, the CALIVER phase III RCT in inoperable CRC liver metastases, the EORTC BOS3 phase III RCT in operable CRC liver metastases

and a phase II study of aflibercept using micro-bubble ultrasound as a PD biomarker) were all cancelled by Sanofi in spring 2015. Some of these had full regulatory and ethical approvals and all have involved very large and now wasted amounts of investigator and CTU time and effort.

9. Impact of CSG activities

The most recent example of major impact of one of our studies on routine clinical practice has been New EPOC. This 'negative' trial which was published in May 2014 has halted the investigation and use of EGFR inhibitors in neo-adjuvant combination regimens in potentially operable colorectal liver metastases.

The FOCUS4 trial has brought together our 2 cancer research networks (the ECMC network for early phase trials and the UK CRNs for late phase trials) in a way that has simply not previously happened. The increasing mutual understanding and closer collaborative work engendered by the FOCUS4 experience will have significant long term value for UK cancer research. FOCUS4 has also been practice changing as an exemplar study in precision medicine, with similar studies coming forward in the USA and in other cancers in the UK such as pancreatic and gastric cancer.

Members contribute to NICE and HTA appraisals and guidelines and have been involved amongst others in the various previous appraisals of Cetuximab, Panitumumab, Bevacizumab and Aflibercept for the treatment of metastatic colorectal cancer. Drs Glynne-Jones, Bridgewater and Harrison were members of the NICE clinical guidelines development group for colorectal cancer including the development of the new guidelines issued in December 2014. Dr Potter was the co-ordinator for NCRI/RCP/RCR/ACP/JCCO and produced our contribution to the Multiple Technology Appraisal (MTA) of Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer in March 2015.

Our collaboration with the charitable sector has increased and will continue to do so. Beating Bowel Cancer are partners in the S-CORT stratified medicine programme. Bowel Cancer UK are partnering our CSG with one of the projects identified as critical in our 2014-19 research strategy. This is the colorectal cancer research gaps analysis project which is currently being set-up under co-Chairs Professors Tomlinson and Wilson.

The Surgical Subgroup has, in particular, sought the engagement of trainees in trial design set-up and delivery with glowing results. The Surgical Subgroup has increasing reach through collaboration with subspecialty associations (ACPGBI/ ESCP), charities and consumers, NIHR, and RCS. Building on from targeting new chief investigators, often from trainee ranks, and encouraging trainee collaborative studies, we are now encouraging medical students to participate in collaborative surgical research (STAR-SURG and GLOBAL-SURG initiatives). This involvement of recently appointed consultants, trainees and now medical students in clinical research is, in our view, the exemplar in the UK for other CSGs.

10. Consumer involvement

Our consumer representatives have continued to provide excellent and very constructive support for the CSG. They make regular contributions to our main and subgroup meetings and provide written comments on various documents sent around for opinions and discussion. We are going

through a period of flux with one longstanding consumer member (Mr Alf Oliver) having rotated off in autumn 2014 and the other (Mrs Ann Russell) leaving in spring 2015. We look forward to meeting Ms Alison Allam in May 2015 at her first CSG meeting and have already organized mentoring for her by Professor Sebag-Montefiore and our trainee member, Dr Jenny Seligmann. A second new consumer member will join us in the summer. Mr Oliver has used his legal background and regularly updated us on developments in this field, such as the recent 'Saatchi Bill' and changes in EU regulations. He will be very fondly remembered by us all for his major contributions over the last decade and more. Mrs Russell has become very involved with multiple groups and projects and was the founding Chair of SPADE (the NIHR Strategic PPI Advice, Delivery and Evaluation panel). The extent of Ann's contributions is truly remarkable. In her recent report, this included:

- Membership of the following subgroup/trial groups/committees/forums/support groups: TREC, FOCUS4, the Surgical Subgroup, the Adjuvant & Advanced Disease Subgroup, TSC member for the Add-Aspirin Trial, co-applicant for CHALLENGE UK, co-author of A Systematic Review and In-depth Analysis of Outcome Reporting in colorectal Cancer Surgery, TMS PPI for SMARTer against Cancer, the PARTNER breast cancer chemotherapy trial, the – Personalised Breast Cancer Initiative, and a study Investigating late reporting of symptoms of colon cancer over the past 10 years.
- As well as her lead role in NCRI's SPADE group, she also sits on its PPI Steering Group and HUB group.
- She has taken part in the Sharing News Study and the DoH Policy Research Programme Project: An investigation of the Patient Experience of MRSA screening.
- She is also a member of the East of England Strategic Clinical Network, East of England Clinical Senate (and a PPI rep involved in developing its Co-production initiative) and the East of England Cancer PPG representing Huntingdonshire/Cambridgeshire

We are delighted that Mrs Russell will stay involved with the NCRI CSGs and Mr Oliver will continue for some time in our Anorectal Subgroup. We also look forward very much to working with Alison and our second new member after their appointment.

11. Open meetings/annual trials days/strategy days

Our Annual Trials Meeting took place in the excellent venue of the Royal College of Physicians in London on 4th March 2015. It was fully subscribed with a large audience from a wide range of disciplines and backgrounds. Professor Sir John Burn gave an outstanding talk on 'Prevention of colorectal cancer by aspirin' which received unanimously superb reviews from the audience. Broadening the themes, we then had a session on behavioural modification and psychosocial issues, with Professor Jane Wardle and Drs Gill Hubbard and Claire Foster discussing lifestyle, screening and prevention, the CRIB exercise trial and the CREW cohort study respectively. Professor Benoit Vandeneynde gave the keynote lecture on the topical issue of 'Immunotherapies in GI cancer'. We then heard updates from the QUASAR2, COPERNICUS and fOCUS4 trials before updates from our 4 subgroups. In our feedback, 76 of 78 responders rated the meeting as good or excellent; 77 said it was mostly or highly relevant to their CPD needs; and 75 found the content of the presentations good or excellent. The free text comments were mostly very positive, and will be used to help us shape next year's meeting.

