CONFIDENTIAL

Experimental Cancer Medicine Centres

Annual Report

2012-13

The Experimental Cancer Medicine Centre Initiative is jointly funded by Cancer Research UK, the National Institute for Health Research in England and the Health Departments for Scotland, Wales and Northern Ireland.

Contents

Introduction

Launched in October 2006, the Experimental Cancer Medicine Centre (ECMC) Network is jointly supported by Cancer Research UK (CRUK) and the health departments for England, Scotland, Wales and Northern Ireland, providing a total of £35 million over five years across the UK. Through collaboration and teamwork within the community, the ECMC Network's vision is to bring together laboratory and patient-based clinical research to speed up the development of new therapies and individualise patient treatment.

Each ECMC is a partnership between an NHS Trust or Board and a university, which enables the best health researchers and clinicians to work together to generate novel approaches. Experimental cancer medicine encompasses those aspects of translational research that involve studies in patients or patient material in clinical trials. The flexibility of ECMC funding enables ECMCs to allocate their funding strategically across a number of research themes. While ECMC funding primarily supports the preclinical, quality assurance (QA) and pharmacodynamic analysis associated with early phase trials, funding is also applied in a range of ways depending on local needs and priorities. Across the UK, ECMCs have had considerable impact in developing and maintaining expertise in experimental medicine, including QA and Good Clinical Laboratory Practice (GCLP), nursing, sample collection and advanced laboratory techniques.

The use of ECMC infrastructure to support or pump-prime activity has leveraged significant additional funding from Trusts and universities, as well as other commercial and non-commercial funders. This has been invested back into the Centres to strengthen capacity and capability, and has allowed Centres to support additional activity not directly funded through CRUK and the four health departments. Locally, this has enabled ECMCs to expand the range of treatments offered to patients. Nationally, this has strengthened the translational research infrastructure of the UK, ensuring that it remains a competitive location for conducting clinical trials. The interaction with commercial partners remains a significant priority for the Network, with 60% of all ECMC supported studies involving a commercial partner as a sponsor and/or funder. Commercial partners are attracted by the ability of the Network to effectively deliver clinical trials and provide access to world-class translational infrastructure, even in a challenging financial and regulatory environment. This is demonstrated by many examples throughout this report.

The international review panel that undertook the quinquennial review of the ECMCs in 2011 highly commended the work delivered by the Centres, but highlighted that more could be done to foster a genuine network. This challenge is being met both by the Secretariat and the Centres themselves, with further initiatives planned for throughout the current quinquennium. In addition to successful pilot activities delivered by the Secretariat in partnership with Centres, the Centres themselves have already made huge strides in installing this ethos in experimental medicine and early phase trials for cancer. ECMCs as a network are at the forefront of exciting new developments in these fields.

This is the first annual report of the new quinquennium, which commenced in April 2012. It is not an exhaustive list of every activity at every Centre; the case studies presented here are representative highlights of the important scientific and clinical achievements delivered by the ECMC Network over the past year. This report is divided into the following sections:

- **Impact** highlighting the most significant scientific and clinical impacts of ECMC-supported preclinical, clinical and translational research
- **Facilities and technologies** demonstrating the role of ECMC funding in maintaining and developing world-class facilities and technologies
- **Progress through phases**, demonstrating the success of the Network in progressing early phase clinical trials to subsequent phases
- **Building on the Network**, demonstrating the success of the Network through external awards, industry collaborations and high-impact publications
- **ECMC Network Strategy**, showcasing the highlights and future projects of the Networking Strategy and Network Groups

- **Collaboration**, highlighting successful studies involving collaborations between ECMCs
- **Paediatric Network**, demonstrating the scientific and clinical impact, progression through the phases, networking, future perspectives and significant publications of the Paediatric Network
- **Initiatives**, demonstrating the success of the Network in the ECMC Combinations Alliance and CRUK's Stratified Medicine Programme
- **Future perspectives**, highlighting exciting new Network activities in 2013-14
- **The ECMC Portfolio**, showing the breakdown of the ECMC portfolio, including analysis of the portfolio size and diversity, performance, resources and collaborations
- Appendix 1: **Selected Publications**
- Appendix 2: **Network Groups**

Impact

The funding provided to the ECMCs is influential both strategically and operationally. The following case studies are examples of pioneering ECMC-supported research with significant scientific and clinical impacts. These include studies that have significantly changed cancer research or clinical practice, demonstrated early patient benefit, investigated new treatments, targeted rare cancers or cancers of unmet need, progressed to late phase trials or are examples of exceptional collaborative projects.

Clinical trials

Two significant first-in-class trials have opened at the Newcastle ECMC. The first is a Phase I trial of an ATR inhibitor in combination with gemcitabine. It requires intensive sampling and has multiple translational end points, including 18-fluorothymidine positron emission tomography imaging as a non-invasive pharmacodynamics biomarker. The second is a MCT1 inhibitor Phase I trial, for which intensive pharmacokinetic sampling and multiple pharmacodynamic end points have been validated and will be performed within the ECMC. An exploratory magnetic resonance spectroscopy imaging end point for this trial has been validated by the Newcastle and ICR ECMCs.

A novel Bayesian adaptive trial design was developed in Cambridge to guide dose escalation in a Phase I study. The trial is testing the γ-secretase inhibitor MK-0752 in combination with gemcitabine in stage IV pancreatic ductal adenocarcinoma patients and was based on preclinical studies in a relevant mouse model. ECMC funding, including nursing support and laboratory analysis, at Cambridge has supported the study.

The Birmingham ECMC is leading a collaborative Phase I trial requiring a tight network of Haematological Centres across the UK. PICLLe is a Phase I/II clinical trial to assess the efficacy and safety of olaparib, a PARP-inhibitor, in relapsed and refractory chronic lymphocytic leukaemia patients with an 11q deletion or ATM mutation, and relapsed/refractory patients with T-prolymphocytic leukaemia and mantle cell lymphoma. ECMC funding supports the organisation of this trial, including travel and meetings, ATM analysis and stratification of patients.

The Cardiff ECMC has completed the first Phase Ib trial in which conventional chemotherapy for older acute myeloid leukaemia patients is combined with the HSP90 inhibitor ganetespib and the tyrosine kinase inhibitor AC220 (quizartinib). This ECMC AML18 pilot trial involved eight other ECMCs, and is now part of the National Cancer Research Institute (NCRI) AML18 trial.

Leicester ECMC is running the CUFOX Phase I/II trial, which involves the addition of curcumin to FOLFOX in advanced colorectal cancer patients to reduce treatment side effects. The trial aims to decrease FOLFOX dosage and side effects by sensitising cancer cells to the treatment using curcumin, allowing patients to remain on the treatment for longer. ECMC funding provides for a nurse, a pharmacist, a QA manager and a laboratory scientist. This trial has led to significant media coverage.

The Oxford ECMC has introduced patient stratification into the PACMEL trial in time to inform treatment allocation. ECMC Network support has allowed the Oxford ECMC to introduce NRAS stratification in PACMEL, a multi-centre clinical trial in wild-type BRAF melanoma. Oxford and the ECMCs at Manchester, Birmingham and ICR perform the test in time to inform treatment allocation. The Oxford ECMC has also delivered a trial of the use of neo-adjuvant metformin in breast cancer, which included dynamic positron emission tomography analysis correlated with gene expression analysis to stratify patients.

The Sheffield ECMC has set up a trial for the rare cancer Kaposi's sarcoma in collaboration with AstraZeneca and the ECMC Network. The trial tests the addition of MEK inhibitor selumetinib in combination with highly active anti-retroviral treatment for HIV-associated Kaposi's sarcoma. This trial is now recruiting nationally. ECMC funding supports a range of activities in this trial, including recruiting patients and laboratory analysis.

The Southampton ECMC has completed a Phase I trial central to a successful application for European Union framework funding (€6 million) for follow-on studies with four European Centres. The trial evaluated the effect of anti-CD40 monoclonal antibody given intravenously weekly for 4 weeks in advanced malignancies refractory to conventional cancer treatment.

The Southampton ECMC has completed a Phase I/II study of combination immunotoxin antibody therapy for lymphoma that has led directly to a first-line National Institute of Health Research (NIHR) Cancer Research Network (NCRN) study. The study of inotuzumab ozogamicin in diffuse large B-cell lymphoma is funded by Pfizer and has been approved by CRUK's Clinical Trials Awards and Advisory Committee (CTAAC). It will open in the second quarter of 2013.

The Leeds ECMC has completed the GSK1070916A Phase I clinical trial as part of the CRUK Clinical Development Partnership with GlaxoSmithKline. The trial and pharmacokinetic analysis was carried out in collaboration with the Barts ECMC and CRUK's Drug Development Office (DDO).

