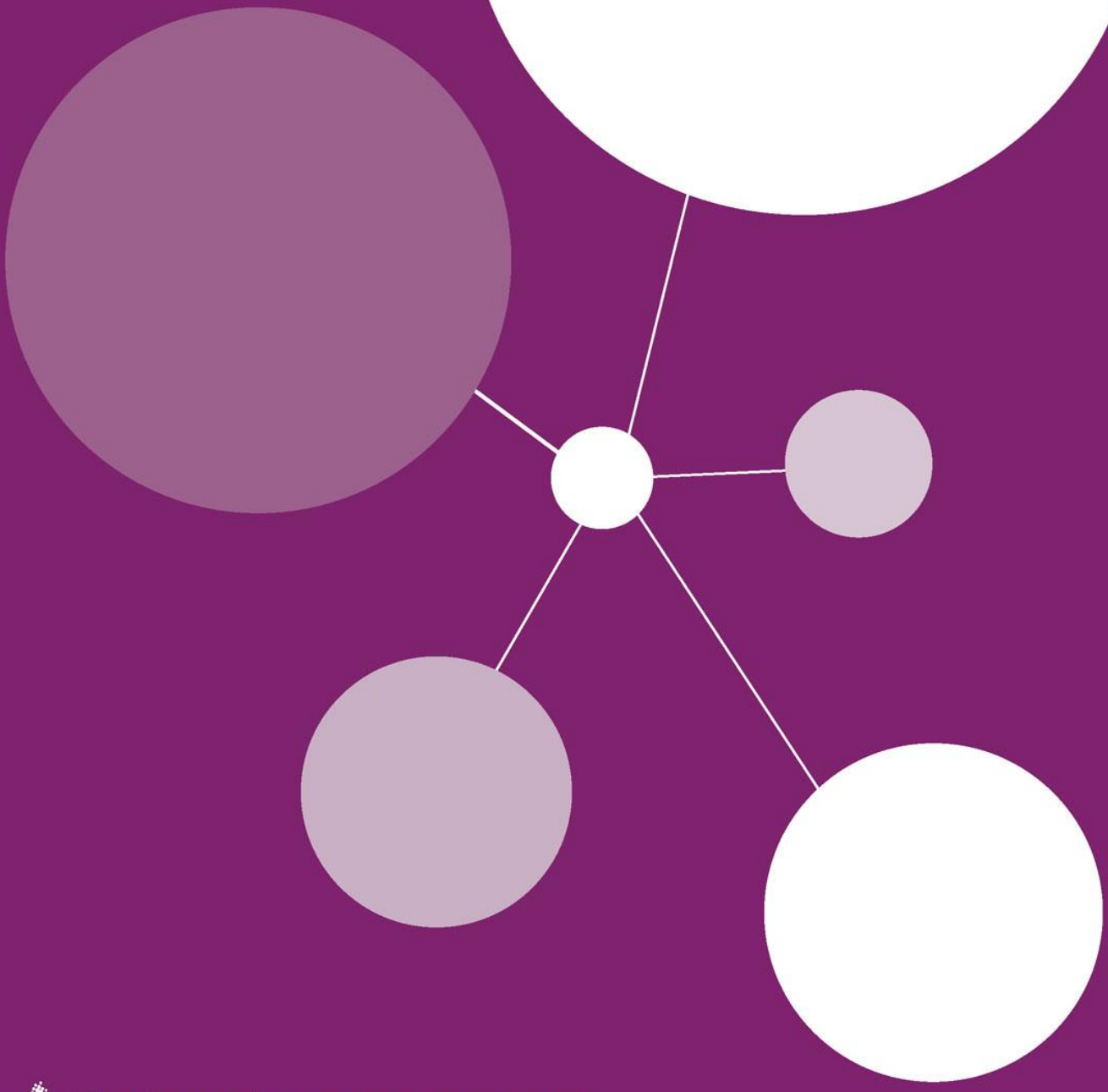
NCRI
National
Cancer
Research
Institute

NCRI Children's Cancer and Leukaemia Group

Annual Report 2019-20



Partners in cancer research

The NCRI Group Annual Reports 2019/2020 span the time period April 2019 – March 2020. The reports were submitted during a challenging time for all in the healthcare sector due to the COVID-19 pandemic. This has had an unprecedented impact on the activity of both the Research Group itself and wider research activities, ranging from the time available for research work versus clinical commitments to the funding of new trials and the recruitment of existing trials. Due to this the NCRI significantly extended the deadline for submission of annual reports and allowed the Groups to submit reduced reports, if time permitted, with the following sections at a minimum:

- Achievements (section 1 of the report)
- Funding Submissions over the last 12 months (section 5)
- Priorities and Challenges (section 7)

In addition to this, Consumer representatives of each Group were asked to only complete their sections if they feel able to. Most of our Consumers have submitted reports, however where reports have *not* been submitted this was due to extended periods of ill health, or additional work/home life constraints, as a result of COVID-19.

NCRI Children's Cancer and Leukaemia Group Annual Report 2019-20

1. Top 3 achievements in the reporting year

Achievement 1

Continued excellent progress against 2018-21 strategy.

Leukaemia portfolio

1. Successful application to Cancer Research UK (CRUK) for trial in Philadelphia positive acute lymphoblastic leukaemia (ALL) (EsPhall), Nov 2019.
2. Trial proposal in relapsed Acute Myeloid Leukaemia has been developed for funding application.
3. A proposal for a randomised study assessing the role of antibiotic prophylaxis in acute lymphoblastic leukaemia induction therapy (substudy of ALLTogether ALL study) has been developed with a view to funding application.

Neuroblastoma portfolio

1. Funding agreed for new trial in High Risk neuroblastoma.
2. New arms in BEACON study opened 2019 and development of BEACON 2 study proposal in relapsed/refractory neuroblastoma.

Personalised medicine/novel agents:

1. Stratified Medicine Paeds (SMPaeds – UK led) and closely linked eSMART study opened in UK in 2019.
2. International leadership of biologically informed trials eg eSMART arms, NF1 and non NF1 Low Grade Glioma trials along with UK-led molecular diagnostics platform for all LGG patients – submitted for CRUK funding March 2020.
3. Experiment Cancer Medicine Centres (ECMC) network: regional relapse meetings functioning well and facilitating access to early phase trials in relapsed patients; facilitation of new commercial partnerships.

Soft tissue sarcoma:

1. VIT 9010 study presented ASCO 2019: based on results of this randomised trial then new standard of care chemotherapy in relapsed rhabomyosarcoma is vincristine, irinotecan and temozolomide.

Achievement 2

Successful transfer of the Non-Hodgkin's Lymphoma Subgroup from the NCRI Lymphoma Group/High grade lymphoma subgroup to become a new subgroup within the Children's Group with aim of supporting ability to develop trials in paediatric NHL.

Achievement 3

Review of the structure and timing of the Annual Trials Meeting in 2019 led to an important collaboration with the UK Children's Cancer and Leukaemia Group (CCLG). The 7th Annual Trials meeting was held in January 2020 immediately after the 2-day CCLG Winter Meeting at the same venue. The programme was varied and included presentation of the portfolio renal tumour study (UMBRELLA) developed through the CCLG Renal Special Interest Group with the support of the NCRI Children's Group as well as trials developed by NCRI Children's Subgroups. The new approach was well received, and we are actively working with CCLG on plans for a similar format of meeting in early February 2021.

2. Structure of the Group

In line with NCRI strategic changes and with the agreement of the membership, the Group was renamed as the NCRI Children's Research Group in October 2019.

In autumn 2019 the paediatric Non-Hodgkin's Lymphoma (NHL) subgroup of the Lymphoma Research Group transitioned into the Children's Research Group to form a new subgroup, with Dr Mary Taj as the Chair. This was a strategic move to support the subgroup's work in developing paediatric NHL trials.