12. Progress towards achieving the CSG's 3 year strategy

We have extended collaborations with the ECMC Network, Supportive & Palliative Care, Psychosocial Oncology & Survivorship, and Primary Care CSGs. Our international collaborations are increasing in rare cancer, anorectal and surgical studies, but we also plan to extend FOCUS4 and Add-Aspirin internationally. Engagement with consumers, early career researchers and clinical trainees is improving, and we are maintaining excellent imaging, surgery, pathology and radiotherapy QA. A stratified medicine approach is being applied across prevention, adjuvant and advanced settings. Professor Quirke is leading a novel study on tumour heterogeneity in post mortem tissues. We have broadened CSG/subgroup membership, and filled gaps in gastroenterology, statistics, molecular pathology and imaging. We have expanded our activities in screening, prevention and early diagnosis, and are engaging with a wider range of funders. We have commenced a partnership with Bowel Cancer UK on identifying critical CRC research gaps. The S-CORT stratified medicine programme will investigate CRC biology using portfolio trials and translational studies to improve our understanding of CRC molecular subtypes, develop predictive biomarker stratifications for current and novel therapies and enable personalised therapy to improve outcomes in CRC. Professor Tomlinson led a successful CRC GECiP bid which involves many CSG/subgroup members.

We have extended the Screening & Prevention Subgroup membership, enhanced research links with the bowel cancer screening programmes; Primary Care CSG; the ECMC UK Therapeutic Cancer Prevention Network; NAEDI and SPED. We are developing more biology-based chemoprevention studies and promoting new studies using generic and repurposed drugs.

The Surgical Subgroup trials portfolio is increasing with new trials being developed in organ preservation. We have increased the UK surgical consultants involved in research and integrated more surgical trainees into our work.

The Anorectal Subgroup are using more complex designs, have received funding approval for an anal cancer phase II/III trial and are developing trials for organ preservation, for testing the effectiveness of systemic treatments replacing resection in rectal cancer, improving toxicity and PROM assessment, and combination trials of radiotherapy with novel agents.

The Adjuvant & Advanced Disease Subgroup are developing early phase studies to lead to future phase II/III RCTs, have enhanced relationships with the Upper GI CSG (in CRC liver metastases, peritoneal malignancies and small bowel cancer studies), and, through S-CORT, are developing studies on predictive biomarkers in the neo-adjuvant, adjuvant and advanced disease settings. We continue to work on a large pragmatic adjuvant study, a large pragmatic 1st line study, and studies in second-line and beyond. Discussions are underway with pharmaceutical partners about future CRC immunology trials.

13. Priorities and challenges for the forthcoming year

The 3 priorities for the Colorectal CSG for 2015-16 are to:

- Increase the number of, and accrual to, interventional trials
- Fill the significant portfolio gaps mentioned above in early and late CRC

- Explore and understand the reasons for the failure of immune checkpoint inhibitors to date in mismatch repair proficient CRC and to develop immune-oncology trials in CRC

The 3 challenges for the Colorectal CSG for 2015-16 are:

- Delivery of our complex trials across all the UK nations in a time of increasing NHS capacity blocks and withdrawal of time for many NHS consultants to take part in research
- Issues around equitable, reasonable and consistent access to drugs that in fact change over time and vary across the 4 UK devolved nations, particularly the vagaries that have come with the Cancer Drugs Fund in England
- The difficulties that have come for cancer research from the national reconfiguration in England of the Comprehensive Research Network and also the recent re-organisation of infrastructure and support for clinical cancer research in Wales.

14. Concluding remarks

The Colorectal CSG is grateful for the opportunity to have its work peer reviewed both by an international panel in April 2015, but also annually by the NCRI, and for the guidance we will receive and act on. We believe we are addressing many of the challenges we face, and achieving some of our new strategic aims, but are very aware of, and concerned about, the gaps in our portfolio and the falling numbers taking part in interventional studies. We would particularly like to give our thanks for the outstanding work of all of the team in the NCRI Secretariat in supporting our CSG, under the leadership of Dr Eileen Loucaides for many years, and in the future under her successor, Ms Nicola Keat, and for the help we receive throughout the year from Miss Laura Chambers and Ms Ulla Ventham.

15. Appendices

Appendix 1 – Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – Surgical Subgroup Strategy
- C – Anorectal Subgroup Strategy
- D – Screening & Prevention Subgroup Strategy
- E – Adjuvant & Advanced Disease Subgroup Strategy

Appendix 3 – Portfolio Maps

Appendix 4 – Publications in previous year

Appendix 5 – Major international presentations in previous year

Professor Richard Wilson (Colorectal Cancer CSG Chair)

Appendix 1

Membership of the Colorectal CSG

Name	Specialism	Location
Professor Diana Eccles	Clinical Geneticist	Southampton
Dr Richard Adams	Clinical Oncologist	Cardiff
Dr Mark Saunders	Clinical Oncologist	Manchester
Professor David Sebag-Montefiore	Clinical Oncologist	Leeds
Dr Ricky Sharma	Clinical Oncologist	Oxford
Professor Richard Wilson (Chair)	Clinical Oncologist	Belfast
Miss Alison Allam	Consumer	York
Mrs Ann Russell	Consumer	St Neots
Professor Mark Hull	Gastroenterologist	Leeds
Dr Janet Graham	Medical Oncologist	Glasgow
Dr Vanessa Potter	Medical Oncologist	Nottingham
Dr Sheela Rao	Medical Oncologist	London
Dr Jenny Seligmann*	Medical Oncologist	Leeds
Professor Will Steward	Medical Oncologist	Leicester
Dr Dawn Storey	Medical Oncologist	Glasgow
Professor Anne Thomas	Medical Oncologist	Leicester
Ms Katharine Williams	Nurse	Sheffield
Professor Manuel Salto-Téllez	Pathologist	Belfast
Dr Rohit Kochhar	Radiologist	Manchester
Dr Louise Brown	Statistician	London
Mr Simon Bach	Surgeon	Birmingham
Mr James Hernon	Surgeon	Norwich
Mr James Hill	Surgeon	Manchester
Mr Angus McNair*	Surgeon	Bristol
Professor Dion Morton	Surgeon	Birmingham
Mr Paul Ziprin	Surgeon	London

