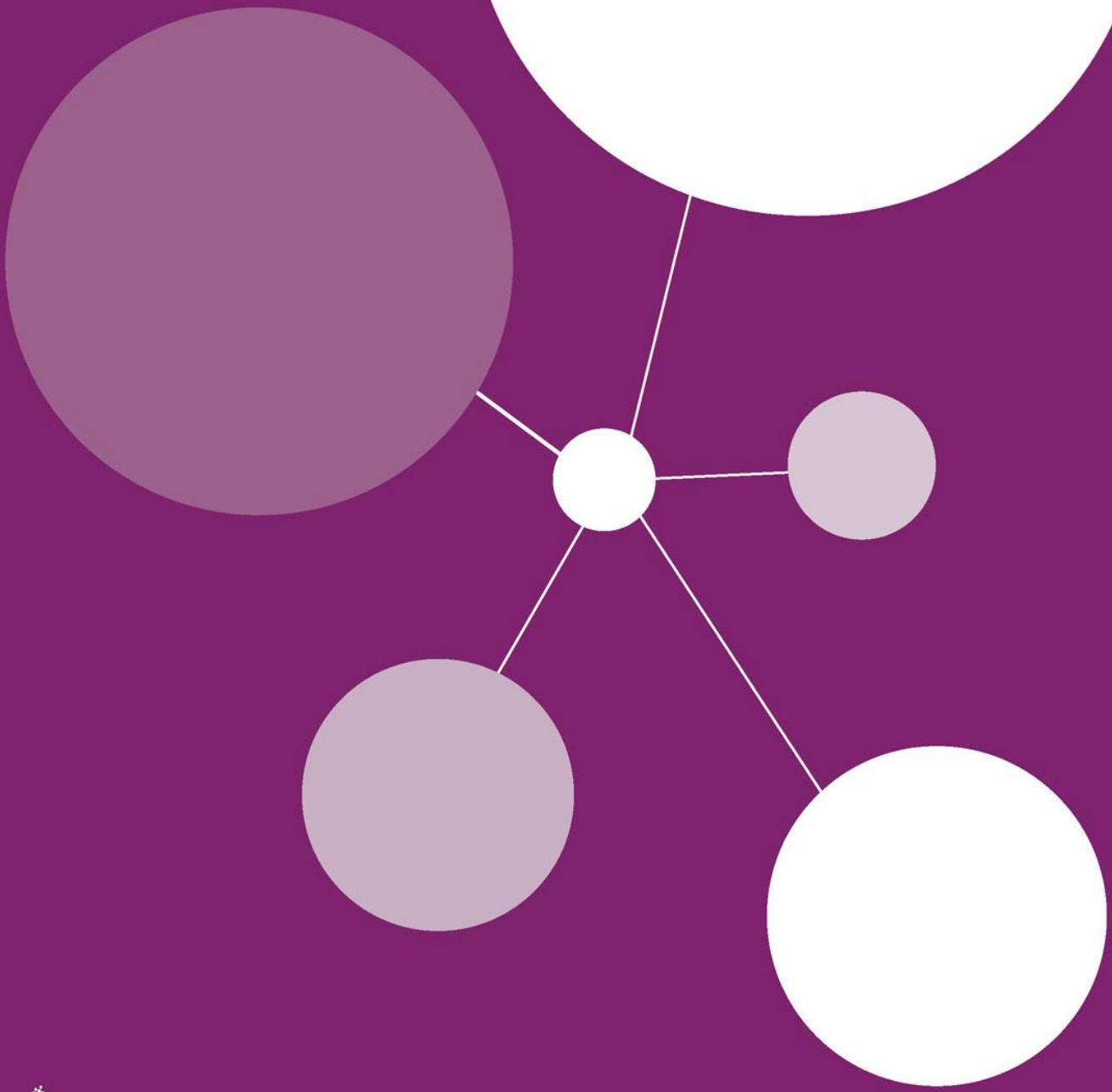
NCRI
National
Cancer
Research
Institute

NCRI Gynaecological Group

Annual Report 2018-19



Partners in cancer research

NCRI Gynaecological Group Annual Report 2018-19

1. Top 3 achievements in the reporting year

Achievement 1

The first achievement is the impact of our trials on the management of women with gynaecological cancers. In the past year, SOLO1 has shown conclusively that maintenance PARP inhibition dramatically extends progression-free survival in first-line management of ovarian cancer in women with germline *BRCA1/2* mutations, PREMIUM has indicated that metformin is unlikely to have any meaningful biological activity in endometrial cancer, answering a question that has long been postulated, and the combined long term CHORUS/EORTIC pooled individual patient data analysis confirmed that neoadjuvant chemotherapy and primary surgery are equivalent in women with advanced ovarian cancer.

Achievement 2

The second achievement is the breadth of our portfolio. We continue to run a portfolio of studies across the spectrum of gynaecological malignancies. We are pleased that there are now academic studies in relapsed endometrial and cervix cancer (COPELIA and COMICE respectively), our rare gynaecological cancer study has opened (RANGO) and new studies in the areas of risk and prevention are in development. We continue to have large phase III studies in first-line treatment of all three main gynaecological cancers, and we have good interactions with the pharmaceutical industry.

Achievement 3

The third achievement is our international influence. The NCRI Gynaecological Cancer CSG is a key member of both ENGOT (European Network of Gynaecological Oncology Trials Groups) and GCIG (Gynecologic Cancer InterGroup) and is leading major studies through both organisations – ICON8B, ICON9 and ATHENA in ovarian cancer, INTERLACE in cervix cancer and STATEC in endometrial cancer. Moreover, the Chair of the GCIG Cervical Cancer Research Network, which is driving uptake of clinical trials in cervix cancer in low and middle-income countries, is a former CSG member. Finally, CSG members were integral to a recent international consensus guideline publication on management of gynaecological cancers in Lynch Syndrome patients.

2. Structure of the Group

Following the strategy review meeting of March 2018, there has been a reorganisation of the Gynaecological Cancer CSG to reflect the fact that clinical trials design and decision making in this CSG is driven by the subgroups/workstreams rather than by the wider CSG. Although there are still three workstreams (Ovarian, Endometrial and Cervix/Vulva) based upon primary disease site, the key changes have been to move towards a devolved structure, whereby CSG members are primarily affiliated with a workstream rather than the main group, with the creation of a smaller Executive Group to oversee the portfolio and wider strategic decisions. The Executive Group consists of the Chair, the workstream chairs, a consumer member as well as the NIHR CRN Research Delivery Manager. As a result, a decision was made not to alter CSG membership for 12 months to allow the changed structure time to embed itself. However, a new Ovarian Workstream chair, Dr Shibani Nicum, was appointed. She replaces Dr Ros Glasspool, whom the Group thanks sincerely for her efforts and dedication to the CSG, in particular as a representative at ENGOT and GCIG meetings.