Ms Veronica Moroz and Mrs Julie Evans resigned from the group in 2019 owing to changes in their own circumstances. Dr Mark Gaze completed his second term on the group in Jan 2020. Dr Sara Stoneham completed her second term of office in Jan 2020 and will step down later in 2020 once a new Germ Cell Tumour (GCT) subgroup chair has been appointed.

Invited member Dr James Nicholson, retiring Chair of the Children's Cancer and Leukaemia Group stepped down from the group and the new CCLG Chair Professor Richard Grundy took his place in March 2020.

The group welcomed new members Dr Mark Davies, Dr Bob Phillips and Professor Simon Gates in March 2020. In our next recruitment round we will be seeking a nursing representative and a member to provide a NCRI CTRad link.

Trainees remain active in the subgroups and their membership will be reviewed in 2020.

2. Children's Cancer and Leukaemia Group & Subgroup strategies

Children's Cancer and Leukaemia Group

Portfolio development

Following an extremely successful year in 2018-19 the group has seen further successful funding applications for trials which will close recent portfolio gaps, notably trials in High Risk Neuroblastoma, Philadelphia positive ALL, and anaplastic large cell lymphoma (ALCL) as well as the opening of the ICONIC trial in osteosarcoma. There has also been good progress towards availability of trials for all the major Central Nervous System (CNS) tumour subtypes. The Novel Agents group remains exceptionally active (see below). Opening of the national molecular profiling study (SMPaeds) for relapsed patients, with results discussed at the new national molecular tumour board and the associated eSMART study, the first European paediatric adaptively designed multi-arm phase I/II personalised medicine basket trial of molecularly targeted agents alone and in combination, are of particular note.

There have been unexpected delays in opening some key trials such as ALLtogether in acute lymphoblastic leukaemia and FaR-RMS in rhabomyosarcoma with plans in place to open these in 2020.

The recent arrival of COVID-19 has delayed panels reviewing funding applications for low grade glioma and relapsed AML trials and has delayed the opening of some trials. COVID-19 is expected to have some ongoing impact on our ability to further develop the portfolio in the short to medium term.

Increasing early phase activity and participation

Through the activity of the Novel Agents Group, early phase clinical trials activity continues to increase with trials available across the disease and age spectrum, new trials opening in the reporting period and others in development. These include inbuilt novel pharmacodynamic (PD) biomarker studies, pharmacokinetic (PK) studies and functional imaging studies. Novel agent studies also now are included in large platform studies such as FaR-RMS (frontline and relapsed rhabdomyosarcoma) and planned in rEEcur (relapsed Ewings sarcoma).

The opening in 2019 of SMPaeds, the national molecular profiling study, and launch of the associated national molecular tumour board has facilitated access of relapsed patients to a number of molecular enrichment/biomarker-driven studies in both the academic and commercially sponsored settings. These include eSMART, Alectinib, dabrafenib/trametinib and TRK inhibitor studies and others. Novel Agents Group members lead internationally on a number of studies, including several arms within the eSMART study.

The ECMC network regional relapse meetings are now working well weekly or biweekly to inform local clinicians about early phase trials available for relapsed patients and facilitate access to such trials within ECMC network centres.

Members of the group remain extremely active at international level through platforms such as ACCELERATE, with the aim of improving collaboration with industry, regulatory authorities and consumers to improve access to novel agents.

Successful delivery of clinical trial

The paediatric oncology community remains committed to delivering care in the context of clinical trials wherever possible as evidenced by the development of new trials across the portfolio. Recruitment to available trials has remained good. However, the slowing of recruitment seen in 2018-19 primarily related to the closure of the UKALL 2011 trial for acute lymphoblastic leukaemia (ALL) has persisted in 2019-20, pending the opening of new frontline trials in some of the major paediatric tumour groups, namely ALL, rhabdomyosarcoma and high-risk neuroblastoma. In addition, COVID-19 forced temporary trial closure in some centres and sponsor halt on some trials and will likely impact on trial recruitment figures for Q4 2019-20 and 20-21.