* denotes trainee

Membership of the Subgroups

Surgical Subgroup		
Name	**Specialism**	**Location**
Mr Angus Mcnair*, **	Clinical Lecturer in Academic Surgery	Bristol
Mrs Ann Russell	Consumer	St Neots
Mr Simon Bach (Chair)	Surgeon	Birmingham
Mr James Hernon	Surgeon	Norwich
Mr James Hill	Surgeon	Manchester
Miss Nicola Fearnhead	Surgeon	Cambridge
Professor Dion Morton**	Surgeon	Birmingham
Mr Tom Pinkney**	Surgeon	Birmingham
Mr Jared Torkington	Surgeon	Cardiff
Mr Dale Vimalachandran	Surgeon	Chester
Mr Paul Ziprin	Surgeon	London
Mrs Julie Cornish*	Surgeon	
Mr Aneel Bhangu*	Surgeon	

Screening & Prevention Subgroup		
Name	**Specialism**	**Location**
Professor Diana Eccles	Clinical Geneticist	Southampton
Mrs Lindy Berkman	Consumer	
Professor Julietta Patnick**	Director NHS Cancer Screening Programmes	Sheffield
Professor Wendy Atkin	Epidemiologist	London
Professor Roger Blanks	Epidemiologist	Oxford
Professor John Burn	Epidemiologist	Newcastle
Dr Christian von Wagner	Epidemiologist	London
Professor Mark Hull (Chair)	Gastroenterologist	Leeds
Professor Colin Rees	Gastroenterologist	Newcastle
Professor Annie Anderson	Nutritionist & Dietician	Dundee
Professor John Saxton	Physiologist	East Anglia
Mr Simon Bach**	Surgeon	Birmingham
Professor Bob Steele	Surgeon	Dundee

Anorectal Subgroup		
Name	**Specialism**	**Location**
Dr Richard Adams (Chair)	Clinical Oncologist	Cardiff
Dr Duncan Gilbert	Clinical Oncologist	Brighton
Dr Simon Gollins	Clinical Oncologist	Denbighshire
Dr Mark Harrison	Clinical Oncologist	Watford
Dr Leslie Samuel	Clinical Oncologist	Aberdeen
Professor David Sebag-Montefiore	Clinical Oncologist	Leeds
Mr Alf Oliver	Consumer	Hull
Dr Sheela Rao	Medical Oncologist	London
Professor Phil Quirke	Pathologist	Leeds
Dr Gina Brown	Radiologist	London
Mr Andrew Renehan	Surgeon	Manchester

Adjuvant & Advanced Disease Subgroup		
Name	**Specialism**	**Location**
Dr Leslie Samuel	Clinical Oncologist	Aberdeen
Dr Mark Saunders	Clinical Oncologist	Manchester
Professor Richard Wilson	Clinical Oncologist	Belfast
Mrs Ann Russell	Consumer	St Neots
Dr John Bridgewater	Medical Oncologist	London
Dr Ian Chau	Medical Oncologist	London
Dr Janet Graham	Medical Oncologist	Glasgow
Dr Tim Iveson**	Medical Oncologist	Southampton
Professor Gary Middleton**	Medical Oncologist	Birmingham
Dr Paul Ross**	Medical Oncologist	London
Professor Anne Thomas (Chair)	Medical Oncologist	Leicester
Professor Phillip Quirke	Pathologist	Leeds
Professor John Primrose	Surgeon	Southampton

* denotes trainee

**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

- Extend and formalise our interactions and collaborations with a number of groups including:
  - ECMCs and ECMC Network
  - Supportive & Palliative Care CSG
  - Psychosocial Oncology & Survivorship CSG
  - Primary Care CSG
  - Imaging Advisory Group
  - Molecular Biomarkers Advisory Group
  - Screening, Prevention and Early Diagnosis (SPED) Advisory Group
  - CTRad
  - Upper GI CSG on studies in CRC liver metastases, peritoneal malignancies and small bowel cancer
- Work collaboratively on an international scale to facilitate delivery of practice changing studies in the fields of colorectal cancer, anal cancer, small bowel cancer and peritoneal malignancies, particularly in rare cancers and in rare sub-groups of more common cancers
- Increase our engagement with:
  - consumers
  - early career researchers and clinical trainees
  - CIs of UKCRN Cancer portfolio trials who do not currently liase with the Colorectal
  - CSG
- Maintain excellent imaging, surgery, pathology and radiotherapy QA in all our clinical trials through active engagement with:
  - diagnostic radiology
  - pathology
  - imaging and biomarkers expertise
  - CTRad
- Move forward a stratified medicine approach to research across prevention, adjuvant and advanced disease settings through:
  - increasing the use of biomarkers in trials
  - increasing the number of biomarker-driven trials in the portfolio
- Systematically collect germline and tumour DNA, normal and tumour tissue throughout the disease pathway (including investigation of post mortem studies)
- Develop a comprehensive tissue access policy which includes access to venous blood, normal and tumour tissue and extracted nucleic acids where there no longer exists a functioning TMG/TSC for the individual trial
- Develop a data access policy which covers access to both historical and prospective clinicopathological and outcome datasets
- Regularly review our membership to ensure:
  - appropriate statistical, GI and molecular pathology, imaging and other specialist expertise on the main group with equitable rotation