The ICR ECMC is completing first-in-man evaluations of three new agents from AstraZeneca. The ICR ECMC remains a key location for the first-in-man evaluation of new drugs and their progression into later phase trials, as described in the 'Progress through phases' section of this report. In addition, the ICR ECMC is a key location for pharmacodynamic assessment of these agents.

The Leicester ECMC is clinically evaluating a BTK-specific inhibitor developed by ONO Pharmaceuticals in a first-in-man Phase I clinical trial for B-cell malignancies. In addition to this, the Leicester ECMC is performing detailed *in vitro* studies of the mechanisms of action of the agent.

Preclinical and translational research

The Cambridge ECMC has pioneered work on circulating tumour DNA as a 'liquid biopsy' and biomarker for molecular stratification, tumour monitoring and non-invasive analysis of acquired resistance to therapy, with concomitant high-impact publications. A collaboration with Manchester is planned on circulating tumour DNA and circulating tumour cells (CTCs) in colorectal cancer, and blood samples are already passing between laboratories for analysis. This work is supported by ECMC-funded nurses and data management staff.

The Leicester ECMC has supported the development of a novel *ex vivo* tumour explant system for the preclinical testing of chemopreventive agents and anticancer drugs, which is of considerable interest for in-house drug development and industry. This includes testing of drugs targeting the tumour microenvironment, and was enabled through collaboration of an ECMC-funded scientist and use of ECMC-funded technicians to obtain tissue.

Scientists at the Manchester ECMC published a seminal paper in the *Journal of Clinical Oncology* in 2012 on the prognostic significance of CTCs in small cell lung cancer (SCLC) and have set up CTC analysis in five SCLC trials. They have developed analysis of CD56 in SCLC CTCs, which will be applied in the NORTH trial in collaboration with Immunogen. CTC work at Manchester is supported through an ECMC-funded Senior Research Assistant.

The Imperial ECMC continues to support late phase translational research through a number of biomarker studies linked to Phase III trials (SCOTROC1 and SCOTROC4). These have led to a range of international collaborations with the Ovarian Cancer Association Consortium and high-impact publications. Imperial ECMC funding for molecular archiving and technical positions supports the Imperial College Biomarker Resource Centre, which in turn supports research in a range of areas.

The new Edinburgh/Dundee ECMC has identified a subgroup of ovarian cancer (based on expression microarray analysis and unsupervised hierarchical clustering) that has significantly improved outcome in multiple datasets. ECMC Network funding was used for consenting patients and funding laboratory staff in this study. The subgroup is characterised by a low level of angiogenic gene expression and the main clinical impact will depend upon whether it predicts efficacy of anti-angiogenic therapy. This hypothesis is currently being tested using the tissue set from the Medical Research Council (MRC)-led ICON7 study of bevacizumab in ovarian cancer.

Facilities and technologies

Support provided by ECMC funding for QA, GCLP and biobanking expertise enables Centres to deliver high-quality systems and technologies in support of translational research. The long term stability of ECMC funding enables Centres to maximise utilisation of local facilities.

Funding provided to the **Belfast ECMC** has supported the activities of the Northern Ireland Biobank. This biobank provides access to prospectively collected and 15 years of archived tumour tissue with linked clinical information for high-quality Clinical Pathology Accreditation (CPA)-standard biomarker assay validation and delivery. The biobank has provided over 10,000 samples for analysis in ECMC-supported studies.

The Good Manufacturing Process (GMP) production facility at **Kings,** with ECMC quality management support, has produced cell and gene therapy-based investigational medicinal products for clinical trials in all phases. A Phase I trial of CD80/IL-2 immune gene therapy of poor prognosis acute myeloid leukaemia has recently opened that draws on these facilities.

The ECMC-supported biobank in Manchester has been a key Centre in sample collection for CRUK's Stratified Medicine Programme (see 'Initiatives'). The **Manchester ECMC** has a specific interest in the integration of GCLP-compliant laboratory QA systems into early clinical trials. Manchester is a world leader in the early clinical evaluation of novel mechanism-based therapies and provides pharmacokinetic and innovative pharmacodynamic biomarker analyses to GCLP standards using state-of-the-art technologies.

In **Leeds,** ECMC funding continues to contribute to maintenance of the GCLP sample processing facility, which enables processing of clinical samples for translational aspects of clinical trials, local biomarker studies and Research Tissue Banks, which are accessed by groups for specific local, national or international biomarker studies. In Bradford, the Institute of Cancer Therapeutics conducts studies to GCLP, all governed by a well-established strict QA program and supported by a Quality Control Manager. ECMC support has been essential to creating a central hub in Bradford for trial sample receipt and despatch of specimens across the UK. For example, seAFOod is a large MRC/NIHR-sponsored trial investigating polyp prevention by aspirin and fish oil with 50 Centres, 900 patients and 17,000 samples. The Bradford hub has created laboratory manuals/standard operating procedures, and trial worksheets and laboratory packs for use across these Centres and will measure multiple eicosanoids in plasma, urine and rectal mucosa by liquid chromatography-tandem mass spectrometry for the trial. Currently, 1436 samples from 173 patients are stored awaiting analysis.

The **Edinburgh/Dundee ECMC** has developed software to allow a single point of access to search for specimens in either Centre's tumour banks. The Dundee process was audited by the Edinburgh QA manager.

The Sir Bobby Robson Cancer Trials Research Centre carries out all phases of cancer trials, coordinates North of England Cancer Network studies and is an integral part of the **Newcastle ECMC**. It is a designated unit for the administration of first-in-human experimental cancer drugs, and has many years expertise in the regulatory submission and running of clinical trials. Among the specialist services are GCLP-compliant pharmacology and pharmacodynamic assessment laboratories, which are underpinned by ECMC funding.

Gestational trophoblastic disease tumour cells secrete multiple forms/fragments of hCG that can be missed by commercial assays. The **Imperial ECMC** is developing a next-generation hCG cancer assay that detects all known forms of hCG with almost equal sensitivity so that one form is not over- or under-read compared to another. The prototype assay is now undergoing clinical testing against the existing gold standard assay. Preliminary data in over 100 patients suggests that the new assay is globally more sensitive than the existing assay and is performing well at detecting all forms of hCG.

Progress through phases

ECMCs provide the environment for clinical trials to progress through the drug development pathway, providing patients with access to new agents. Several exciting early phase studies which have progressed are highlighted below.

The **ICR and Manchester ECMCs** carried out a Phase I trial of the AKT inhibitor AZD5363, which is now moving into multi-centre Phase I and II trials, including a randomised Phase II trial in prostate cancer. This trial was sponsored and funded by AstraZeneca, and results were presented at the 2013 meeting of the American Association for Cancer Research. The two Centres also worked on a first-in-man Phase I study on AZD2014, again sponsored and funded by AstraZeneca, which was presented at the 2012 meeting of the American Society of Clinical Oncology (ASCO). This has progressed to Phase II evaluation within the ZEBRA trial, led by the Barts ECMC.

GlaxoSmithKline sponsored and funded a Phase I open-label dose-escalation study of the focal adhesion kinase inhibitor, GSK2256098, in subjects with solid tumors, which was carried out at four ECMCs (**Imperial, Glasgow, Manchester and Newcastle**). The results were presented at the 2012 ASCO meeting, and the trial has now progressed to a Phase Ib combination study with a MEK inhibitor.

ECMC funding previously played a key role in a significant Phase I study of the PARP inhibitor AG014699 (rucaparib). Led by the **Newcastle ECMC**, this trial was supported by ECMC funding at Newcastle, **Belfast, Oxford** and **Glasgow**, in collaboration with CRUK's DDO and Pfizer/Clovis. This study added to the growing evidence that PARP inhibitors have the potential to become new anti-cancer therapies - particularly for patients with BRCA mutations. This has since progressed to a Phase II trial in melanoma (which involves the **Manchester** and **Birmingham ECMCs**). This study, published in Cancer Chemotherapy and Pharmacology in 2013, showed that temozolomide can safely be given with a PARP inhibitory dose of rucaparib with increased progression-free survival over historical controls in metastatic melanoma patients. CRUK's DDO has also launched a Phase II trial of rucaparib as a single agent in breast and ovarian cancer, again led by Newcastle and involving the ECMCs at **Glasgow, UCL, Birmingham, Manchester** and **Leeds.**

RADVAN is a randomised double-blind Phase II trial of whole-brain radiotherapy with or without vandetanib in metastatic melanoma patients with brain metastases, sponsored by the University of Oxford and also involving the **Sheffield ECMC** as a recruiting Centre. Its progression to Phase II was made possible by identification of a safe combination dose of the agent with whole-brain radiotherapy.