UK wide and international links

Owing to the rarity of paediatric cancers, almost all paediatric oncology trials are now collaborative national or international academic and/or industrial partnership efforts. Most of the newly funded or opened trials in 2019-20 are international trials, in collaboration with European partners e.g. eSMART; High Risk Neuroblastoma (HR-NBL2, Philadelphia positive ALL (EsPhALL), relapsed Ewing Sarcoma (rEEcur). Partnerships continue to work well. SMPaeds is the national molecular profiling platform for UK relapsed patients and aligns with other national efforts such as INFORM in Germany and MAPPYACTs in France to facilitate access to molecular enrichment/biomarker driven international trials.

Members of the Group and its Subgroups are active members of European and international tumour specific-specific consortia involved in clinical trial design.

Through closer collaboration with the UK CCLG, we have strengthened links with CCLG Special Interest Groups that coordinate portfolio developments in other areas of children's cancer not specifically represented within the NCRI Children's Group (e.g. Wilms tumour, Langerhans Cell Histocytoma, Supportive Care).

As yet there is no direct impact from Brexit but the Group is mindful of potential future changes and will proactively collaborate with partners across Europe to ensure ongoing access to European trials for UK children. Our close link with the CRCTU in Birmingham is critical in negotiating the changing European landscape.

Group structure and function

Dr Julia Chisholm took over as Chair of the Group in April 2019.

The past year has seen the successful transition of the paediatric Non-Hodgkin's Lymphoma group from Lymphoma to the Children's Research Group to support trial development in the paediatric types of NHL (which differ from adult types of high grade NHL).

We reviewed the structure and timing of the Annual Trials Meeting in 2019 leading to an important collaboration with the UK Children's Cancer and Leukaemia Group (CCLG). The 7th Annual Trials meeting was held in January 2020 immediately after the 2-day CCLG Winter Meeting at the same venue in Nottingham. The new approach was well received and we are actively working with CCLG on plans for a similar format of meeting in early February 2020.

New members of the group appointed in March 2020 have brought new skills in supportive care and evidence-based medicine (Dr Bob Phillips) and adult oncology with genetics (Dr Mark Davies) which may allow further diversification of the portfolio.

We have undertaken a comprehensive review of our portfolio maps in early 2020 to ensure accuracy. Review remains ongoing.

We are preparing for the group's Quinquennial Review (QQR) planned in December 20200

Consumer involvement and impact

The consumer members of the Group remain extremely active and make an important and significant contribution to the activities of the Group, including invaluable peer review comments and speaking at the Annual Trials Meetings. Members of the Group also ensure regular and sustainable patient and public involvement at all stages in the development of clinical trials.

The consumer members are participating in the NCRI Consumer Forum, the ongoing James Lind Alliance (JLA) Priority Setting Process for children's cancer research, the Child Cancer Smart Stakeholder Advisory Group and the CCLG Research Advisory Group as well as other national PPI groups.

Our consumers have very strong international Public and Patient Involvement links. In particular one member is Lead the for Society for Paediatric Oncology (SIOPe) Childhood Cancer International (CCI) Participation in Research work stream (European PPI strategy) and is a Stakeholder member involved in the World Health Organisation (WHO) Global Initiative for Childhood Cancer. This member is herself undertaking a PhD into the communication of late effects to female childhood cancer survivors.

Raising Profile

The Chair continues to present the trial portfolio annually at the Children's Cancer and Leukaemia Group (CCLG) Winter meeting and collaboration with CCLG over the Annual Trial Meeting will be important in continuing to raise national awareness of the Group's Work. The CCLG funds trainees to attend the Subgroups, exposing them to clinical trials development and the Chair and Chief Executive of CCLG are invited members of the Children's Research Group.

In 2019 group members participated in a workshop with CTRad to develop radiotherapy research ideas. Two Children's Group members (Chair and GCT subgroup chair) also are members of the Teenage Young Adults and Germ Cell Tumour Group (TYA and GCT) and these links have helped to strengthen the links, co-working and common interests of these two NCRI groups.

Group members are participating in the JLA Priority Setting Process for Children's Cancers which will inform the research agenda and trial funding opportunities going forward.