    - appropriate subgroup membership (from both members and non-members of the main CSG) and equitable rotation
- Develop and promote pragmatic studies as a balance to our niche studies in order to maintain high levels of recruitment and trial access to all recruiting sites
- Expand our research activities in screening, prevention and early diagnosis
- Expand the range and number of funding bodies to which our funding submissions are made and improve their likelihood of funding success
- Increase our work in the field of survivorship
- Review our and others clinical and translational research portfolio to identify research gaps in CRC and ensure a comprehensive, balanced and innovative study portfolio
- Develop a research programme on colorectal cancer biology using our current and historical portfolio clinical trials and translational studies to improve our understanding of the molecular subtypes within CRC, develop biomarker stratifications that predict outcomes from current and novel therapies and enable personalised therapy to improve outcomes in early and late stage CRC.

B – Surgical Subgroup Strategy

The strategic aims for the Surgical Subgroup are to:

- Enhance the portfolio of surgical trials including the development of two new surgical trials by the end of 2015
- Develop a study for patient optimisation prior to surgery
- Develop a new study in organ preservation
- Set up new studies on the role of surgery in advanced disease
- Develop device studies
- Include biomarker validation within our RCTs
- Increase the number of surgical consultants across the UK involved in research
- Integrate surgical trainees into the work of the subgroup

C – Anorectal Subgroup Strategy

The strategic aims for the Anorectal Subgroup are to:

- Develop a seamless portfolio of trials that allow timely follow-on with no significant gaps between trials
- Use complex design in the delivery of future trials, e.g. MAMS design, umbrella trials
- Develop and get funded a phase III trial for anal cancer
- Develop trials for organ preservation in rectal cancer
- Develop trials which test the effectiveness of systemic treatments replacing resection in resectable rectal cancer
- Explore the options for a trial in synchronous resectable metastatic disease from rectal cancer
- Develop a study which focuses on improving toxicity and PROM assessment
- Continue to develop combination trials of radiotherapy and novel agents
- Link with other CSGs on understanding the biology of and advancing trial development in HPV-driven cancers

D – Screening & Prevention Subgroup Strategy

The strategic aims for the Screening & Prevention Subgroup are to:

- Increase the subgroup membership to include more members of the CSG and a wider
- UK representation
- Expand the trial portfolio to include more UK wide trials
- Enhance research links with the 4 UK national bowel cancer screening programmes; the Screening and Prevention Sub-group of the Primary Care CSG; the ECMC UK Therapeutic Cancer Prevention Network (UK-TCPN); the National Awareness and Early Diagnosis Initiative (NAEDI) and with the UK Screening, Prevention and Early Diagnosis Advisory Group (SPED)
- Develop strategies to increase participation in screening and prevention studies and
- programmes, particularly from 'hard to reach' populations
- Develop more lifestyle studies in primary and secondary prevention of CRC
- Develop more biology-based chemoprevention studies
- Encourage a seamless transition from screening to studies of novel treatment for early stage disease
- Encourage and support studies of generic prevention agents including re-purposed drugs

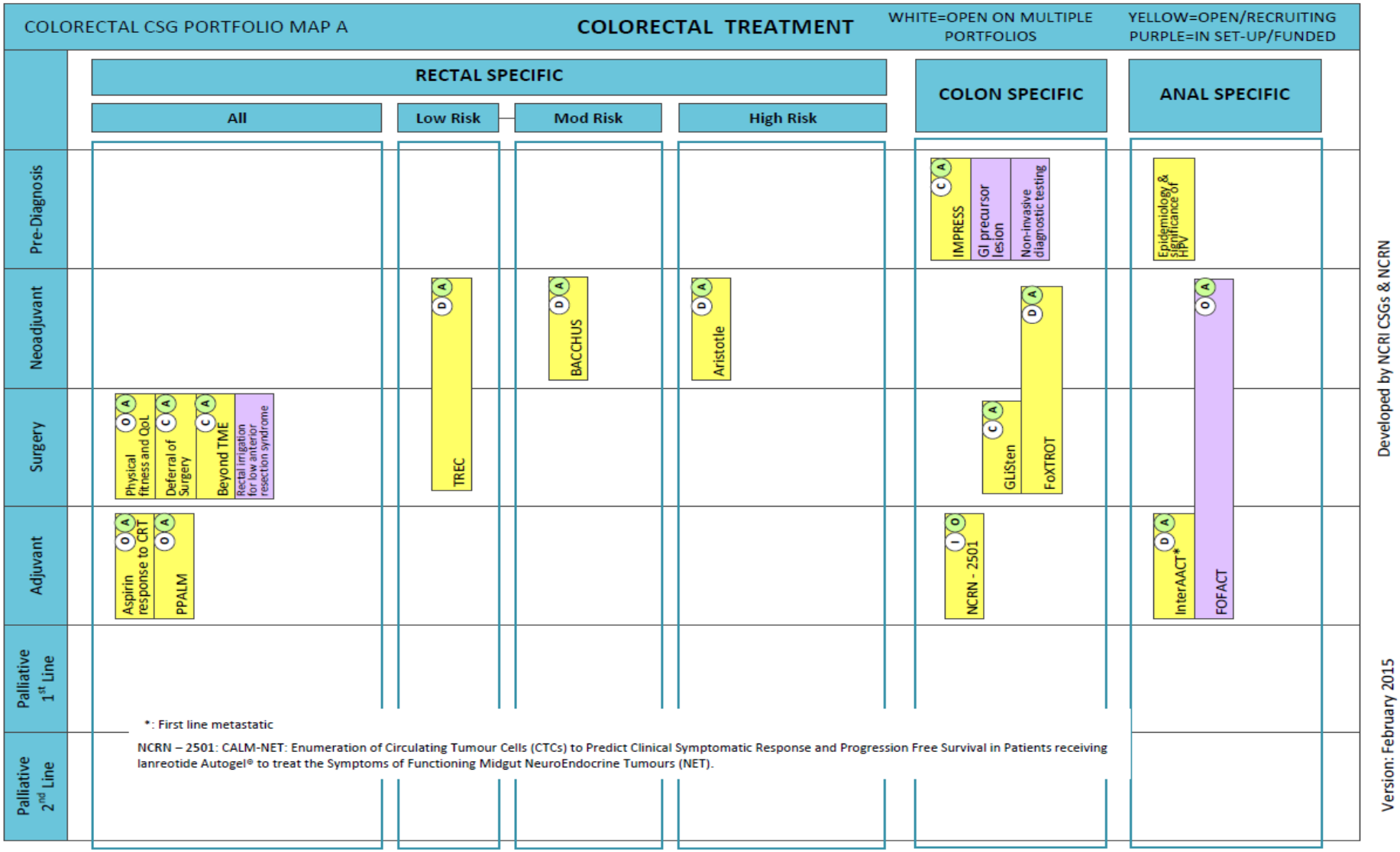
E – Adjuvant & Advanced Disease Subgroup Strategy