Three new trainee members, Dr Michael-John Devlin, Dr Jaya Nautiyal and Dr Vanitha Sivalingam, were appointed in late 2018 – they will be affiliated with the ovarian, endometrial and cervix/vulva subgroups/workstreams respectively. As part of their training, they will each be appointed to the Trial Management Group of one of our portfolio trials and will be developing specific research proposals with their mentors. Overall, the Gynaecological Group remains an enthusiastic supporter of the trainee member programme.

A third consumer member was appointed in March 2019. Hilary Morrison will join the Executive Group as its consumer member and act as liaison with the NCRI Consumer Forum. We welcome Hilary and hope that she finds the work interesting and stimulating.

3. Group & Workstream strategies

Gynaecological Group

Overall trials strategy

The core mission of the CSG remains to develop and conduct high quality trials in gynaecological cancer. At the Strategy Day in March 2018, three keys strategic priorities were highlighted

1. There should be a CSG-led phase III trial in first line management for each of the main three gynaecological cancers (ovary, endometrium, cervix) open at all times.
2. Risk and prevention have both been historically under-represented in the portfolio. New trials are required in these areas.
3. Incorporation of novel imaging modalities and novel imaging endpoints into clinical trials was vital, given the strength in imaging in gynaecological cancer in the UK.

For aim 1, ICON8B (ovarian), STATEC (endometrial) and INTERLACE (cervix) remain open. ATHENA is a new phase III academically-led, industry-funded study in first-line ovarian cancer, discussed below.

For aim 2, there is significant research interest in gynaecological cancer risk and prevention, especially in ovarian cancer and endometrial cancer. The PREMIUM study of metformin in women at high risk of endometrial cancer has reported, whilst the Phase I of the ProGREsS study (Personalised Genetic Risk Estimates for Cancer Screening and Prevention) has already recruited 1000 patients via GP practices in North West London.

For aim 3, the MROC study is still recruiting, addressing the role of multi-parametric MRI in treatment decisions in ovarian cancer. In addition, new radiomic algorithms are being evaluated in the ICON8 CT scans. These studies will be translated into prospective trials in coming years.

Thus, the CSG is making solid progress towards the aims elucidated in the March 2018 strategy.

Membership

As stated in Section 2, there has been a re-organisation of the CSG in the past 12 months. As a result, membership has not changed. However, it has previously been noted that CSG membership remains dominated by medical oncologists, and also has a bias to those from South East of England. Previous targeted recruitment priorities (e.g. radiology, pathology) have been successful and the targeted priorities for 2019 – 2020 will include further clinical oncology and clinical nurse specialist appointments.

One key strategy to widen participation has been to hold meetings outside London – the ovarian subgroup/workstream has for many years met in Glasgow each February in conjunction with the Scottish Gynaecological Clinical Trials Group, and the endometrial/cervix workstreams will again have a joint meeting in Manchester in June 2019.

Workstreams

The main driver of the reorganisation of the CSG was the desire to empower the subgroups/workstreams and to reflect their importance in developing trial ideas and creating a balanced portfolio. The intention is that the reorganisation will strengthen the subgroups/workstreams, widen participation, improve consumer involvement and maximise recruitment.

The three workstreams will continue to have two meetings per year, and the endometrial and cervix/vulva workstreams will continue to meet jointly, following the successful meetings in June and December 2018. The practice of the open meetings, as pursued by the ovarian workstream for many years and now adopted by the other workstreams, will continue.

Subspecialty leads and regional recruitment

Several Network Subspecialty Leads (SSLs) attended the Strategy Day in 2018 and it was agreed that communication between the CSG and SSLs needs to improve. A new procedure was developed whereby communication, about site selection in particular, will be channelled via the SSLs and the subgroup/workstream Chairs. It was also agreed that SSLs would routinely be invited to subgroup meetings – obtaining up to date lists of SSLs has continued to prove challenging, but we will continue to endeavour. The SSLs will be invited to meet with the CSG Executive Group in November 2019 immediately prior to the CSG Trials Meeting.

Consumers and charity partners

One key aim of the reorganisation is to improve the opportunities for participation by the consumer member by increasing their opportunities to influence trial strategy and design. A key strategic aim for 2018 onwards is that consumer members will attend subgroup meetings as their key priority – it was thus disappointing that neither member was able to attend to the joint endometrial/cervix subgroup/workstream meeting in December 2018. It is hoped that the appointment of a new consumer member to the Executive Group will help to drive an improved consumer agenda.

There are several very strong and effective gynaecological cancer charities, and representatives of these charities are regular attenders at Ovarian Subgroup meetings. This is an effective mechanism for disseminating information about clinical trials. Invitations will be extended to other charity partners to attend the Endometrial and Cervix/Vulval Subgroups.

Cervix/Vulva Workstream (Chair, Dr Emma Hudson)

Two very successful meetings of the Cervical/Vulval Workstream took place in 2018 in conjunction with the endometrial subgroup, in Manchester (June) and London (December). They were both well attended and multiple trial ideas in both cervical and vulval trials were presented, several of which were approved for further development.

Recruitment to the flagship trial INTERLACE has been extended until April 2020. With 365 patients already recruited, the target of 500 is eminently achievable.

The UK is the 4th highest recruiter to the international surgical SHAPE trial of simple vs radical hysterectomy in early cervical cancer; 600 out of the target 700 patients have already been recruit, and SHAPE is on schedule to complete in December 2019.

There is strong scientific rationale for the use of immunotherapy in HPV-related disease. Trials are being developed in both the radical and palliative setting. The phase 2 single arm IVoRY trial is an investigator-initiated concept trial developed by the CSG that has been accepted by MSD for full submission. It explores the benefit of adding pembrolizumab to chemoradiotherapy in locally advanced vulval cancer.

Open new trials in relapsed disease

COMICE is a CSG-developed trial investigating olaparib and cediranib in recurrent or metastatic cervical cancer and opened in early 2019. To date 2 centres have opened and 4 patients have been recruited. Several other centres are in set up and due to open shortly.