Central Nervous System Subgroup (Chair, Prof Simon Bailey)

Improve Event Free and Overall Survival

The portfolio of trials in development is increasing steadily in an attempt to improve the Event Free Survival (EFS) and Overall Survival (OS) particularly amongst children with those tumours with a poor outcome. This is described in more detail in the number of clinical trials segment. In addition, alongside trial development, treatment guidelines for the majority of tumours have been developed primarily by members of the group for most of the CNS tumours that occur in children and young people (via CCLG). This is a year on year aspiration.

Better identify prognostic and predictive biomarkers and implement their usage

There are a number of programmes based both in the UK as well as in collaboration with European and worldwide partners that are investigating biological material to determine prognostic and predictive biomarkers to inform future trials. This is an ongoing programme and a number of biomarkers identified by group members are in routine clinical use as well as embedded in current trials. These include current trials PNET 5, Ependymoma 2, upcoming low-grade glioma trials, high risk medulloblastoma, diffuse midline glioma trial (BIOMEDE 2) and ATRT. There is a robust mechanism in the UK for centralised molecular diagnostics with pathology review for a number of CNS tumour types which is being adapted to include the genomic hubs when they come online. SMP paeds is now open which identifies targetable mutations in tumours at relapse includes CNS tumours.

Increase the number of clinical trials for children with CNS tumours

There has been a significant increase in the number of trials open, about to open and in advanced planning. All of the trials in paediatric CNS tumours are international trials due to the relatively rarity of the individual tumour types. PNET 5 (standard risk medulloblastoma), Ependymoma 2 (all ependymoma) and SMP paeds are all open and recruiting well, high risk medulloblastoma (HRMB) will open post COVID-19 (funded and ready to open), LOGGIC and NF-1 LGG (funding applied for), ATRT (funding applied for in Germany), BIOMEDE 2 (diffuse midline gliomas – funding applied for in France). Infant Medulloblastoma is in planning. There are also a number of quality of survival trials and surgical trials (cerebellar mutism) that are ongoing.

Application of molecular diagnostics to routine clinical practice

There is a robust mechanism in the UK for centralised molecular diagnostics with pathology review for a number of CNS tumour types (medulloblastoma, ependymoma) which is being adapted to include the regional genomic hubs when they come online. These underpin the international trials in the aforementioned diseases but are also in place for future trials and these systems are planned to be replicated for all tumour types.

Neuroblastoma Subgroup (Chair, Dr Juliet Gray)

Strategy development

Members have continued to follow the strategy set by the Neuroblastoma Subgroup for 2018-2021.

The subgroup is a diverse, inclusive one, with knowledgeable, experienced individuals from the medical specialties of paediatric and clinical oncology, surgery and imaging, with biologists, clinical trial professionals, and lay parent/charity representation. It works nationally and internationally. The mission is to improve the survival of children with neuroblastoma, and to reduce the impact of treatment on quality of life. It develops and maintains a wide-ranging and comprehensive portfolio of clinical trials and studies for neuroblastoma including those for:

- First line treatment of high risk disease
- Poor responders
- Patients with relapsed disease
- Patients with better prognosis disease
- Imaging techniques
- Radiotherapy
- Surgery
- Immunotherapy
- Epidemiology
- Pharmacology
- Toxicity and late effects
- Biology, staging and prognosis
- Novel agents in early phase assessment

The subgroup also:

- Works with the NICE, CCLG, charities and other stakeholders to ensure early adoption of innovative treatments by the National Health Service (NHS) once the evidence of benefit is available.
- Educates other healthcare professionals in neuroblastoma clinical trials and best practice through meetings, courses, newsletters and authoritative guidance.
- Develops the next generation of neuroblastoma specialists.