The strategic aims for the Adjuvant & Advanced Disease Subgroup are to:

- Continue to develop early phase studies to feed through to our future phase II and III RCTs
- Extend our links with the ECMC network and with the pharmaceutical and biotechnology industries to increase the number of early phase trials in our portfolio
- Ensure close working relationships with the Upper GI CSG with respect to CRC liver metastases, peritoneal malignancies and small bowel cancer studies
- Collaborate with the Psychosocial Oncology & Survivorship, Supportive & Palliative Care and Primary Care CSGs to ensure appropriate input into our and their colorectal cancer studies and, where appropriate, develop joint studies
- Standardise our approach to measuring late effects
- Set up a post mortem tumour heterogeneity study
- Explore the development of studies for different subgroups of patients and at different stages of the patient journey
- Develop studies on biomarkers that will help us to define which patients do and do not benefit from therapy in the neo-adjuvant, adjuvant and advanced disease settings
- Increase work in the field of survivorship (in particular as regards lifestyle issues) in both the adjuvant and advanced disease settings
- Develop trials to cover all our disease settings, and in particular
    - a large pragmatic adjuvant study (in addition to Add-Aspirin)
    - a large pragmatic 1st line study (in addition to FOCUS4)
    - studies in second-line, third-line and beyond third-line metastatic disease
    - studies on tissue/tumour heterogeneity
- Develop our biological research and trials in tumour immunology in CRC