A Phase I study of brentuximab vedotin administered sequentially and concurrently with multi-agent chemotherapy as front-line treatment in patients with CD30-positive mature T-cell and natural killer cell neoplasms, including systemic anaplastic large cell lymphoma, was carried out by the **Southampton and Manchester ECMCs**. Sponsored and funded by Seattle Genetics, results of this study were presented at the 2012 meeting of the American Society for Haematology. This has now progressed to a company-sponsored international Phase III trial.

The LUME-Lung3 study is a Phase I/II trial of continuous oral treatment with BIBF 1120 in combination with standard gemcitabine/cisplatin therapy in first-line non-small cell lung cancer (NSCLC) patients with squamous cell histology, sponsored and funded by Boehringer-Ingelheim. The study is supported by ECMC funding at **UCL and Manchester**. Phase I is now completed and the trial has progressed to Phase II.

Building on the Network

ECMCs continue to be recognised for their achievements through new collaborations with industrial partners, high-impact publications and presentations at major conferences, and leverage of additional funding. These are all crucial in maintaining the UK as a key location for translational research. Selected publications can be found in Appendix 1.

PANTHER is a Phase II study investigating pre-nephrectomy pazopanib in metastatic renal cancer completed by the **Barts/Brighton ECMC**, and was the only investigator-led study in renal cancer accepted for oral presentation at ASCO 2013.

The **Birmingham ECMC** has received a £1.7 million award for the ENDCaP-C trial from the Efficacy and Mechanism Evaluation programme of the NIHR, work that was pump-primed by ECMC funding. This project investigates enhanced neoplasia detection and cancer prevention in patients with chronic colitis.

Funding for the **ICR ECMC** has contributed to the impact made by the cancer therapeutics team at ICR, recognised by their award of the American Association of Cancer Research (AACR) Team Science Award 2012, the first time the Award has gone to a non-US site. Overall, the work carried out by this multidisciplinary team over the last 6 years provides an outstanding example of the non-profit cancer drug discovery and development model that they have pioneered, as well as exemplifying a meritorious ability to collaborate productively with industry to accelerate patient benefit. Work supported by funding provided to the ICR ECMC also resulted in the presentation of an ASCO 2012 Merit Award and the CRUK 2013 Translational Research Award.

The Analytical Services Unit is the centrepiece of the **Glasgow ECMC**. The Analytical Services Unit supports sample acquisition, handling, processing and reporting, and several industrial partners, including Roche, Wilex and Vertex, have utilised the unit in the last year.

The **Cambridge ECMC**'s world-renowned expertise in biomarkers for breast cancer has led to collaborations with Genentech, Pfizer and Novartis, who are using the METABRIC dataset to identify novel therapeutic targets and biomarkers. The Cambridge ECMC has also received funding from AstraZeneca for biomarker studies and early phase/translational trials.

Astex have provided drug and funding to the **ICR ECMC** for a Phase I/II clinical trial of AT13387, a resorcinol HSP90 inhibitor, in combination with abiraterone for prostate cancer patients.

The Phase I (Europe) unit of Quintiles is co-located with the **KCL ECMC** on the Guy's Hospital campus, leading to close collaboration, including a Phase I trial with Quintiles administrative and regulatory support. A joint Oncology Clinical Fellowship has also been established.

Establishment of the AmpliSeq Cancer Panel at the **Oxford ECMC,** and its use in routine practice, has attracted companies looking for specific sub-groups in which to evaluate treatment (e.g., Novartis, GlaxoSmithKline and Millenium).

Researchers at the **Sheffield ECMC** are co-investigators on a collaborative project funded by AstraZeneca and the MRC (£1 million) investigating the effects and mechanisms of action of the Src/Abl inhibitor saracatinib on cancer-induced bone pain.

Cellectis, a specialist genome engineering company, uses proprietary genome engineering technologies to manufacture T-cells that specifically target and destroy cancer cells. They have established a broad collaborative agreement with **UCL ECMC** investigators, who are global leaders in adoptive immunotherapy

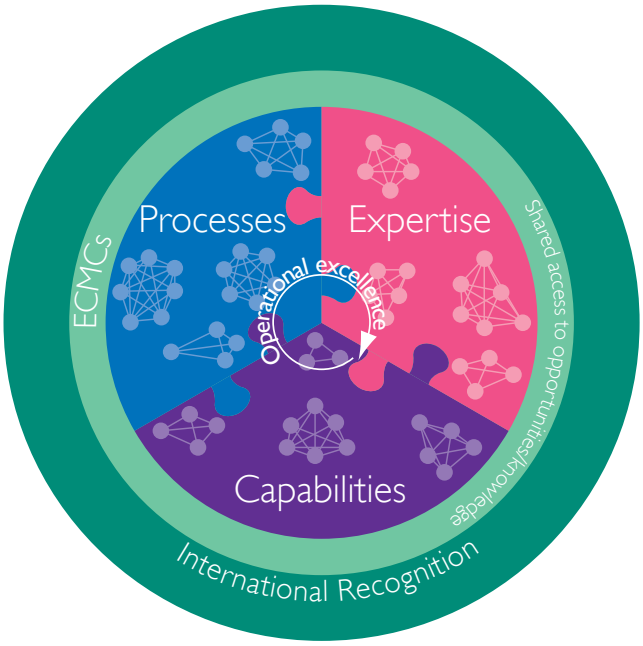
MErCuRiC is a second-line metastatic colorectal cancer trial led by the **Belfast ECMC** in collaboration with the **Oxford ECMC** and other European Centres that has received €6 million from the European Union Framework 7 funding programme. It uses biomarker stratification of aberrant c-MET signalling with subsequent randomization between the novel agent combination of a c-MET inhibitor and a MEK inhibitor, and standard chemotherapy. This trial builds on preclinical scientific observations characterizing novel-novel combinations in RAS wild-type colorectal cancer with overexpressed c-MET, and RAS-mutant colorectal cancer. Belfast is also leading on the molecular pathology aspect of the associated translational research and biomarker studies.

ECMC Network Strategy

Background

The strategic aims for building the Network over the current quinquennium were agreed by the ECMC Steering Committee in January 2012:

- **Faster set up and delivery times** for multi-centre studies through harmonised trial management processes.
- More Centres will conduct studies of the **highest quality** due to improved staff training.
- **Efficient delivery** of high impact research, through the sharing of resources and personnel.
- **New partnerships** will be established with industry and other research organisations from greater promotion of the Network at both a national and international level.



Highlights

Radiopharmacy task force
A radiopharmacy task force has been established to address issues in this area following a successful workshop in October 2012.

NCRI Confederation of Cancer Biobanks
A total of 17 out of the 18 ECMCs are now linked up with the NCRI Confederation of Cancer Biobanks, which is driving improvements in biosample collection and access.

Capability map
A successful pilot to develop an ECMC capability map was completed. This will be used to profile the Centres' unique selling points on the ECMC website and help establish new collaborations. This will be extended to provide a searchable online capability tool for internal and external stakeholders.

Pilot training day
A highly successful pilot training day for ECMC junior investigators was run in January 2013, paving the way for future training events and peer networking. A Junior Investigator Network is now being established to enable more peer-to-peer contact and exposure to senior investigators across the Network.

Cross-centre training scheme
A new cross-centre training scheme was launched, which provides funding to support ECMC operational staff undertaking training at other Centres.

Communications materials
New ECMC communications materials have been produced, including an industry-focused slide deck, a new brochure and an induction pack for ECMC staff.

Clinical Portfolio Management System
Initial agreement has been made with the NIHR that ECMC-supported trials will be visible on the Clinical Portfolio Management System as the new system rolls out. This will improve the visibility of ECMC supported studies, and help to integrate early and late phase portfolios.

Cultural shift
There are promising early signs of a cultural shift, moving from competition to collaboration, led by the ECMC Leads. Leads from 15 out of the 18 Centres have volunteered their time and input during Year 1 of the Networking Strategy (2012-13).

Moving forward

Changes to the NIHR Clinical Research Networks (CRNs) have meant that some plans (e.g., the recruitment of an ECMC Clinical Lead) have been moved to Years 2-5 of the Networking Strategy. These changes are also expected to create new opportunities for greater integration with the late phase trial community via the NCRI Clinical Study Groups.

Further engagement work will be carried out with the ECMCs to ensure that they are all actively involved in projects and initiatives.

As Trusts, Universities and Health Boards are separate legal entities with their own processes and governance structures, adopting a 'one size fits all' approach to trial management harmonisation in a single step is considered unfeasible. Therefore, a series of process improvement initiatives between subgroups of ECMCs will be piloted before changes are rolled out across the Network.