Two other trials in relapsed cervical cancer are due to open in the UK in 2019. Both are in second or further line cervical cancer and neither conflicts with COMICE. The first, ENGOT-cx-8, in collaboration with ENGOT, investigates tisotumab in combination with other agents in recurrent or Stage IVB Cervical Cancer. Cemiplimab is a PD1 inhibitor that is being compared to investigator's choice chemotherapy in 2nd or further line cervical cancer. This study is due to open in 5 UK sites in Q2-3 2019.

Develop a therapy trial in relapsed vulval cancer with associated tissue collection

This remains an area of unmet clinical need where a clinical trial is very much needed. Ideally this would be in collaboration with other CSGs although this is somewhat challenging given the trials already open in anal cancer. However, the IVoRY study (see above) is being submitted to MSD as an investigator-initiated study concept.

Prevention

Prevention remains a key strategy for the NCRI cervical and vulval subgroup. The NOVEL trial is exploring the role of HPV vaccination post-conization for high risk CIN and has been successful in securing an NIHR EME grant. This large study will open in late 2019.

Work is ongoing to secure funding for the RT3 trial to explore the topical treatment of VIN following a positive phase 2 trial. Unfortunately funding through CRUK has been declined but other sources are being explored.

Endometrial Workstream (Chair, Professor Emma Crosbie)

The endometrial cancer portfolio has trials covering prevention, first line treatment, survivorship and management of recurrent and metastatic disease. The March 2018 CSG strategy day highlighted the importance of screening, prevention and early detection trials to clinicians, consumers and charity representatives, and these are underway. FORECEE has completed recruitment and analysis is underway to identify genomic, metabolomic and microbiome biomarkers that predict breast, ovarian, endometrial and cervical cancer risk. The suite of pilot trials from Manchester looking at weight loss, metformin and the Mirena coil for endometrial cancer prevention has completed; these will inform a large prevention trial. A diagnostic test accuracy study of a novel endometrial cancer detection tool is underway and the role of circulating ctDNA in monitoring treatment and recurrent disease is in planning.

STATEC, an international surgical endometrial trial developed in the UK, has opened but recruitment has been challenging. It is an important trial since it will provide important answers related to the role of lymphadenectomy and adjuvant therapy in endometrial cancer, as well as to allow the development of sentinel node techniques. The trial is open in several UK and international sites, with more in set up phase. An application to CRUK is in progress to change the primary endpoint from overall to relapse-free survival to help with recruitment challenges and other measures are being put in place to boost interest in the trial.

COPELIA, a trial of cediranib and olaparib in relapsed and metastatic disease, is open and brings trials of new targeted therapies to endometrial cancer for the first time in an investigator-led study developed through the subgroup/workstream. New commercial trials, ATtEND and LEAP, investigating immune checkpoint inhibitors via ENGOT collaboration, are in development, with a view to opening in 2020.

There will be two endometrial subgroup meetings in 2019 (June and December) held in conjunction with the Cervix/Vulva Subgroup.

Launch a new study of primary prevention of endometrial cancer in high risk women A prevention trial concept was discussed at the Endometrial Subgroup Meeting in December 2018 and was received well. There is a willingness to support such a trial but there are many challenges to address, specifically identifying 'high risk' (obese postmenopausal women vs women with Lynch syndrome), which intervention to test (Mirena, weight loss, metformin), placebo or control intervention, primary endpoint, duration of follow up, whether or not to take biopsies at the start/end of the trial.
Test a new endometrial cancer detection tool in symptomatic women In Manchester, a diagnostic test accuracy study of a new endometrial cancer detection tool is underway. The recruitment target is 2,000 women with postmenopausal women and a quarter have been recruited to target so far.
Test non-surgical treatments in early stage and pre-invasive disease The combination of weight loss and intrauterine progestin for the conservative management of endometrial cancer and atypical hyperplasia is being tested in a small pilot study with promising results.

Ovarian Workstream (outgoing Chair, Dr Ros Glasspool)

The workstream again had two well-attended meetings, in London (Sept 2018) and Glasgow (Feb 2019) and continues to support a broad portfolio of studies. Importantly, there are still academic studies in the all treatment settings with ICON8B (first line), ICON9 (>6 months relapse), OCTOVA (<12 months relapse) and DICE (<6 months relapse). The rare tumour portfolio is strong with NiCCC, PEACOCC and RANGO recruiting and ATARi in set-up. Work continues on a first line, international randomised trial in low grade serous ovarian cancer in collaboration with GCIG, whilst CENTURION will investigate PARP inhibitor-immune checkpoint inhibitor combinations in the relapsed setting.

In screening and prevention, the OCTAGON and PROTECTOR trials continue, and PROMISE has completed recruitment. The RRESDo survey is investigating the views of women at increased risk of OC on Risk Reducing Early Salpingectomy & Delayed Oophorectomy as a two stage OC prevention strategy and the SIGNPOsT aims to evaluate the impact of systematic genetic testing on psychological health and quality of life. The CLoCS (Cancer Loyalty Card Study) was successful in gaining funding and will recruit 500 women with newly diagnosed ovarian cancer in the first phase of the trial; this novel study will investigate purchasing patterns on store loyalty cards, initially looking retrospectively at women with a new diagnosis of ovarian cancer, to identify potential early patterns of spending that might indicate symptomatic ovarian cancer.

Two imaging/diagnostic studies, MROC and Rockets continue to recruit as does the supportive study HORIZONS. The MICA trial, a phase II trial examining bermekimab (anti-IL1 alpha) effects on muscle, physical function and appetite, in lung, pancreatic or ovarian cancers, is due to open soon. MONITOR, a phase IV trial of safety, tolerability and patient reported outcomes in women on niraparib maintenance therapy has been funded. In surgery the TRUST trial continues and the national surgical audit has been launched. Socqer 2 has completed recruitment and analysis of results is ongoing.

A number of other projects are in development or working towards grant submissions including BRITROC2 and a second arm for the OCTOPUS trial.

We are working with the Supportive and Palliative care CSG on a proposal to investigate a supportive care intervention for women on PARPi (niraparib) maintenance therapy and also working with the TYA and Germ Cell CSG on the AGCT1531 trial, a phase 3 study of active surveillance for low risk and a randomized trial of carboplatin vs. cisplatin for standard risk paediatric and adult patients with germ cell tumours.

The group continues to collaborate actively with international groups, in particular the GCIG and ENGOT. ENGOT groups have joined ICON8B, ICON9 and ATHENA, and we are collaborating on the FIRST, OREO, NEO and TRUST trials. We are also participating in EORTC 1508 Study, EORTC 1514-QLQ-GCG trials and the EORTC is participating in NiCCC.

The group is contributing to the development of new ESGO/ESMO mobile apps for the management of rare gynaecological cancers and several members participated in the ESGO-ESMO consensus conference on ovarian cancer in April 2018.