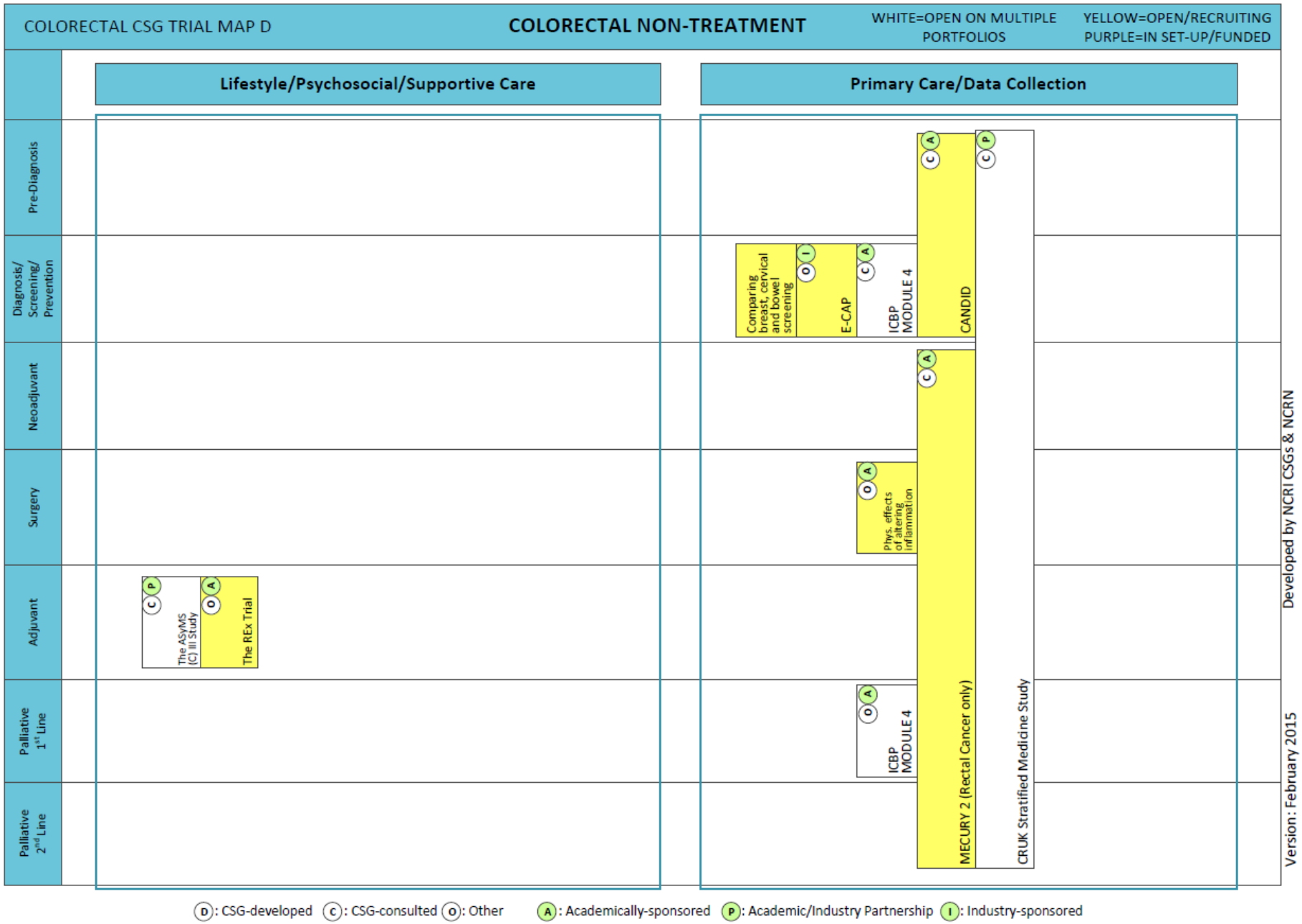
Appendix 3

Portfolio maps



COLORECTAL CSG TRIAL MAP B
COLORECTAL TREATMENT
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
NON-SPECIFIC
Pre-Diagnosis
Neoadjuvant
Surgery
Adjuvant
Radiotherapy
Palliative 1st Line
Palliative 2nd Line
Palliative 3rd Line
seAFOod
EORTC 40091/ BOS2
HART
Pringle vs PVC
Pre-Op Oral Supplement
PulMICC
Vascular changes during colorectal surgery
Add-Aspirin
OPTIMAL
Physical Activity Rehab for Cancer survivors
NCRN - 2888
CAPITAL
NCRN 2614
NCRN 2689
NCRN 2336
NCRN 3246
CANC 3358
CANC 3395
CANC 3465
TacTICC
FOLFOX + Curcumin
PANTHER
FOCUS4
ICE CREAM
AXMUS-C
NCRN396
MErCuRIC1
CANC – 3358: Efficacy and safety of RO5520985 + FOLFOX vs Bevacizumab + FOLFOX
CANC – 3395: Immunomodulatory maintenance treatment during induction treatment
CANC – 3465: Xilonix in symptomatic CRC patients refractory to standard therapy
NCRN 135: Parp inhibitor + chemotherapy in advanced solid tumours
NCRN 396: BASKET - Vemurafenib in patients with BRAF V600 mutation-positive cancers
NCRN 477: Efficacy and safety of FOLFIRI + MEHD7945a vs FOLFIRI + Cetuximab
NCRN – 2336: Nintedanib + best supportive care (BSC) vs placebo + BSC in refractory patients
NCRN – 2614: GSK1120212 (MEKi), GSK2118436 (BRAFi) and panitumumab in BRAF V600 mutation-positive patients
NCRN – 2689: Regorafenib vs placebo
NCRN – 2888: MEDI4736 in Advanced Solid Tumours
NCRN – 3246: Masitinib/Placebo + FOLFIRI
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored
Developed by NCRI CSGs & NCRN
Version: February 2015

COLORECTAL CSG TRIAL MAP C
COLORECTAL NON-TREATMENT
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
Diagnostics/Imaging
Genetics/Mechanisms
Biomarkers
Pre-Diagnosis
Diagnosis/ Screening/ Prevention
Neoadjuvant
Surgery
Adjuvant
Palliative 1st Line
Palliative 2nd Line
SYMPTOM Study
The USEFUL study
Improving Bowel Cancer Screening
DWIBS
Streamline C
MARVEL
CONSCOP
Flexi sigmoidoscopy
Negative FOBT
SERENADE
ASCIT**
MARVEL
TRANS-SCOT
Raman Colon Diagnosis
CRUK Stratified Medicine Study
PROSPECT
Impact of robotic surgery on teamwork
miRNA
CORGI
COGS2
Pop based DNA collections
Characterising immune response
SOCCS3
Metabolism of polyphenol
PRESENT
Functionality of potential drug targets in patients with colorectal cancer by tissue microarray.
BRAFV600E IHC
Role of N-WASP
JAM-A expression and function
Targeting miRNAs for therapy
Molecular Pathology of Colorectal cancer
NSCCG
Role of STAT1
DWIBS
Tumour Angiogenesis
Functionality of potential drug targets in patients with colorectal cancer by tissue microarray.
** study suspended
Version: February 2015
Developed by NCRI CSGs & NCRN
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored


COLORECTAL CSG TRIAL MAP D
COLORECTAL NON-TREATMENT
WHITE=OPEN ON MULTIPLE PORTFOLIOS
YELLOW=OPEN/RECRUITING
PURPLE=IN SET-UP/FUNDED
Lifestyle/Psychosocial/Supportive Care
Primary Care/Data Collection
Pre-Diagnosis
Diagnosis/ Screening/ Prevention
Neoadjuvant
Surgery
Adjuvant
Palliative 1st Line
Palliative 2nd Line
The ASyMS (C) III Study
The REx Trial
Comparing breast, cervical and bowel screening
E-CAP
ICBP MODULE 4
CANDID
Phys. effects of altering inflammation
ICBP MODULE 4
MECURY 2 (Rectal Cancer only)
CRUK Stratified Medicine Study
Developed by NCRI CSGs & NCRN
Version: February 2015
(D): CSG-developed (C): CSG-consulted (O): Other
(A): Academically-sponsored (P): Academic/Industry Partnership (I): Industry-sponsored

Appendix 4

Publications in the reporting year

ACT2

Glynne-Jones R, Adams RA, Jitlal M, Meadows H. End points in anal cancer: hopes for a common language. *J Clin Oncol*. 2014 Apr; 32(12): 1281-2.