Network Groups

In support of the increasing need for collaborative and cross-centre working, a number of Network groups were established by the ECMC Network in order to enable a unified approach, and to ensure that the highest possible scientific and operational standards are delivered. The groups provide access to support and training by leading experts in many areas of clinical cancer research to improve outcome and survival rates for cancer patients. Details of the groups and examples of their recent activities are in Appendix 2.

Collaboration

In addition to the formal networking activities, collaboration between ECMCs is key in the delivery of a wide range of studies. Below are examples of where ECMC funding has enabled network collaboration for patient benefit.

OPPORTUNE is a biomarker-driven pre-operative window study involving the ECMCs at **Barts/Brighton, KCL, Edinburgh/Dundee** and **Sheffield,** and is the first investigator-sponsored study supported by Genentech.

The Trials Acceleration Programme funded by Leukaemia & Lymphoma Research (LLR; with **Birmingham ECMC** support) aims to accelerate early phase trials in haemato-oncology. With the Birmingham ECMC as a central coordinating hub, the Trials Acceleration Programme works at 13 leukaemia Centres, including the **Oxford, Southampton, Glasgow, Cardiff, Belfast, KCL, Barts, Imperial** and **Leeds ECMCs**.

BRITROC-1 is a multi-centre, non-randomised sample collection study in patients with recurrent high-grade serous ovarian, primary peritoneal or fallopian tube cancer who have received prior platinum-containing chemotherapy. The study is primarily funded by Ovarian Cancer Action. The primary objective is to demonstrate the safety and feasibility of acquiring tumour biopsies from women with relapsed ovarian cancer in multiple Centres. It is co-led by Principal Investigators at the **Cambridge and Glasgow ECMCs**, and also involves the ECMCs at **Edinburgh, Imperial, Manchester** and **Leeds.**

The **ICR ECMC** is leading a study of abiraterone in breast cancer patients with either oestrogen receptor-positive disease or oestrogen receptor-negative androgen receptor-positive disease, in collaboration with the **KCL, Glasgow, UCL and Birmingham ECMCs**. This investigator-initiated trial is being run across the UK and is the first to show a hormonal treatment that works in patients with oestrogen receptor-negative androgen receptor-positive advanced breast cancer.

The **Leicester, Oxford and Belfast ECMCs** are collaborating on the DEBIOC trial, which investigates AZD8931 (a pan-ERB inhibitor) in combination with chemotherapy in oesophagogastric adenocarcinoma. The Clinical Investigator is at the **Leicester ECMC, Oxford**

OPPORTUNE Trials Acceleration Programme **BRITROC-1** Abiraterone in breast cancer patients DEBIOC QUICKSTEP **DREAM** AB03 Cross-centre training **Expanded haematology portfolio** International collaborative effort Network of complex molecular diagnostics in lymphoma Consortium for predictive biomarkers evaluation **OPPORTUNE** Trials Acceleration Programme BRITROC-1 **Abiraterone in breast cancer patients** DEBIOC QUICKSTEP DREAM **AB03** Cross-centre training Expanded haematology portfolio **International collaborative effort** Network of complex molecular diagnostics in lymphoma Consortium for predictive biomarkers evaluation OPPORTUNE **Trials Acceleration Programme** BRITROC-1 Abiraterone in breast cancer patients **DEBIOC** QUICKSTEP DREAM AB03 **Cross-centre training** Expanded haematology portfolio International collaborative effort Network of complex molecular diagnostics in lymphoma **Consortium for predictive biomarkers evaluation** OPPORTUNE Trials Acceleration Programme BRITROC-1 Abiraterone in breast cancer patients DEBIOC **QUICKSTEP** DREAM AB03 Cross-centre training Expanded haematology portfolio International collaborative effort **Network of complex molecular diagnostics in lymphoma** Consortium for predictive biomarkers evaluation

ECMC provides sponsorship and the Clinical Trials Unit, and **Belfast ECMC** leads on translational work.

QUICKSTEP is a trial investigating the use of novel agents as monotherapy for a short duration prior to resection of colorectal cancer to prove mechanism of action (e.g., inhibition of target or surrogate molecular marker). QUICKSTEP is a collaboration between the ECMCs at **Leicester, Birmingham, Leeds, Belfast and Cardiff.**

The **Manchester ECMC** has particular expertise in ISET analysis, a technique which involves isolation by size of epithelial/trophoblastic tumor cells analysis. The Centre has incorporated the analysis into a number of feasibility studies and into clinical trials with Chugai, AstraZeneca and several CRUK DDO trials (e.g., the DREAM trial) and into ECMC trials of chemotherapy in colorectal cancer (**Leicester, Cardiff and Manchester**) and the AB03 trial in hepatobiliary cancer (**Manchester** and **UCL**).

The **Belfast** and **Newcastle ECMCs** have collaborated to establish cross-centre training and to share expertise and transferable skills.

The **Oxford ECMC** has significantly expanded its haematology portfolio, including investigator-initiated trials, building links with new partners (**Liverpool**) and new groups within existing relationships (e.g., **Southampton, Birmingham and Manchester**).

The **Southampton ECMC** is developing network immunoassays, in particular T-cell and more recently natural killer cell readouts for immunotherapy protocols. This is part of an international collaborative effort spanning over 200 laboratories from academia and industry to harmonise immunotherapy read-outs.

The **Southampton, Leeds, Cambridge** and **Barts/Brighton ECMC**s are developing a network of complex molecular diagnostics in lymphoma, which is proving highly attractive to pharmaceutical companies wishing to test novel targeted therapies. This is built upon a national Phase II/III study and will bring new Phase I/II work to the UK.

The **Southampton, Birmingham, Liverpool, Leeds, Cardiff, ICR** and **UCL ECMCs** are developing a consortium for the evaluation of predictive biomarkers in head and neck squamous cell carcinoma. This consortium will also develop a portfolio of early phase translational immunotherapeutic studies. This will be facilitated by European Union Framework 7 funding and by a collaboration between the **Barts** and **Southampton ECMC**s. The consortium is currently investigating use of a small molecule inhibitor for ablating immunosuppressive regulatory T cells in head and neck squamous cell carcinoma and pancreatic cancer.

Paediatric Network

Introduction

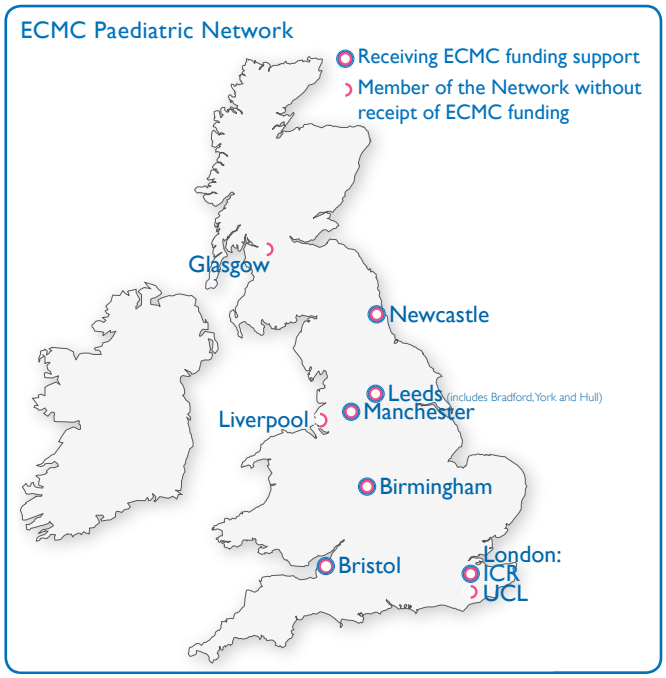
The NIHR provides funding to support infrastructure for early phase trials for children with cancer. This funding is provided to six paediatric ECMCs, which form a subset of the paediatric Phase I/II Centres in the UK. ECMC support for clinical trials infrastructure has helped to increase the capacity of the paediatric ECMCs to conduct early phase trials. The ECMC Paediatric Network has reported a number of achievements over the last 12 months; a reflection of the six ECMCs working together as a Network and in conjunction with the three other paediatric Phase I/II Centres.

Impact

Creation of the Paediatric ECMC Network has formalised relationships between UK early phase Centres, and led to a clear and transparent system of study allocation to ensure equity of access across the UK. This has increased the international profile of the Centres for early phase trials in children, and increased the number of early phase studies opening and being developed across the Paediatric Network: in January 2013, 28 early phase trials were open or in set up, in comparison with 17 in 2012. Nationally, there is now a single point of access for academia, industry and Innovative Therapies for Children with Cancer (ITCC) studies, ensuring that there is a cross-network strategy for early phase activity. This has improved referral of patients between ECMCs, and from non-ECMC principal treatment Centres.