Finally, the workstream would like to pay tribute to Professor Martin Gore, who died in January 2019. Martin had been a stalwart supporter of clinical trials in ovarian cancer for many years and was a key member of the early collaborative groups, including the London Gynaecological

Oncology Group and the Advanced Ovarian Triallists' Group, forerunners of the CSG and the GCIG. Martin was also mentor to many members in the CSG over several decades and a provider of copious sage and witty advice. Ovarian cancer in the UK has lost one of its most trenchant advocates.

Trials in the frail/elderly The FAIR-O study, led by Dr Susie Banerjee, has been funded by Wellbeing of Women. This will open later in 2019. Ovarian cancer has also been included in an application to investigate the integration of the Electronic Frailty Index into routine practice (Dr Aggie Michael).
Biomarker stratification trials Professor Gordon Jayson is leading an application for an observational study to validate Tie2 in patients receiving bevacizumab – Gordon's work on ICON7 samples has indicated that plasma Tie2 levels are a valid vascular response marker that will be prospectively validated in the proposed study. This would be the first biomarker for anti-angiogenesis therapy in ovarian cancer.
Surgical trials The CSG is participating in TRUST. This study, led by the German AGO group, investigates primary chemotherapy vs primary surgery but is restricted to centres that undertake radical debulking surgery and have received ESGO Advanced Ovarian Cancer Surgery certification. The study has now reached its target of 700 patients.

4. Task groups/Working parties

The Gynaecological Cancer Group had no task groups or working parties during the reporting year.

5. Funding applications in last year

CSG members continued to apply regularly for trial grants in the past 12 months. Three out of six applications to CRUK Clinical Research Committee were successful, with most of the applications being developed by the CSG itself.

One of the aims of the past year has been to diversify our funding applications beyond CRUK, and we were very pleased that Dr Susie Banerjee's application to Wellbeing of Women and Dr Sadaf Ghaem-Maghami's application to The Eve Appeal were both supported. The Chair's own application for an MRC Experimental Medicine Challenge grant was rather less successful, but the group (and indeed the Chair) remain resolute!

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)					
Study	**Application type**	**CI**	**Outcome**	**Level of CSG input**	**Funding amount**
May 2018					
ROCKETS-GEN: Earlier detection of ovarian cancer using novel genomic technology	Biomarker Project Award	Dr Sudha Sundar	Supported	Developed by CSG	
REGENCY: Stereotactic radiotherapy for recurrent gynaecological cancer	Early Phase & Feasibility Study	Dr Alexandra Taylor	Not Supported	Developed by CSG	NA
Risk stratification of HPV infection using a multiplex assay for the improved detection of cervical disease and cancer	Biomarker Project Award	Dr Kate Cushieri	Not Supported	Supported by CSG	NA
TRANS CeNtuRIOn: translational sample collection for CeNtuRIOn, an open-label, randomised, phase II trial of ruCaparib combinEd with Nivolumab wiTh/without ipilimUmab to augment Response In homologous repair deficient patients with relapsed Ovarian caNcer	Sample Collection	Dr Marcia Hall	Supported	Developed by CSG	£198,000

November 2018					
ATARI: ATr inhibitor in combination with olaparib in gynaecological cancers with ARId1A loss or no loss	Clinical Trial Award	Dr Susana Banerjee	Supported (endorsement)	Developed by CSG	NA
Randomised Trial opTimising Treatment of anal/Vulval Intraepithelial Neoplasia – 2 (RT3VIN2)	Clinical Trial Award Outline	Dr Sadie Jones	Not Supported	Supported by CSG	NA
Other committees					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**	**Funding amount**
FAIR-O. Improving outcomes in older women: Feasibility of frailty assessment and implementation of geriatric interventions in women over the age of 70 with epithelial ovarian cancer in the oncology clinic	Wellbeing of Women – Clinical Trial Award	Dr Susie Banerjee	Supported	Developed by CSG	£176,000
Rapid tissue diagnosis of endometrial cancer in patients with abnormal uterine bleeding	The Eve Appeal – Pilot award	Dr Sadaf Ghaem-Maghami	Supported	Supported by CSG	£50,000
BriTROC-2 - Identifying active mutational processes in ovarian high grade serous carcinoma	Ovarian Cancer Action – translational trial grant	Professor Iain McNeish	Pending	Developed by CSG	£295,000
SCOTROC-6 – epigenetic regulation of drug resistance in ovarian high grade serous carcinoma	MRC - Experimental Medicine Challenge Award	Professor Iain McNeish, Dr Ros Glasspool	Not supported	Developed by CSG	£1.8M

6. Consumer involvement

The Group would like to pay tribute to Sue Ballard, consumer representative on the Ovarian subgroup/workstream, who died of ovarian cancer in 2018.

Hilary Morrison was recently appointed as the consumer member of the Executive Group in March 2019.

7. Priorities and challenges for the forthcoming year

Priority 1 The CSG is unapologetic that its first priority for the coming year is the same as last year: It is essential that we maintain recruitment to time and target in all our trials. This is particularly important for the flagship studies, including ICON8B, STATEC, ICON9, INTERLACE and ATHENA. Our strategy for maintaining recruitment includes ensuring that trials are available in as many centres as possible, regular meetings with investigators to identify barriers to recruitment and encouraging Chief Investigators to interact with recruiting sites. It is pleasing to see that there has been a further increase in the percentage of women with gynaecological cancers entering interventional trials (see Appendix 5).
Priority 2 The development of new trials in novel areas, including prevention and risk, as well as therapeutic trials in vulval and vaginal cancers, remains a priority. The risk and prevention areas are progressing well, whilst vulval and vaginal cancers remain areas of unmet need. It will be important to work internationally if we are to obtain sufficient numbers of either cancer type. In addition, working with other CSG for cross-tumour type studies will be important – this is particularly true of vulval cancer, where some biological features are shared with anal cancer.
Priority 3 A medium-term strategy will be to integrate the wealth and depth of translational and imaging science in gynaecological cancer, much of it led by UK investigators, prospectively into our trials. Most of our translational science is either run retrospectively on samples collected during the study, or as separate translational science studies. The CSG has run few genuinely experimental medicine studies where therapy and translational science are completely interlinked.
Challenge 1 Recruitment remains our key challenge as well as our top priority. In many trials, we are recruiting to time and target, but this requires intensive efforts from the Chief Investigator and Trials Unit, as well as the CSG. Of our large trials, ICON8B is a little behind schedule, ICON98 has started well, INTERLACE has picked up significantly, but STATEC continues to pose specific challenges in endometrial cancer – it will answer a critical question, but faces polarised surgical opinion.