Glynne-Jones R, Kadalayil L, Meadows HM, Cunningham D, Samuel L, Geh JI, Lowdell C, James R, Beare S, Begum R, Ledermann JA, Sebag-Montefiore D; ACT II Study Group. Tumour- and treatment-related colostomy rates following mitomycin C or cisplatin chemoradiation with or without maintenance chemotherapy in squamous cell carcinoma of the anus in the ACT II trial. *Ann Oncol*. 2014 Aug; 25(8): 1616-22.

Muirhead R, Adams RA, Gilbert DC, Glynne-Jones R, Harrison M, Sebag-Montefiore D, Hawkins MA. Anal cancer: developing an intensity-modulated radiotherapy solution for ACT2 fractionation. *Clin Oncol* (R Coll Radiol). 2014 Nov; 26(11): 720-1.

ASPECCT

Price TJ, Peeters M, Kim TW, Li J, Carscinu S, Ruff P, Suresh AS, Thomas A, Tjulandin S, Zhang K, Murugappan S, Sidhu R. Panitumumab versus Cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open label, non-inferiority phase 3 study. *Lancet Oncology* 2014; 15(6): 569-579.

BALLAD

Bogaerts J, Sydes MR, Keat N, McConnell A, Benson A, Ho A, Roth A, Fortpied C, Eng C, Peckitt C, Coens C, Pettaway C, Arnold D, Hall E, Marshall E, Sclafani F, Hatcher H, Earl H, Ray-Coquard I, Paul J, Blay JY, Whelan J, Panageas K, Wheatley K, Harrington K, Licitra L, Billingham L, Hensley M, McCabe M, Patel PM, Carvajal R, Wilson R, Glynne-Jones R, McWilliams R, Leyvraz S, Rao S, Nicholson S, Filiaci V, Negrouk A, Lacombe D, Dupont E, Pauporté I, Welch JJ, Law K, Trimble T, Seymour M. Clinical trial designs for rare diseases: studies developed and discussed by the International Rare Cancers Initiative. *Eur J Cancer*. 2015 Feb; 51(3): 271-81.

CHRONICLE

Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, Ledermann J, Sebag-Montefiore D. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. *Ann Oncol*. 2014 Jul; 25(7): 1356-62.

Maas M, Nelemans PJ, Valentini V, Crane CH, Capirci C, Rödel C, Nash GM, Kuo LJ, Glynne-Jones R, García-Aguilar J, Suárez J, Calvo FA, Pucciarelli S, Biondo S, Theodoropoulos G, Lambregts DM, Beets-Tan RG, Beets GL. Adjuvant chemotherapy in rectal cancer: Defining subgroups who may benefit after neoadjuvant chemoradiation and resection: A pooled analysis of 3,313 patients. *Int J Cancer*. 2014 Nov. doi: 10.1002/ijc.29355.

Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, Glynne-Jones R, Counsell N, Bastiaannet E, van den Broek CB, Liefers GJ, Putter H, van de Velde CJ. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol*. 2015 Feb; 16(2): 200-7.

COIN, FOCUS & FOCUS2

Lieu CH, Renfro LA, de Gramont A, Meyers JP, Maughan TS, Seymour MT, Saltz L, Goldberg RM, Sargent DJ, Eckhardt SG, Eng C; Aide et Recherche en Cancérologie Digestive Foundation. Association of age with survival in patients with metastatic colorectal cancer: analysis from the ARCAD Clinical Trials Program. *J Clin Oncol*. 2014 Sep; 32(27): 2975-84.

Shi Q, de Gramont A, Grothey A, Zalcberg J, Chibaudel B, Schmoll HJ, Seymour MT, Adams R, Saltz L, Goldberg RM, Punt CJ, Douillard JY, Hoff PM, Hecht JR, Hurwitz H, Díaz-Rubio E, Porschen R, Tebbutt NC, Fuchs C, Souglakos J, Falcone A, Tournigand C, Kabbinavar FF, Heinemann V, Van Cutsem E, Bokemeyer C, Buyse M, Sargent DJ. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: findings from the analysis and research in cancers of the digestive system database. *J Clin Oncol*. 2015 Jan; 33(1): 22-8.

COIN-B

Wasan H, Meade AM, Adams R, Wilson R, Pugh C, Fisher D, Sydes B, Madi A, Sizer B, Lowdell C, Middleton G, Butler R, Kaplan R, Maughan T; COIN-B investigators. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. *Lancet Oncol*. 2014 May; 15(6): 631-9.

CRIB

Munro J, Adams R, Campbell A, et al. CRIB—the use of cardiac rehabilitation services to aid the recovery of patients with bowel cancer: a pilot randomised controlled trial (RCT) with embedded feasibility study. *BMJ Open* 2014; 4:e004684. doi:10.1136/bmjopen-2013-004684

CUFOX

Glen R. B. Irving, Chinenye O. O. Iwuji, Bruno Morgan, David P Berry, William P Steward, Anne Thomas, Karen Brown and Lynne M. Howells. Combining curcumin (C3-complex, Sabinsa) with standard care FOLFOX chemotherapy in patients with inoperable colorectal cancer (CUFOX): study protocol for a randomised control trial. *Trials* 2015 Mar; 16: 110 doi:10.1186/s13063-015-0641-1

ENROL

Kennedy RH, Francis EA, Wharton R, Blazeby JM, Quirke P, West NP, Dutton SJ. Multicenter randomized controlled trial of conventional versus laparoscopic surgery for colorectal cancer within an enhanced recovery programme: EnROL. *J Clin Oncol*. 2014 Jun; 32(17): 1804-11.