Selected highlights have been:

- Improved referral and recruitment of patients across the Network for three first-in-child studies, with embedded biomarker analysis, open in limited numbers of Centres globally[1].
- The work of the pharmacology group in the Newcastle Paediatric ECMC on patient samples from across the Network has demonstrated sub-optimal dosing of significant numbers of patients with 13-*cis* retinoic acid in the current European high-risk neuroblastoma study, and identified dose changes to maximise patient exposure to this agent. These findings have resulted in changes to 13-*cis* retinoic acid dose regimens across Europe and have been reported in the *European Journal of Cancer*.



Progress through phases

The following paediatric studies have progressed to the next phase:

- The Phase III study of LDE225 is about to open. This builds on the very successful Phase I study of LDE225, which demonstrated that tumours with an mRNA signature indicating activation of the sonic hedgehog pathway had a higher response rate to LDE225. In this Phase III study, patients with tumours with an mRNA signature of sonic hedgehog pathway activation will be randomised to receive either an accepted standard therapy (temozolomide) or LDE225.
- The multi-centre, open-label, non-controlled Phase II study of oral nilotinib in paediatric patients with newly diagnosed Philadelphia chromosome-positive

[1] The three first-in-man studies are the Merck Phase I study of ridaforalimus (Royal Marsden Hospital and Great Ormond Street Hospital), the CRUK Phase I study of AT9283 in solid tumours (Royal Marsden Hospital, and the Birmingham, Leeds and Manchester ECMCs) and the Novartis Phase I study of LDE225 in medulloblastoma (Royal Marsden Hospital and the Newcastle ECMC).

(Ph+) chronic myelogenous leukaemia (CML) in chronic phase, with Ph+ CML in chronic phase or advanced phase (accelerated phase or blast crisis) resistant/intolerant to either imatinib or dasatinib or with refractory/relapsed Ph+ acute lymphocytic leukaemia is about to open. This follows a multi-centre, open-label, pharmacokinetic study of oral nilotinib in pediatric patients with Gleevec® (imatinib)-resistant/intolerant Ph+ CML chronic or accelerated phase or with refractory/relapsed Ph+ acute lymphocytic leukaemia.

- The Phase I/II study of Src/Abl tyrosine kinase inhibitor dasatinib in children and adolescents with relapsed or refractory leukaemia progressed to a Phase II study of dasatanib in children and adolescents with Ph+ leukaemia with resistance or intolerance to imatinib (see 'Significant publications' list below).
- The Plexirafor Phase II trial is due to open later this year following successful completion of Phase I.

Networking

An important example of how the Paediatric Network is benefiting patients can be seen through the linking of the **Newcastle** and **Glasgow Paediatric ECMCs**, which has led to Newcastle becoming part of the Scottish leukaemia multidisciplinary team. This has improved the discussion of options for relapsed patients in Scotland, and allowed them to access novel therapeutic approaches in Newcastle.

Future perspectives

- The MAGIC initiative, led by **Liverpool**, is linking several parts of the ECMC Paediatric Network (the **Leeds, Manchester** and **Newcastle ECMCs,** and **Great Ormond Street Hospital**), to answer novel questions about genetic predisposition to cytotoxic drug toxicity.
- The Phase I/IIa study of oral Dabrafenib in BRAF V600 mutation-positive solid tumours and the Phase I study of LDK378 in paediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK) will require molecular profiling for selection of patients and then referral for early clinical studies.
- Through the NCRN there will be a national audit of the discussion around therapeutic options for patients at relapse, including the process whereby these patients are offered access to early phase clinical trials. Strengthened links between paediatric trial centres and ECMCs, and increased accessibility of information about early phase clinical trials for clinicians and families, should lead to clearly defined pathways for all patients to access experimental options at relapse.

Significant publications

Turnbull C *et al.* A genome-wide association study identifies susceptibility loci for Wilms tumor. *Nat. Genet.* 44, 681-684 (2012).

Zwaan CM *et al.* Dasatinib in children and adolescents with relapsed or refractory leukaemia: results of the CA180018 Phase I dose escalation study of the Innovative Therapies for Children with Cancer consortium. *J. Clin. Oncol.* (2013) (In Press).

Missiaglia E *et al.* PAX3/FOXO1 fusion gene status is the key prognostic molecular marker in rhabdomyosarcoma and significantly improves current risk stratification. *J. Clin. Oncol.* 30, 1670-1677 (2012).

Initiatives

The ECMC Network continues to be an important conduit for delivering new initiatives that have a strong emphasis on collaboration. A number of initiatives, including the ECMC Combinations Alliance and CRUK's Stratified Medicine Programme, have been implemented through the ECMC Network. The contacts and relationships established between ECMCs have proved essential to delivering these initiatives effectively and efficiently. ECMC Principal Investigators have also played an active role by contributing ideas and strategic direction to these initiatives.

ECMC Combinations Alliance

The ECMC Combinations Alliance is now in its third year. The key objectives are to provide an opportunity and consistent framework for academia and industry to work together in the UK, providing UK patients with more combination therapy options for treating their cancer.

In total, 33 patients have been recruited across the portfolio of nine studies, including early and late phase development compounds across eight indications and involving six different anti-cancer agents. Eight of the nine studies have academic sponsors with seven further trials in recruitment plus two in set up. Details of the studies are provided in the table below. All studies are a collaborative effort across several ECMCs and demonstrate that UK academic Centres can work together to deliver key clinical and scientific data to time and quality. Centres also collaborate at an operational level to ensure sharing of best practice in the management of early phase trials.

The Joint Steering Committee, which governs the Alliance, saw several membership changes. Professor Chris Twelves and Professor Mark Middleton stepped down, and Professor Duncan Jodrell and Professor Jeff Evans joined. The Combinations Alliance is currently looking for additional members to support its broadening strategic focus.

The key focus areas of the Combinations Alliance were, and will continue for the coming year, to include the following:

- Ensure timely delivery of the studies in the portfolio
- Attract additional commercial partners
- Collaborate with the NCRI's Clinical and Translational Radiotherapy Research Working Group (CTRad), to increase the number of radiotherapy studies in the portfolio
- Utilise the preclinical capabilities of the ECMC Network to support combination studies

Sponsor/Clinical Investigator	Agent	Study name	Indication	Status
Glasgow/Evans	AZD4547+cisplatin/ capecitabine	FACING	Oesophagastric	Recruiting
Imperial/Seckl	AZD4547 + anastrozole/letrozole	RADICAL	Breast	Recruiting
Leeds/Chester	AZD4547 + gemcitabine/cisplatin	FIESTA	Bladder	Recruiting
Oxford/Thomas	AZD8931 + chemo	DEBIOC	Oesophagastric	Recruiting
Oxford/Talbot	AZD6244 + vandetanib	VANSEL	NSCLC	Recruiting
Christie/Saunders	AZD6244 + AZD2171	DREAM	Rectal	Recruiting
ICR/Banerji	AZD2014 + taxane	TAX-TORC	Ovarian, fallopian, peritoneal	Recruiting
UCL/Hochhauser	AZD8931 + FOLFIRI	PANtHER	Colorectal	Set up
UCL/Sarker/ Thirlwell	Vandetanib + iodine-131 mIBG	VIBRANT	Phaeochromocytoma, paraganglioma	Set up

Stratified Medicine Programme

The CRUK Stratified Medicine Programme - Phase I (July 2011 - June 2013) was a £6 million initiative led by CRUK, in partnership with pharmaceutical companies and the government, that aimed to test the feasibility of a high quality, cost effective and standardised national cancer diagnostic service with routine consent for the collection, storage and research use of genetic and outcomes data.

Delivery of Phase One has involved a network of 26 hospitals coordinated through the ECMCs that collected samples and routine data, three nationally distributed genetic testing laboratories and a central data repository provided by a Cancer Registry.

Phase One met its targets, achieving 100% of the Programme target of 9000 samples with 10,500 patients consented, 8963 samples sent for testing and over 37,000 genetic tests carried out. The Programme has worked with the ECMCs and laboratories to identify a number of key implications for future wider adoption, and the programme is engaging with relevant organisations and authorities to disseminate and develop these findings. These are focused mainly around challenges in collecting clinical data from hospital electronic systems, and standardising sample preparation and analysis processes to enable the best chance of success in obtaining informative results within clinically relevant timescales.

Phase Two of the programme will start in July 2013 and will aim to support a vision of national screening for national trials. The programme will build on the existing model, but extend nationally and focus on screening advanced lung cancer patients for clinical trials, with a minimum target of 2000 patients screened a year. In parallel, the programme will also work with the ECMC Network to develop a 'National Matrix Study' to deliver multiple novel agents through a Phase Ib/IIa exploratory study. Through Phase Two, CRUK aims to address some of the significant challenges in delivering a stratified medicine approach, enabling the UK to remain an attractive place for pharmaceutical companies and academia to deliver research on novel targeted agents, and maximising opportunities for patients to receive new drugs.