Challenge 2 Optimal use of consumer members. As stated in last year's report, the CSG is fully committed to patient and public involvement in its activities – consumer members are invited to attend all subgroup/workstream meetings and are allocated a mentor to provide support and education. However, there is some frustration, both from the consumers and the Chair, that the consumer members could be more effectively deployed. The reorganisation of the CSG with the appointment of a Consumer member of the Executive Group is designed to improve this situation, but this will require careful management.
Challenge 3 At risk of being overtly political, a no-deal Brexit will pose significant challenges. The Gynaecological Cancer CSG is an inherently international group, with close co-operation with ENGOT network in Europe. European co-operation for academically-led trials will be challenging if there is a no-deal Brexit, especially in the area of data sharing and willingness of pharmaceutical companies to make definite plans for inclusion of UK in future trial plans.

8. Collaborative partnership studies with industry

The Gynaecological Group has good partnership with industry, particularly in ovarian cancer. The key exemplar is ATHENA – this is an international phase III study of maintenance PARP inhibition (rucaparib), immune checkpoint inhibition (nivolumab) alone or together following completion of first line surgery and chemotherapy in women with advanced ovarian cancer. The NCRI Gynaecological Group is the lead group in Europe (the NRG group leads in the US), with Rebecca Kristeleit as co-Chief Investigator and Iain McNeish as Translational Lead. The CSG has been closely involved in study concept and design, with representation on the Trial Management Group. Other ovarian cancer studies with industry funding and/or collaboration include PEACOCC (Merck), OCTOPUS, ATARI, ICON9 (all AstraZeneca), CENTURION (Clovis Oncology) and NiCCC (Boehringer Ingelheim), the latter being the first randomised trial in relapsed ovarian clear cell carcinoma.

In non-ovarian cancers, the relationships are less well developed. However, industry is taking an increasing interest in endometrial and cervix cancers – COMICE and COPELIA are in set up (AstraZeneca), and there are several industry-led studies running through the ENGOT network that will be open in the UK, including ATtEND and LEAP. Interesting the pharmaceutical industry in vulval and vaginal cancer is challenging, which will necessitate broader umbrella-type studies.

9. Appendices

Appendix 1 - Membership of Executive Group and workstreams

Appendix 2 – Executive Group and Workstream strategies
A –Group Strategy

Appendix 3 - Portfolio Maps

Appendix 4 – Top 5 publications in reporting year

Appendix 5 – Recruitment to the NIHR portfolio in the reporting year

Professor Iain McNeish (Gynaecological Cancer Group Chair)

Appendix 1

Membership of the Gynaecological Cancer Executive Group

Name	Specialism	Location
Dr Hilary Stobart	Consumer	Cambridge
Prof Iain McNeish (Chair)	Medical Oncologist	London
Professor Emma Crosbie	Gynaecological Oncologist (Surgeon)	Manchester
Dr Ros Glasspool (outgoing)	Medical Oncologist	Glasgow
Dr Emma Hudson	Clinical Oncologist	Cardiff
Dr Shibani Nicum (incoming)	Medical Oncologist	Oxford

Membership of the Workstreams

Cervix/Vulva Workstream		
Name	**Specialism**	**Location**
Dr Vanitha Sivalingam*	Clinical Lecturer in Gynaecological Oncology	Manchester
Ms Emma Hudson (Chair)	Clinical Oncologist	Cardiff
Dr Azmat Sadozye	Clinical Oncologist	Glasgow
Dr Alexandra Taylor	Clinical Oncologist	London
Dr Tara Barwick	Consultant Radiologist	London
Miss Julia Tugwell	Consumer	Exeter
Dr Jenny Forrest	Gynaecological Oncologist	Devon
Mr Jeremy Twigg	Gynaecological Oncologist	Stockton-on-Tees
Professor John Tidy	Gynaecological Oncologist	Sheffield
Dr Susana Banerjee**	Medical Oncologist	London
Dr Rosemary Lord	Medical Oncologist	Merseyside
Dr Asma Faruqi	Pathologist	London
Dr Jackie Martin	Clinical Oncologist	Sheffield

Endometrial Workstream		
Name	**Specialism**	**Location**
Dr Melanie Powell	Clinical Oncologist	London
Ms Beryl Elledge	Consumer	Winchester
Professor Emma Crosbie (Chair)	Gynaecological Oncologist	Manchester
Dr Maria Kyrgiou	Gynaecological Oncologist	London
Dr Esther Moss	Gynaecological Oncologist	Leicester
Professor Kinta Beaver	Health Services Researcher	Lancashire
Dr Andrew Clamp	Medical Oncologist	Manchester
Dr Yvette Drew	Medical Oncologist	Newcastle
Dr Rosemary Lord	Medical Oncologist	Merseyside
Dr Axel Walther	Medical Oncologist	Bristol
Dr Naveena Singh	Pathologist	London
Dr Jaya Nautiyal*	Research Associate	London

Ovarian Workstream		
Name	**Specialism**	**Location**
Dr Michael-John Devlin*	Clinical Research Fellow	London
Professor Christina Fotopoulou	Gynaecological Oncologist	London
Dr Sadaf Ghaem-Maghami	Gynaecological Oncologist	London
Mrs Sundha Sundar	Gynaecological Oncologist	Birmingham
Dr Susana Banerjee	Medical Oncologist	London
Dr Ros Glasspool (Outgoing Chair)	Medical Oncologist	Glasgow
Professor Jonathan Ledermann**	Medical Oncologist	London
Dr Rosemary Lord	Medical Oncologist	Merseyside
Professor Iain McNeish**	Medical Oncologist	London
Dr Shibani Nicum (Incoming Chair)	Medical Oncologist	Oxford
Dr Axel Walther	Medical Oncologist	Bristol
Dr Sarah Williams	Medical Oncologist	Birmingham
Dr Sanjiv Manek	Pathologist	Oxford
Dr Nafisa Wilkinson	Pathologist	London

* denotes trainee member

**denotes non-core member

Appendix 2

A – Group & Subgroup Strategies 2018-2022

Gynaecological Cancer CSG Strategy

This strategy timeline has been produced to define the Gynaecological Cancer Research Strategy Plan and its implementation and will be reviewed and updated at each CSG meeting (supported by All)
The document is composed of the following:

Page : NCRI Gynaecological Cancer CSG Strategy: plan of implementation, containing agreed strategic objectives (1- 6), specific actions, CSG leads and proposed deadlines.