E-SCOUT

Krebs MG, Renehan, AG, Backen A, Gollins S, Chau I, Hasan J, Valle JW, Morris K, Beech J, Ashcroft L, Saunders MP, Dive C. Circulating tumour cell enumeration in a Phase II trial of a four-drug regimen in advanced colorectal cancer. *Clinical Colorectal Cancer* 2014 Jun; 14(2): 115-122.

EXPERT-C

Sclafani F, Gonzalez D, Cunningham D, Hulkki Wilson S, Peckitt C, Tabernero J, Glimelius B, Cervantes A, Dewdney A, Wotherspoon A, Brown G, Tait D, Oates J, Chau I. TP53 mutational status and cetuximab benefit in rectal cancer: 5-year results of the EXPERT-C trial. *J Natl Cancer Inst* 2014 Jun; 106(7). pii: dju121. doi: 10.1093/jnci/dju121.

Sclafani F, Gonzalez D, Cunningham D, Hulkki Wilson S, Peckitt C, Tabernero J, Glimelius B, Cervantes A, Dewdney A, Wotherspoon A, Brown G, Tait D, Oates J, Chau I. TP53 mutational status and cetuximab benefit in rectal cancer: 5-year results of the EXPERT-C trial. *J Natl Cancer Inst*. 2014 Jun 23;106(7).

FOCUS 3

Maughan TS, Meade AM, Adams RA, Richman SD, Butler R, Fisher D, Wilson RH, Jasani B, Taylor GR, Williams GT, Sampson JR, Seymour MT, Nichols LL, Kenny SL, Nelson A, Sampson CM, Hodgkinson E, Bridgewater JA, Furniss DL, Roy R, Pope MJ, Pope JK, Parmar M, Quirke P, Kaplan R. A feasibility study testing four hypotheses with phase II outcomes in advanced colorectal cancer (MRC FOCUS3): a model for randomised controlled trials in the era of personalised medicine? *Br J Cancer* 2014 Apr; 110(9): 2178-86

MERCURY II

Battersby NJ, How P, Moran B, Stelzner S, West NP, Branagan G, Strassburg J, Quirke P, Tekkis P, Pedersen BG, Gudgeon M, Heald B, Brown G; MERCURY II Study Group. Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study. *Ann Surg*. 2015 Mar 27 [Epub ahead of print].

NEW EPOC

Primrose J, Falk S, Finch-Jones M, Valle J, O'Reilly D, Siriwardena A, Hornbuckle J, Peterson M, Rees M, Iveson T, Hickish T, Butler R, Stanton L, Dixon E, Little L, Bowers M, Pugh S, Garden OJ, Cunningham D, Maughan T, Bridgewater J. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014 May; 15(6): 601-11

SIGGAR

Halligan S, Wooldrage K, Dadswell E, Shah U, Kralj-Hans I, von Wagner C, Faiz O, Teare J, Edwards R, Kay C, Yao G, Lilford RJ, Morton D, Wardle J, Atkin W; SIGGAR Investigators. Identification of Extracolonic Pathologies by Computed Tomographic Colonography in Colorectal Cancer Symptomatic Patients. *Gastroenterology* Epub 18 March 2015.

Atkin, W., Dadswell, E., Wooldrage, K., Kralj-Hans, I., von Wagner, C., Edwards, R., Yao, G., Kay, C., Burling, D., Faiz, O., Teare, J., Lilford, R. J,, Morton, D., Wardle, J., Halligan, S.; SIGGAR investigators. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet*. 6;381(9873), pp. 1194-202.

Appendix 5

Major international presentations in the reporting year

Add-Aspirin

Langley RE, Wilson RH, Ring AE, Kynaston HG, Cameron DA, Coyle C, Gilbert DJ, Patrono C, Rowley S, Murphy C, Adlam D, Hubner R, Iveson T, Steele RJ, Thomas AL, Underwood TJ, Jankowski J, Gupta S, Pramesh CS, Parmar M. Add-aspirin trial: A phase III, double blind, placebo-controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. *J Clin Oncol* 2014; 32:5s (suppl; abstr TPS1617).

COIN

Elisabeth Coart, Everardo D. Saad, Qian Shi, Dirkje Willemien Sommeijer, John Raymond Zalcberg, Tim Maughan, Richard M. Goldberg, Hans-Joachim Schmoll, Cornelis J. A. Punt, Eric Van Cutsem, Jean-Yves Douillard, Paulo Marcelo Hoff, Niall C. Tebbutt, Charles S. Fuchs, Alfredo Falcone, Christophe Tournigand, Aimery De Gramont, Daniel J. Sargent, Tomasz Burzykowski, Marc E. Buyse, ARCAD Group. Trial-level association between response-based endpoints (RBEs) and progression-free (PFS)/overall survival (OS) in first-line therapy for metastatic colorectal cancer (mCRC) in the ARCAD database. *J Clin Oncol* 33, 2015 (suppl 3; abstr 666).

IMPALA

David Cunningham, Alfredo Zurlo, Ramon Salazar, Michel Ducreux, Tom Samuel Waddell, Alexander Stein, Christophe Tournigand, Werner Scheithauer, Alberto F. Sobrero, Eric Van Cutsem, Dirk Arnold. IMPALA, a randomized phase III study in patients with metastatic colorectal carcinoma: Immunomodulatory maintenance therapy with TLR-9 agonist MGN1703. *J Clin Oncol* 33, 2015 (suppl 3; abstr TPS791).

ACT II

Robert Glynne-Jones, Helen Meadows, Andrew Renehan, David Sebag-Montefiore, Mark Harrison, Maria Hawkins, Rebecca Muirhead, Andre Lopes, Richard Adams; Patient and tumor characteristics impacting on lymph node metastases rate (LNMR) in squamous cell carcinoma of the anal canal and margin (SCCA) using data from the NCRI randomized phase III ACT II trial: Implications for radiotherapy target volume. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 4032)