Key Early Phase Clinical Trial Activity

- The BEACON trial is an Innovative Therapies for Children with Cancer in Europe multi-arm, multi-stage multicentre Phase II trial for relapsed and refractory disease. The initial design compared backbone chemotherapy with temozolomide alone or with either irinotecan or topotecan, with or without bevicizumab, resulting in six treatment arms. Recruitment to +/- irinotecan, and +/- bevicizumab have completed planned recruitment and preliminary results presented at ASCO 2019 and ASCO 2020 respectively. An amendment to the trial was made in 2019, to evaluate dinutuximab beta immunotherapy in conjunction with the chemotherapy backbone. This opened In August 2019, and has recruited extremely well, and should complete by Q4 2020. Plans for new novel agent Phase II trial – BEACON 2 – are in progress.
- The MINIVAN trial is run by consortium of centres from the UK, the USA and Germany, led by UK investigators, and sponsored by the University of Southampton NHS Foundation Trust. It is an innovative phase I trial combination of molecular radiotherapy with two immunotherapy agents nivolumab and dinutuximab beta for patients with relapsed or refractory high risk neuroblastoma. 8 patients have been recruited so far, all from the UK.
- 1RG-CART is a Phase I study of GD2 targeting CAR-T cells in patients with relapsed / refractory neuroblastoma. This completed recruitment in Q4 2019. A follow on, combinational, study is being considered.
- The YmAbs 201 study is an international, commercial phase II study of a humanised anti-GD2 antibody (hu3F8). Significant numbers of children with relapsed / refractory disease have previously travelled to the US to receive this antibody, but in 2019 the trial was opened in 3 UK centres.

High Risk Neuroblastoma Clinical Trial Activity

- Following completion of recruitment to five separate randomisations, the first SIOPEN high-risk neuroblastoma study closed to recruitment in 2018. Members have worked with colleagues in the European SIOPEN consortium, to develop a new phase III trial for high-risk neuroblastoma (HR2). Uniquely, this trial contains a radiotherapy dose escalation randomisation for residual disease. This will be the world's first phase III radiotherapy randomised trial in neuroblastoma. Other randomisations include a comparison of two induction regimens, and a comparison of single versus double high-dose chemotherapy. Funding for the study has been successfully secured from the charities Solving Kids Cancer and Neuroblastoma UK.
- A joint commercial / SIOPEN initiative has led to the development of novel pilot study of upfront anti-GD2 (dinutuximab beta) and chemotherapy in patients with newly diagnosed

high risk neuroblastoma. This will open in the UK in Q3/4 2020 and if successful will lead to amendment of the SIOPEN HR-2 study to incorporate a randomisation of upfront chemo-immunotherapy.

- Funding was awarded in 2017 by CRUK for VERITAS, a randomised phase II trial of two double high-dose intensification strategies for poorly responding metastatic high-risk neuroblastoma. This will be the world's first randomised trial comparing a molecular radiotherapy-based approach with chemotherapy alone. The trial is open in France, the sponsor nation, and is going through the UK research governance approvals process, due to open as soon as COVID-19 allows.

Other Trial Activity

- The IMAT-neuroblastoma trial, a randomised phase II trial of radiotherapy dose escalation with innovative technology is recruiting well now after a slow start. Eleven centres are now open, and > 80% of the planned total of 50 patients, have been enrolled. The prospective individual patient radiotherapy quality assurance process has worked very well.
- The CRUK Centre for Drug Development trial of 124-Iodine metalodobenxylguanidine PET imaging has been troubled by unreliability of radiopharmaceutical supply for several unconnected reasons. Despite this, seven evaluable patients have been imaged, with five in the PET/MRI sub study. Plans for a follow-on study are being developed.
- Previous pharmaco-kinetic studies have shown the unreliable bioavailability of 13-cisretinoic acid when capsules are opened for children unable to swallow them. A new, tutti-frutti flavoured liquid formulation has been developed for such children, and a pharmacokinetic evaluation of this is recruiting well. The trial completed recruitment in 2019 and results were due to be present at the Advances in Neuroblastoma Research congress in 2020.
- An epidemiological study of survival after relapse, with associated biological data, is now open, offering new insights into the management of relapsed neuroblastoma.