Future perspectives

This section provides a look forward to significant Network activities in 2013-14.

TRACERx

TRACERx is a £14-million CRUK-funded study that will study the evolutionary genomic landscape of NSCLCs between primary and metastatic sites, and the dynamics of intratumour heterogeneity over time, combined with detailed clinical, histopathological and cancer phenotypic annotation for each patient. The aim of the study is to significantly improve the outcomes of NSCLC patients (e.g., to reduce their chance of recurrence and improve survival). Led by Professor Charles Swanton (CRUK London Research Institute and University College London), TRACERx will draw on the expertise of the ECMC Network, and specifically the Centres at UCL, Leicester, Manchester, Birmingham and Cardiff. Researchers will recruit 850 NSCLC patients from across the UK and take samples of their tumour before and following surgery, and subsequently if the disease recurs. Biopsies will be taken from different parts of each patient's tumour and analysed with the latest technology to give a more comprehensive genetic profile, which will indicate levels of tumour heterogeneity, and help to develop new approaches to tackle this disease.

FOCUS4

The FOCUS4 trial is testing new agents in metastatic bowel cancer patients through the innovative design of an adaptive clinical trial, where treatments are personalised to the molecular subtype of an individual's tumour. The trial aims to improve outcomes of metastatic colorectal patients by providing a greater understanding of the molecular diversity of the cancer and their response to novel therapeutic approaches, as well as providing insight into the benefits of biomarker enrichment in the use of novel therapeutic agents. FOCUS4 aims to register 2400 patients, with 1536 patients randomised over the subsequent 4 years. Patients will receive chemotherapy for up to 16 weeks and during this time their tumour/s will be analysed for mutations (KRAS, NRAS, BRAF and PIK3CA) alongside a comprehensive panel of protein and mRNA biomarkers. The statistical design of FOCUS4 allows non-beneficial agents to be identified and halted as soon as possible, with minimal risk of prematurely stopping beneficial therapies by chance. The novel design of FOCUS4 has a number of strengths, including its employment in a relatively early disease setting, randomisation of each agent against controls and the multistage design. Led by Tim Maughan (Oxford) and Richard Wilson (Belfast), FOCUS4 is a truly collaborative endeavour, involving the ECMCs at Oxford, Belfast, Cardiff, Leeds, Birmingham, Imperial and Leicester for different elements of the trial, and collaboration with the NCRN Network across the UK.

Peer network for junior investigators

During the development of the ECMC Network Strategy, a training need for ECMC staff was identified. Part of this training need focuses on junior investigators; a pilot training day for whom was held in January 2013 for clinical and translational researchers. Following the training event and the workshop held at the ECMC Annual Network Meeting it was agreed that a peer network for junior investigators would be set up to help improve the pathway from junior to senior investigator and better prepare the next generation of ECMC Leads.

The pilot training event was hugely successful and the ECMC Secretariat has agreed to expand this to a two-day session incorporating a number of topics identified as knowledge or experience gaps from the one-day event. There were a number of topics the Junior Investigator Steering Committee wanted to address in the two-day event, such as ethics, imaging, how ECMCs fit into the UK trial infrastructure, completing studies with novel combinations, careers advice and assay development. However the Junior Investigator Steering Committee were also keen that much of the content from the pilot day remain, including: sessions on the life/process of a trial, future horizons for biomarkers, an example of an adaptive trial design and the interactive break-out sessions used for both groups. These included worked examples of incorporating biomarkers for the translational trainees, and feedback and advice on study ideas for the clinical trainees.

The two-day event will include trainees interested in early phase cancer research from clinical and non-clinical

specialties, and also additional sub-specialties such as haematology, paediatric oncology, imaging and surgery. The two days will be a mix of lectures, interactive sessions, parallel sessions and one-to-one meetings at stands during the lunch break to ensure that attendees are able to access all the information and advice on offer during the two days. Attendees will also include senior investigators from the ECMCs who will be sharing their experience in a number of ways throughout the event. Each session will encourage networking and collaboration with other trainees and the senior investigators in attendance.

The ECMC Portfolio

An ECMC study is defined as a study that uses ECMC resources to support its delivery. Individual ECMCs will report a study if it uses ECMC resource(s) at their Centre. The same study may be reported through different Centres, and the resources used to support the study in different locations may differ.

A particular study can be run at multiple sites and, therefore, a number of Centres can report the same study. In order to distinguish between study-specific information and site-specific information, the analysis that is conducted on a study level is referred to as 'studies hosted by the Network' and the analysis conducted on a site specific level is referred to as 'total study activity'. These terms are referenced throughout the report.

The data presented here differ slightly from those presented in previous years, and are divided into specific thematic areas:

- **Portfolio size and diversity**, which provides an indication of the number and range of studies supported by ECMC funding. ECMCs play a key role in delivering scientifically important early phase clinical trials in a range of disease types.
- **Performance**, which summarises the Network's record in delivery of translational research, in terms of completion, speed and patient recruitment.
- **Resources**, which summarises the impact of ECMC funding on the ability of the Centres to provide the necessary resources for delivery of experimental medicine.
- **Collaborations**, which shows how the Centres lead on delivery of experimental medicine, working with each other, industry and other partners.

The metrics presented here represent the first year of a new quinquennium and will provide the basis for monitoring the ECMC portfolio through the next 4 years. Expectations for progress against these metrics are noted in the text.

No metrics for biomarker studies are presented in this year's report. In previous years, only data on the volume of biomarker studies supported by ECMC funding were presented, with little interpretation of their impact. Following consultation with ECMC leads and working with colleagues at CRUK, the ECMC Secretariat plans to include a new set of reporting metrics for biomarkers from the second year of the new quinquennium. Important biomarker studies are highlighted within the narrative section of this report.

Portfolio size and diversity

ECMC funding continues to support a wide range of trial types. Diversity of the portfolio is important; it demonstrates that ECMC funding supports a suitable variety of treatment types across the range of cancer disease sites. A challenge for the Network in the coming years is to ensure that patient access to these trials continues to improve.

Figure 2.1 summarises the number of new studies hosted by the Network and total study activity in the first year of the new quinquennium, divided into early phase trials, randomised Phase II trials, and other studies reported. The number of new studies hosted by the Network in the first year of this quinquennium compares favourably with the same number from the last year of the previous quinquennium, which may indicate that the number of studies hosted by the Network is beginning to stabilise. This will become more apparent as the quinquennium progresses. ECMC funding supports the delivery of trials but the majority of costs in most cases will be provided by the funder of the study. This means that the prevailing financial climate is likely to be an influential factor in the size of the ECMC portfolio. Of the 806 studies hosted by the Network, 741 (92%) were led by an ECMC.

Figure 2.1. Number of new studies hosted by the Network and total study activity in the first year of the new quinquennium, by study type.

Type	Studies hosted by the Network	New studies hosted by the Network	Total study activity
Early phase[†]	516	93	946
Randomised phase II	184	36	394
Other[‡]	106	31	115
Total	806	160	1455

[†] Includes phase I, Phase I/II and non-randomised Phase II studies.

[‡] Includes studies with an experimental medicine component and where sample collection for biobanking is the primary purpose.

Figure 2.2 summarises the purpose of all early phase and randomised Phase II trials hosted by the Network. Not surprisingly, the vast majority of studies are focused on drug or biological therapy. There is considerable diversity within this category. It is hoped that the portfolio will begin to include more combination studies in future years, and potentially more studies involving other treatment modalities such as radiotherapy and surgery.

Centres have provided information on the importance of each study. For early phase trials, the top five reasons for importance of the study listed by Centres were:

- First in man for new agent or novel combination
- First trial in this group of patients
- May lead to a change in clinical practice
- Proof of biological concept
- Will contribute significantly to the international knowledge base

The high quality of cancer biology research and the translational capabilities associated with clinical trials in the UK make it a key location for commercial funders. In future years, the Secretariat will take more of an active role in monitoring the number of trials focused on first-in-man, first-in-class and first-in-indication treatments/agents.

For randomised Phase II trials, the top three reasons for importance of the study listed by Centres were:

- Investigating Phase II efficacy
- May lead to a change in clinical practice
- Will contribute significantly to the international knowledge base

Again, it is reassuring that scientifically important work is being supported by ECMC funding. It is also heartening that efficacy of agents in Phase II trials is a part of the portfolio, supporting the narrative information provided elsewhere in this document on the influence of ECMC funding on the progress of new agents through phases.