Gynaecological CSG members	Responsibility
Professor Kinta Beaver (KB)	**Professor of Cancer Nursing, Lancashire**
Dr Rebecca Bowen (RB)	Consultant Medical Oncologist, Bath
Dr Emma Crosbie (EC)	Clinical Senior Lecturer, Manchester
Ms Beryl Elledge (BE)	Consumer
Dr Ros Glasspool (RMG)	Consultant Medical Oncologist, Glasgow
Dr Emma Hudson (EH)	Consultant Oncologist, Cardiff
Dr Susan Lalondrelle (SL)	Consultant Clinical Oncologist, London (Royal Marsden)
Dr Michelle Lockley (ML)	Reader in Medical Oncology, London (Barts and UCH)
Professor Iain McNeish (IMcN)	Professor of Oncology, London (Imperial)
Dr Agnieszka Michael (AM)	Consultant Medical Oncologist, Surrey
Mr Jim Paul (JP)	Senior Research Fellow, Glasgow
Professor Evis Sala (ES)	Professor of Oncology Imaging, Cambridge
Ms Julia Tugwell (JT)	Consumer
Ms Laura Chambers (NCRI)	Administration Manager
Ms Nicola Keat (NCRI)	Head of Research Groups
Ms Aifric Müller (NCRI)	CSG Coordinator

Strategic objective	Action	CSG Lead	Date	Outcomes
1. Current CSG membership 1a – to widen diversity of specialties	Active encouragement of applications from clinical oncology, nursing, virology and epidemiology. Not possible to restrict geographical applications but active encouragement of applications from all of UK	IMcN	Dec 2018	Two more clinical oncology members; one more nurse member
1b – Re-organisation	Given the diverse nature of gynae cancers, aim to discuss with NCRI Central possibility of reducing overall CSG membership (e.g. to 10) to make the main CSG a strategic/oversight body, with much greater delegated to the subgroups as the decision-making forum for the CSG. This would allow an increase in the number of core sub-group members (e.g. 14 per subgroup) and increase the input from consumers.	IMcN	By time of next formal CSG review	Reduction in CSG membership; increased membership of subgroups

Strategic objective	Action	CSG Lead	Date	Outcomes
2. Subgroups 2a - Subgroup numbers	Subgroup meetings to remain the critical forum for trial and protocol development. To continue with three subgroups (ovary, endometrial, cervix/vulva)	EC, EH, RG, IMcN	On-going	CSG to continue to have three subgroups
2b - Subgroup meetings	Joint endometrial and cervix/vulva meetings to take place twice per year	EC, EH,	Mar 2019	Two face-to-face meetings of endometrial and cervix/vulva subgroups to have taken place by April 2019
2c - Subgroup chairs	Time as subgroup chair not to count in 3+3 year membership of CSG – vital to gain necessary experience prior to becoming subgroup chair.	IMcN	Dec 2018	Subgroup chairs to be allowed to continue beyond 3+3 year membership of CSG
2d - Subgroup membership	To widen membership, especially if numbers of subgroup members can increase. Increased participation/membership from basic scientists and charity representatives, especially in cervix/vulva subgroup	EC, EH, RG, IMcN	Mar 2019	At least one charity representative to be invited to cervix/vulva subgroup; invitation for basic scientists with interest in translational research to attend subgroup meetings

Strategic objective	Action	CSG Lead	Date	Outcomes
3.Subspecialty leads interactions 3a - Full list of SSL	NIHR central to provide accurate and up to date list of Gynae SSL	PW	Jul 2018	Accurate and up to date SSL list
3b - Improved dialogue between SSL and CSG	Subgroup chairs to liaise with SSL rather than individual sites for site selection	EC, EH, RG	On-going	Site identification to be devolved to SSL

Strategic objective	Action	CSG Lead	Date	Outcomes
4. Consumers and charity partners 4a - Consumer role	Consumer members to be embedded within subgroups rather than main CSG	EC, EH, RG, IMcN	Dec 2018	Consumer members to attend subgroup meetings rather than main CSG meetings
4b - Charity partners	Patient organisation/charities to be regularly invited to attend endometrial and cervix/vulva subgroup meetings – already attending ovarian subgroup meetings	EC, EH	Mar 2019	Eve Appeal, Jo's Trust,

Strategic objective	Action	CSG Lead	Date	Outcomes
5. Overall trials strategy 5a - First line intervention trials	The CSG should aim to have a first line trial in all three common gynaecological cancers – endometrium, ovary, cervix – and aim to have future trials in planning at time of opening of current trial	All	On-going	A major phase III first-line intervention trial open at all times for all three common gynaecological cancers
5b - Risk/prevention studies	To expand CSG-led studies that address identification of high risk patients prior to diagnosis of cancer and/or studies addressing prevention of gynaecological cancer	All	Jun 2019	One national risk/prevention study led by the CSG funded/ approved
5c - Early diagnosis/ rapid diagnosis	Develop a trial/protocol with primary care CSG to improve speed of diagnosis in ovarian cancer	All	Jun 2020	
5d - Imaging studies	RECIST has multiple flaws as a reporting tool, particularly in ovarian cancer. Action to incorporate novel imaging endpoints into future phase III trials	All	Jun 2021	Incorporation of novel imaging analysis as co-primary or secondary endpoint in phase II or phase III trial.