Achievements

- Publications of trial outcomes:
    - LuDO trial (Phase II trial of new agent 177-Lutetium DOTATATE (Eur J Nucl Med Mol Imaging, 2020)
    - SIOPEN HR-1 trial (Cancers 2019, 2020, Lancet Oncology 2018, Lancet Oncology 2017)
    - SIOPEN Long Term Infusion trial (Oncoimmunology 2019, Cancers 2018, Mabs 2018)
- Members of the Subgroup contribute to a regular monthly virtual National Neuroblastoma Advisory Panel. One of the main aims of this is to promote entry into clinical trials.
- The fourth annual Neuroblastoma Clinical Trials Day was held in London in September 2019. This was well attended and highly rated. The key aim is to increase awareness of the wide portfolio of neuroblastoma trials, especially for those who work in centres not represented on the Subgroup.

- In November 2019, the group ran an inaugural 2-day multidisciplinary course on neuroblastoma.
- The groups has a trainee member who has actively contributed to a number of projects and helps to fulfil our objective of developing the next generation of neuroblastoma specialists.

Novel Agents Subgroup (Chair, Dr Lynley Marshall)

Developing new trials with academic and industry partners

The Novel Agents Subgroup and its 11 Paediatric ECMC Network member centres have remained very active over the past year.

Our early phase clinical trials activity has increased. Within this reporting year there have been 33 early phase clinical trials of novel drugs open across the Network at some point including 26 dose finding (phase I/IB/II) and 7 later phase II trials. Of these, 18 (54.5%) are commercially sponsored and 15 (45.5%) academic sponsored (some with industry support). Twenty-nine include biologically targeted agents (involving 38 different drugs). Combination studies include novel molecularly targeted agents combined with cytotoxic drugs, other novel targeted agents (including antibodies/immunotherapies), radiotherapy or MIBG therapy, twelve studies include immunotherapy drugs and six of these include immune checkpoint inhibitors.

ESMART, the first European paediatric adaptively designed multi-arm phase I/II personalised medicine basket trial of molecularly targeted agents alone and in combination opened in December 2019 (UK Chief Investigator Dr Lynley Marshall). Study entry is based on multi-omic molecular tumour profiling conducted on biopsy taken at relapse and processed via the CRUK-sponsored Stratified Medicines Paediatrics (SMPaeds) study (CI Professor Louis Chesler/Clinical Molecular Tumour Board Lead Prof Darren Hargrave). ESMART has been developed within the Innovative Therapies for Children with Cancer (ITCC) European early phase trials consortium. It has to date had 10 study arms and 4 pharma partners; three of these written and led by NCRI Novel Agents Subgroup Investigators (Dr Marshall, Dr Susanne Gatz) with academic funding via a CRUK grant in the UK. There are five new study arms about to be added via a substantial amendment in Q2/3 2020; three are combination arms written and led by Dr Marshall and Dr Gatz, and based on preclinical/translational work conducted in UK translational laboratories (Chesler/Shipley, ICR). ESMART tests classes of drugs of significant interest to the paediatric/TYA cancer population but many not previously readily accessible, including: CDK4/6 inhibitor, PARP inhibitor, WEE1 inhibitor, TORC 1 &2 inhibitor, anti-PD-L1 antibody, MEK inhibitor, IDH2 inhibitor, anti-KIR antibody; new arms include CDK2/9 inhibitor, PARP inhibitor/ATR inhibitor combination and pan-FGRF inhibitor.

Multiple other new phase I/II clinical trials (academic and commercially sponsored), are in various stages of set-up to open in 2020/21. This includes the DETERMINE Study which will be academically sponsored by the CRUK Centre for Drug Development (CDD), with a CRUK funding application deferred for 3 months due to the COVID-19 pandemic, from March to June

2020. DETERMINE is designed to be tumour-agnostic and age-agnostic, including adults and children, with a specific focus on rare tumours and childhood/TYA cancers (CI Dr Matthew Krebbs, Paediatric Lead Dr Marshall). It will include the testing of licensed drugs in as yet unlicensed indications, based on molecular tumour profiling. It will include drugs from multiple pharma partners, with the first six drugs and considerable financial support for the study already committed by Roche; four of these drugs are of considerable interest in paediatric/TYA cancers and will provide access to novel targeted therapies to patients with an unmet need.