Figure 2.2. **Purpose of all early phase and randomised Phase II trials hosted by the Network.**

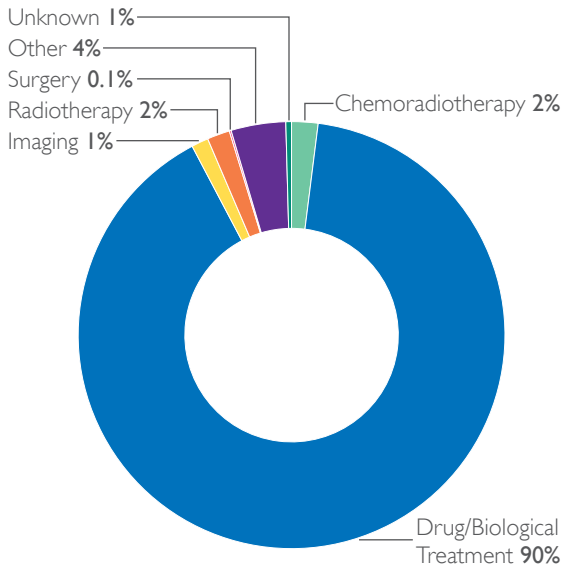
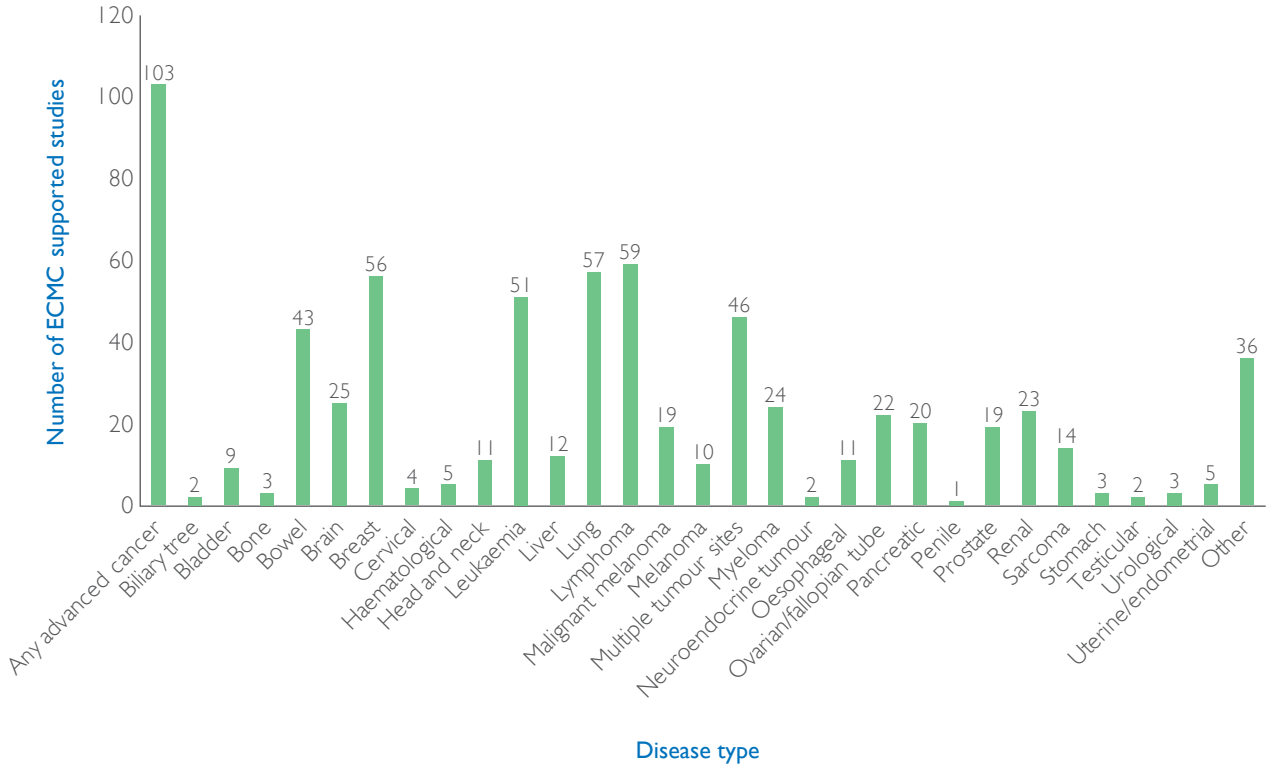


Figure 2.3 summarises the disease sites targeted by ECMC-supported studies, demonstrating that a wide spectrum of disease sites are covered. The analysis is similar to that obtained from the same data collected in the first quinquennium. One area of interest in future years will be the change in the number of studies of rare cancers and cancers of unmet need. Despite the overall reduction in studies hosted by the Network and total study activity, there are now more trials in bone, liver, and stomach cancers than reported in 2011-12.

Figure 2.3. Studies hosted by the network, by disease type.



Performance

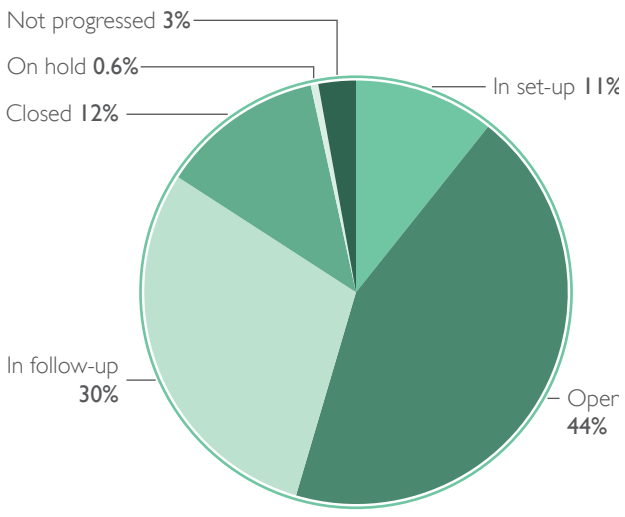
ECMCs must strike a delicate balance between supporting challenging, scientifically driven clinical trials and their responsibility to complete trials to target and to time. Continued delivery in these areas is crucial for maintaining the reputation of the Network.

Figure 2.4 summarises the status of all ECMC-supported studies in the portfolio. Over 50% are either in set-up or open. These studies will be monitored through the next 4 years of the Initiative to show the efficiency of the Network in study delivery.

Around 40% of open supported studies have defined recruitment targets. Of these, 40% recruited at 100% of target, 10% at over 80% and 33% at over 60%.

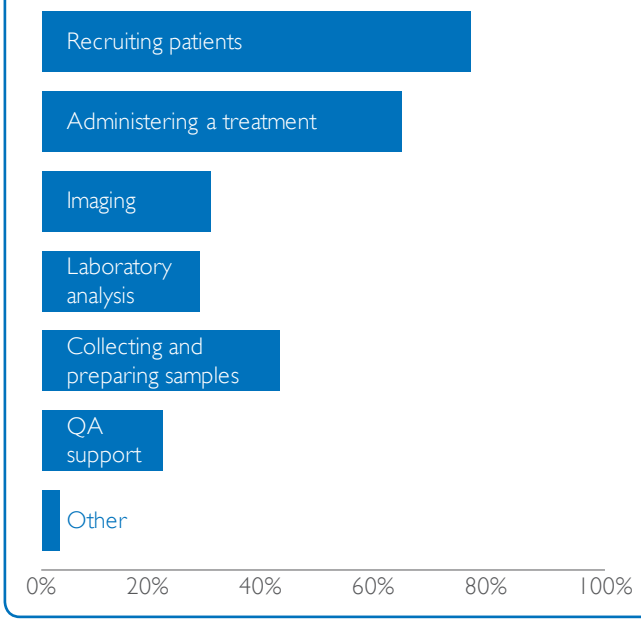
From 2013, the NIHR will publish outcomes for clinical trials, against set benchmarks, including the benchmark of 70 days or less from the time a provider of NHS services

Figure 2.4. Status of studies hosted by the Network.



receives a valid research application to the time when that provider recruits the first patient for the study. In the future, NIHR funding to providers of NHS services will become conditional on meeting this 70-day benchmark. The NIHR has made this a condition of new contracts from autumn 2011 and performance will affect funding from 2013. The same information has been collected by the ECMC Secretariat for the first time this year. A total of 41% of entries were valid (i.e., included both the National Research Ethics Committee (NREC) submission date and the date the first patient was recruited). Of those studies for which valid data were provided, the time taken was under 70 days for 20% of studies, and under 140 days for a further 35%. Several Centres have reported difficulty in collecting this data retrospectively. The Secretariat will continue to collect this data for new studies only to monitor the Network's performance against the NIHR benchmark.

Figure 2.5. Resources used to support studies at ECMCs.



Resources

ECMC funding supports a range of specific activities, which may differ from Centre to Centre. Many of these activities are crucial in the delivery of experimental medicine studies, strengthening the Network's reputation and promoting the UK as a competitive location for translational research.