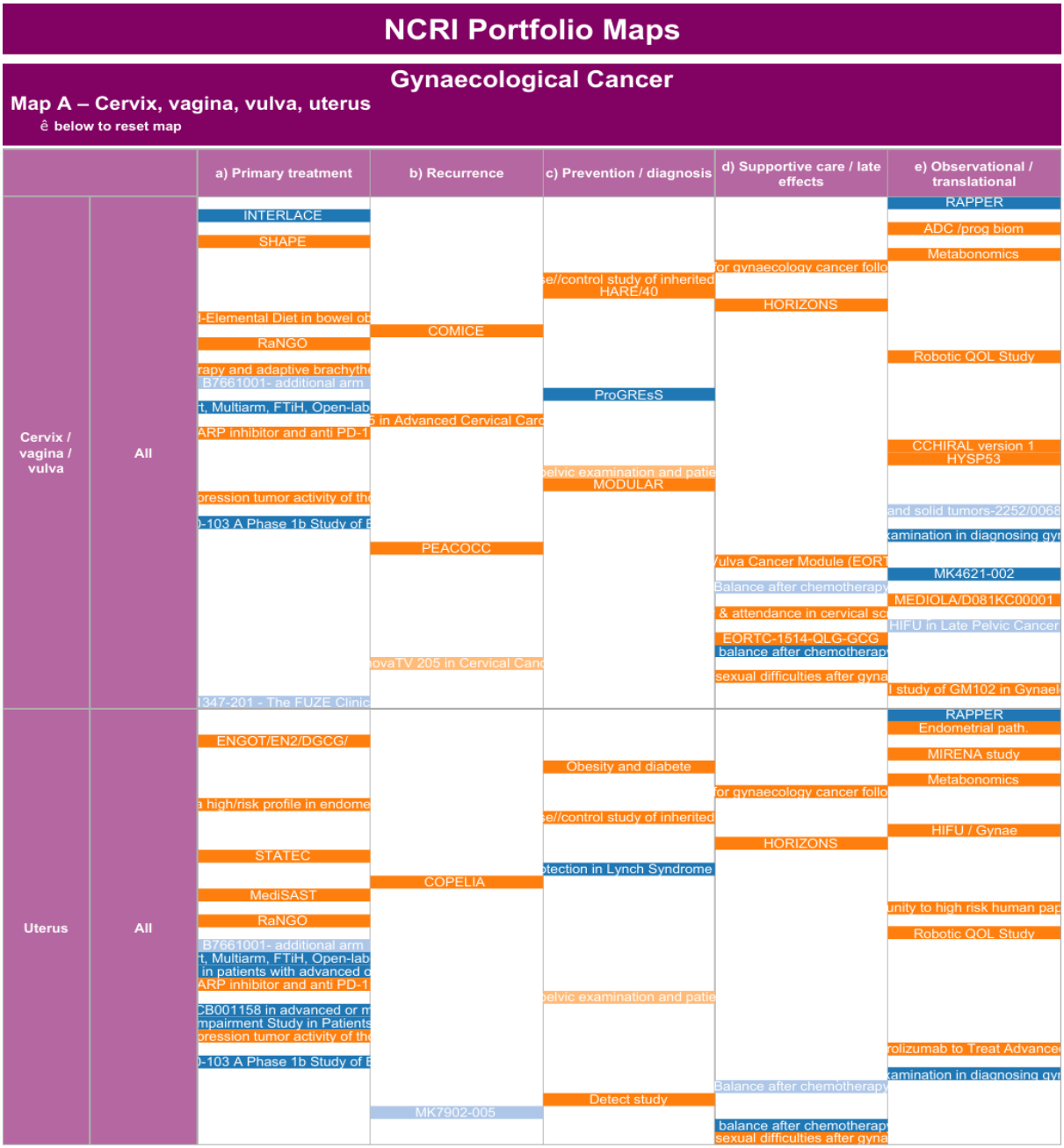
Strategic objective	Action	CSG Lead	Date	Outcomes
6.1.Disease-specific research: Vulva Cancer 6.1a - First line trial in locally advanced vulval cancer	Develop a first line trial in locally advanced/recurrent vulval cancer – combination of radiotherapy and immune checkpoint inhibition deemed most likely to be funded. Consider IRCI badging given the rarity of vulval cancer	EH, SL	Jun 2020	Funding or industry support for trial
6.1b - Joint HPV-positive study	Aim to develop joint protocols for HPV-positive cancers within gynae tumours and to include anal cancer subgroup +/- head and neck CSG	EH, IMcN	Jun 2020	Joint protocol for HPV positive gynae/ anal malignancies funded/supported by industry
6.2 Disease-specific research: Ovarian cancer 6.2a - Ovarian cancer in the frail/elderly	Development of trial evaluating geriatric assessment tool and chemotherapy treatment in the frail/elderly	AM, SB, RMG IMcN	Jun 2020	One new trial in which geriatric assessment tool is utilised and/or that evaluates chemotherapy specifically in the frail/elderly

Strategic objective	Action	CSG Lead	Date	Outcomes
6.2b - Molecular stratification	Urgent need to develop trial in which patients with newly diagnosed ovarian cancer are stratified according to molecular classifiers	All	Jun 2020	First line trial in which molecular stratification is an integral component to be
6.2c -Surgical trial	There is still robust debate as to which patients gain benefit from primary surgery vs interval debulking, and which patients may not benefit from surgery at all. Action to develop study in which surgical decision algorithm is integral to study design	All	Jun 2021	First line trial in which surgical decision algorithm is integral to stratification and/or treatment allocation
6.2c Screening	Following failure of UKCTOCS, there remains a need to screening study in ovarian cancer, both for high risk populations and unselected population. Such a study would have to incorporate molecular markers and improved imaging.	All	Jun 2022	Development of pilot protocol for screening study with stage shift as primary endpoint.
6.2d - Platinum-resistant trials	Outcomes for women with platinum-resistant disease remain very poor. CSG needs to have a portfolio of trials for women with resistant disease, including those who have had multiple prior lines of therapy	All	On-going	At least two trials open at all times for women with platinum-resistant disease

Strategic objective	Action	CSG Lead	Date	Outcomes
6.3 Disease-specific research: Endometrial cancer 6.3a - Prevention	Significant strength in endometrial cancer prevention within CSG. National primary prevention study women at high risk of developing endometrial cancer required	EC	Jun 2020	National primary prevention study in high risk women to be funded/supported by industry
6.3b Survivorship	Outcome for women with endometrial cancer is good. Need to develop protocols to minimise hospital visits and maximise QoL for women treated for endometrial cancer	KB	Jun 2020	Multi-centre study investigating survivorship in early stage endometrial cancer
6.3c- Recurrent endometrial cancer	Although overall prognosis for endometrial cancer is good, prognosis for those with relapsed disease is very poor with no licensed new drugs. CSG needs to develop portfolio of trials in relapsed endometrial cancer	All	Jun 2019	At least one national trial open in relapsed endometrial cancer

Strategic objective	Action	CSG Lead	Date	Outcomes
6.3d Molecular stratification	Recent advances in the understanding of endometrial cancer biology means that stratification by molecular subtype should be incorporated into first line endometrial cancer trials	All	Jun 2020	Molecular stratification to be incorporated into next first line intervention trial in newly-diagnosed endometrial cancer
6.4 Disease-specific research: Cervical cancer 6.4a - Screening	Uptake of cervical cancer screening remains low. Studies required to assess methods to increase screening uptake in partnership with primary care CSG	All	Jun 2020	Study addressing interventions to increase cervical screening uptake funded
6.4b Recurrent disease	Prognosis for recurrent cervix cancer is very poor. CSG needs to ensure that there are studies open for women with recurrent disease	All	Jun 2019	At least one multi-centre study open in recurrent cervical cancer.

Appendix 3 – Portfolio maps



NCRI Portfolio Maps

Gynaecological Cancer

Map B – Ovary, fallopian tube

ê below to reset map

		a) Primary treatment	b) Recurrence	c) Prevention / diagnosis	d) Supportive care / late effects	e) Observational / translational
Ovary / fallopian tube	All	varian Tumour DNA Methyla ICON8 CEBOC UK P3BEP Trial RaNGO EORTC 1508 Patients with Platinum-Res TRUST Trial CANC 5651 B7661001- additional arm ARP inhibitor and anti PD-1 B9991030 FIRST 1347-201 - The FUZE Clinic	NiCCC Trial OCTAVE Masitinib + Gem Phase I of MOv18 IgE HIPROC OCTOPUS MOLTO OCTOVA OReO ICON9 b Maintenance Monotherap rs for ovarian cancer risk as PEACOCC PROMPT CINOVA ab+M6620+Carboplatin in P therapy in HRRm or HRD P	ROCkeTS e//control study of inherited elvic examination and patie ALDO PROTECTOR RRESDO Survey Study	for gynaecology cancer follo HORIZONS rspectives on Peritoneal Me Balance after chemotherapy EORTC-1514-QLG-GCG	varian Tumour DNA Methyla CR UK Stratifie Correlation of CTCR/OV04 ovarian tissue cult. Biomkrs ib Ovarian Path Metabonomics IROC: MR in Ovarian Cance surplus blood for ovarian ca Robotic QOL Study PGRx-Ovarian Cancer DICE version 1.0 HYSP53 pping new tests for ovarian and solid tumors-2252/0068 xamination in diagnosing gyn MK4621-002 MEDIOLA/D081KC00001 y of RO6870810 and Atezol ATHENA varian cancer stem cell nich MATINS TARGET FAL01 - V1 l study of GM102 in Gynael CA125 PET/MRI OLALA Trial alone and in combination i

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All, **LCRN**: None

In Setup / multi res.. Open / multi resea.. Suspended / singl..
In Setup / single re.. Open / single rese..

Appendix 4

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. New England Journal of Medicine. 2018; 379(26):2495-505.	SOLO1 will redefine first-line treatment of advanced ovarian cancer in women with germline and somatic *BRCA1/2* mutations – olaparib maintenance following platinum-based chemotherapy produced a dramatic and highly significant improvement in PFS (primary endpoint) and PFS2 (one of the secondary endpoints).	SOLO1 was an international, multi-centre, industry-funded, GCIG and ENGOT trial. NCRI was a key participating group and there were two UK authors - Dr Susie Banerjee, current CSG member, and Professor Charlie Gourley, former CSG member.
Macintyre G, Goranova TE, De Silva D, Ennis D, Piskorz AM, Eldridge M, et al. Copy number signatures and mutational processes in ovarian carcinoma. Nature Genetics. 2018; 50(9):1262-70.	BriTROC-1 was a translational study that aimed to identify critical genomic features of ovarian high grade serous carcinoma, in particular how the disease changed from diagnosis to relapsed and how the complec copy number features of HGSC could be classified. This paper identifies Copy Number signatures in HGSC genomes that will have utility both in patient straification and also, potentially, treatment allocation.	Developed by the CSG
Vergote I, Coens C, Nankivell M, Kristensen GB, Parmar MKB, Ehlen T, et al. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC	CHORUS and EORTC 55971 were separate phase III trials that compared primary surgery vs primary neoadjuvant chemotherapy in women with newly diagnosed advanced ovarian cancer. Both studies showed no differene in PFS and OS in primary analysis. This pooled individual patient data analysis allowed longer follow up and increased statistical power. The data confirm no difference in OS and	CHORUS was developed by the CSG. This pooled analysis with the parallel EORTC 55971 trial was pre-planned.

55971 and CHORUS trials. The Lancet Oncology. 2018; 19(12):1680-7.	PFS between the two arms. There is, however, improved PFS and OS in stage 4 disease treated with primary chemotherapy. This study will help guide initial management of women with advanced disease at presentation (c.70% all ovarian cancer patients)	
Kitson S, Maskell Z, Sivalingam VN, Allen JL, Ali S, Burns S, et al. PRE-surgical Metformin In Uterine Malignancy (PREMIUM): a multi-center, randomized double-blind, placebo-controlled phase 3 trial. Clinical Cancer Research. 2018. doi: 10.1158/1078-0432.CCR-18-3339 [published Online First: 20th Dec 2018]	Endometrioid endometrial cancer is strongly associated with obesity and insulin resistance. Observational data suggested that metformin may have anti-cancer activity by reversing insulin resistance. This double-blind, placebo-controlled trial randomised women with atypical hyperplasia or endometrioid endometrial cancer to receive metformin (850mg daily for three days, and twice daily thereafter) or placebo for 1-5 weeks until surgery. The primary outcome was post-treatment immunohistochemical expression of Ki-67. Results indicated no change in Ki67 and suggested that metformin does not have any biological activity in endometrial cancer.	Developed by the CSG
Lin KK, Harrell MI, Oza AM, Oaknin A, Ray-Coquard I, Tinker AV, et al. BRCA Reversion Mutations in Circulating Tumor DNA Predict Primary and Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. Cancer Discovery. 2019; 9(2):210-9.	PARP inhibitors are now widely used as maintenance treatment in platinum-sensitive recurrent ovarian cancer (and soon in first line treatment in *BRCA1/2* mutation carriers – see SOLO1 study above). The mechansisms by which tumours acquire resistance to PARP inhibitors are numerous and complex. This study quantifies the rates of secondary mutations in *BRCA1/2* identified in circulating cel-free DNA in women with germline mutations in *BRCA1/2* enrolled in the ARIEL2 study. It shows that secondary mutations can be identified in ctDNA, that their presence precludes benefit from PARP inhibitor treatment, and that the rate of secondary mutations doubled between initiation of treatment and progression, suggesting that acquired secondary mutations are likely to be a major driver of acquired PARP inhibitor resistance in these patients.	ARIEL2 was developed by the CSG in conjunction with Clovis Oncology.

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Gynaecological Group portfolio, 14 trials closed to recruitment and 33 opened.

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
2014/2015	899	891	705	869	4.0	5.0
2015/2016	930	1312	883	1058	5.04	6.04
2016/2017	1053	2297	953	1100	5.44	6.28
2017/2018	878	3192	773	1087	4.42	6.21
2018/2019	1206	2905	469	1410	2.68	8.05