ECMCs are asked to report how ECMC funding has supported each study. **Figure 2.5** summarises the responses on a total study activity basis. These data show the importance of ECMC funding in providing support for crucial activities across the experimental medicine pathway. Over 20% of studies draw on the QA support that is a particularly positive feature of ECMC funding provision.

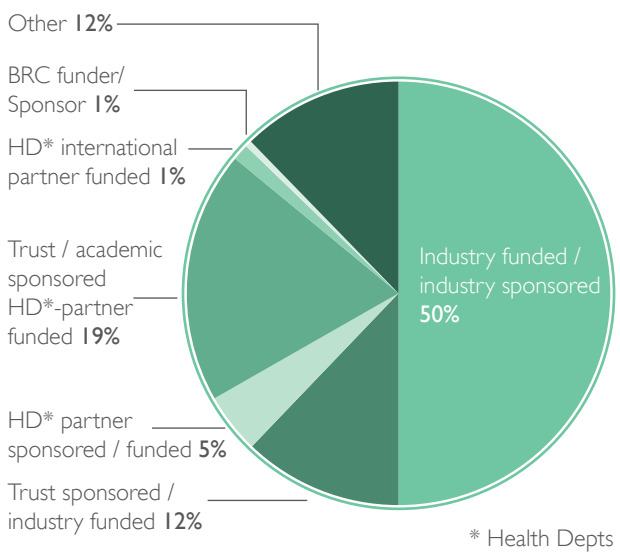
One of the unique advantages of the ECMC Initiative is the world-class laboratory infrastructure across the Network. ECMC funding supports sample collection for pharmacokinetic and pharmacodynamic analyses, which are crucial in delivering high-level translational research and support for early phase clinical trials. A total of 656 studies involved sample collection for pharmacokinetic analysis, the majority of which were blood samples. A total of 674 studies involved sample collection for pharmacodynamic analysis, the majority of which were blood or blood and tissue samples. The expectation is that these numbers will increase over the quinquennium as the number of trials requiring these analyses increases.

Collaborations

As detailed elsewhere in this report, networking is a crucial focus for ECMCs in the current quinquennium. The increase in the stratification of patients for early phase trials necessitates some trials opening at a number of sites in order to recruit sufficient patients. Centres also collaborate based on the individual expertise they bring to a trial or other translational studies. We intend to measure this collaboration space through the quinquennium.

Figure 2.6 summarises the funders and sponsors of ECMC-supported studies hosted by the Network. This confirms the importance of ECMCs in industry collaborations - 62% of studies involve a commercial funder or sponsor, a similar number to that of the first quinquennium.

Figure 2.6. Funders and sponsors of ECMC-supported studies.



Appendix 1: Selected Publications

Centre	Title of paper	Reference
Barts/Brighton	Smaller sample sizes for Phase II trials based on exact tests with actual error rates by trading-off their nominal levels of significance and power.	*Br. J. Cancer* 107, 1801-1809 (2012).
Belfast	Epiregulin (EREG) and amphiregulin (AREG) gene expression to predict response to cetuximab therapy in combination with oxaliplatin (Ox) and 5FU in first-line treatment of advanced colorectal cancer (aCRC).	*J Clin Oncol* 30, (suppl; abstr 3516) (2012)
Birmingham	Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial.	*Lancet Oncol.* 13, 1152-1160 (2012).
Cambridge	Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA.	*Sci. Transl Med.* 4, 136ra168 (2012).
	The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups.	*Nature* 486, 346-352 (2012).
Cardiff	Optimisation of chemotherapy for younger patients with acute myeloid leukaemia: results of the MRC AML15 trial.	*J. Clin. Oncol.* doi:10.1200/JCO.2012.47.4874 (2013) (Epub ahead of print).
Edinburgh/Dundee	Expression of steriod receptor coactivator 3 in ovarian epithelial cancer is a poor prognostic factor and a marker for platinum resistance.	*British Journal of Cancer* 108: 2039-2044 (2013)
Glasgow	Phase I evaluation of the effects of ketoconazole and rifampicin on cediranib pharmacokinetics in patients with solid tumours.	*Cancer Chemother. Pharmacol.* 71, 543-549 (2013).
	Patient selection for oncology Phase I trials - a multi-institutional study of prognostic factors.	*J. Clin. Oncol.* 30, 996-1004 (2012).
ICR	Prognostic value of blood mRNA expression signatures in castration-resistant prostate cancer: a prospective, two-stage study.	*Lancet Oncol.* 13(11), 1114-1124 (2012).
Imperial	EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis.	*J. Clin. Oncol.* 31(2), 280-286 (2013).
	GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer.	*Nature Genet.* 45(4), 362-370 (2013).
KHP	Dual targeting of ErbB2 and MUC1 in breast cancer using chimeric antigen receptors engineered to provide complementary signaling'	*J. Clin. Immunol.* 32(5), 1059-1070 (2012).
	The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups'	*Nature* 486, 346-352 (2012).
Leeds	Cell carriage, delivery and selective replication of an oncolytic virus in tumor in patients.	*Sci. Transl. Med.* 4, 138ra77 (2012).
	Feasibility of preoperative chemotherapy for locally advanced operable colon cancer: the pilot phase of a randomised controlled trial.	*Lancet Oncol.* 13(11), 1152-1160 (2012).
Leicester	FOLFERA: a randomized Phase II study of irinotecan, 5-fluorouracil (5-FU), and folinic acid (FOLFIRI) with or without addition of the endothelin receptor antagonist (ETAR) zibotentan in patients with metastatic colorectal cancer after failure of oxaliplatin-containing chemotherapy.	*J. Clin. Oncol.* 30(Suppl. 34), Abstract 406 (2012).
Manchester	Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study.	*Lancet Oncol.* 13(1), 65-77 (2012).
	Biomarker evaluation of the mechanisms of cell death induced by the vascular disrupting agent OXi4503 during a Phase I clinical trial.	*Br. J. Cancer* 106, 1766-1771 (2012).
Newcastle	Human $\alpha(2)\beta(1)$(HI) CD133(+VE) epithelial prostate stem cells express low levels of active androgen receptor.	*PLoS One* 7(11), e48944 (2012).
Oxford	Common variants at the MHC locus and at chromosome 16q24.1 predispose to Barrett's esophagus.	*Nature Genet.* 44, 1131-1136 (2012)
Sheffield	Serum lactate dehydrogenase is prognostic for survival in patients with bone metastases from breast cancer: a retrospective analysis in bisphosphonate-treated patients.	*Clin. Cancer Res.* 18, 6348-6355 (2012).
	Prevention of anastrozole induced bone loss with monthly oral ibandronate: final 5 year results from the ARIBON trial.	*J. Bone Oncol.* 1, 57-62 (2012).
Southampton	Effect of short duration chemoimmunotherapy plus radioimmunotherapy produces high response rates in relapsed follicular lymphoma: a UK NCRI lymphoma group study, CR UK/07/038.	J. *Clin. Oncol.* 30(Suppl.), Abstract 8056 (2012).
UCL	A common single-nucleotide variant in T is strongly associated with chordoma.	*Nat. Genet.* 44(11), 1185-1187 (2012).

Appendix 2: Network Groups

Network Group	Remit	Example of recent activity
Quality Assurance and Translational Science (QATS)	Supports and enables ECMCs to conduct translational research to the highest achievable levels of quality and regulatory compliance, utilising validated cutting-edge technologies	A workshop on "Biomarkers Fit for Purpose" held in Belfast in October 2012, focusing on the development of fit-for-purpose biomarkers, which was attended by translational scientists, laboratory staff and quality managers involved in biomarker research and biomarker development programmes
Imaging	Disseminates best imaging practice to increase the number and quality of trials at ECMCs that used advanced imaging approaches and facilitates advanced imaging approaches to multi-centre trials	Introductory course on computed tomography and magnetic resonance imaging in clinical trials held jointly with the Research Nurse Network Group in September 2012. This meeting was organised with the Wolfson Molecular Imaging Centre and the Christie Hospital and was aimed at nursing staff involved in the recruitment of patients to clinical trials with imaging components. It gave delegates an introduction to computed tomography and magentic resonance imaging, and their role in clinical trials
Research Nurse	Promotes quality care for patients taking part in early phase research through peer support, training and guidance for research nurses working in early phase and translational research	Submitted a poster to be displayed at the UK Oncology Nursing Society conference, detailing the work that the group had carried out to promote patient safety in cancer clinical trials through a survey of out-of-hours systems in ECMCs
Operational	Shares best practice amongst research teams involved in early phase trials and translational research and helps to find solutions to bottlenecks in the setting up and coordination of these studies	Provision of a directory of expertise across the ECMC Network for improved operational activity

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