New commercial phase I/II clinical trials in set up within the Network include studies of Olaparib (AstraZeneca), Idasanutlin Roche), Alectinib (Roche), Venetoclax (AbbVie), Lenvatinib (Eisai), Ramicirumab (Eli Lilly), Erbumine (Eli Lilly), Abemiciclib (Eli-Lilly), 2 Omburtumab studies (YMabs), 2 Ponatinib studies (Incyte, Takeda), Quizarinib (Daichi Sankyo), LOXO292 (LOXO), and a Niraparib/Dostarlumab combination (Tesaro/GSK)

Novel agents for poor prognosis tumours at diagnosis and relapse

Our early phase clinical trial portfolio includes novel therapeutic options for paediatric/TYA patients across the age and disease spectrum, with disease-specific, target-specific and broader eligibility trials. In this reporting year, 20 trials have been open to patients with extracranial solid tumours, 14 to patients with central nervous system (CNS) tumours and 12 to patients with haematological malignancies (leukaemia or lymphoma). Fourteen trials have been open across multiple disease groups, with six having truly tumour agnostic eligibility based on molecular tumour profiling.

For the worst prognosis high risk malignancies e.g. diffuse midline glioma (DMG), upfront studies such as the BIOMEDE phase II trial (UK CI Prof Darren Hargrave) can test novel targeted agents in combination with radiotherapy in newly diagnosed patients, based on tumour biology. The BIOMEDE trial was temporarily halted during part of this period after an interim analysis demonstrated that none of the three agents being tested would definitively be shown as superior. An amendment is underway to add a new arm of ONC201 (targeting the driving H3K27 histone mutations) in combination with radiotherapy, randomised against everolimus and radiotherapy, and with the addition of a placeholder for nested sub-studies for particular molecular subgroups.

For other poor prognosis tumours, adaptively designed combination phase II studies aim to define the optimal backbone regimen upon which to add novel agents (eg BEACON for neuroblastoma – CI Dr Lucas Moreno - new arms including the anti-GD2 antibody Dinutuximab beta opened in 2019 and are recruiting ahead of target); rEEcur for Ewing sarcoma – CI Dr Martin McCabe – a new novel combination arm including a CDK4/6 inhibitor is in set-up: Frontline and Relapse Rhabdomyosarcoma study (Far-RMS) – CI Dr Meriel Jenney; Relapse Study Lead Dr Chisholm, in late stages of set-up, will provide novel options for rhabdomyosarcoma patients throughout their disease journey.

Clinical trials of new agents targeting strong oncogenic drivers (BRAFv600, the MAPK pathway, ALK, NTRK) have advanced from phase I single agent to phase II combination trials, including (in some diseases) to upfront testing (MEK inhibitors in low grade glioma; ALK inhibitors in

inflammatory myofibroblastic tumours and soon in ALK-mutant neuroblastoma, NRTK inhibitors in infantile fibrosarcoma and infant high grade glioma).

Develop and deliver biomarker and pharmacokinetic studies

The CRUK-funded Stratified Medicine Paediatrics (SMPaeds) national molecular profiling study was launched in March 2019 and recruited its first patient in early April 2019. 116 patients have been enrolled this year. Via this programme, patients undergoing tumour biopsy and molecular profiling of their disease relapse can be considered for more personalised medicine predictive biomarker-based clinical trials of novel agents. Alongside this programme, we have continued to drive forward molecular enrichment/biomarker-driven studies in both the academic and commercially sponsored settings e.g. E-SMART (multiple targets and pathways, including new arms, as above), CRISP (Crizotinib combinations), Lorlatinib and Alectinib (ALK/ROS/MET), Dabrafenib/Trametinib (BRAF/MEK inhibitor combinations), Larotrectinib and Entrectinib (NTRK), LOXO292 (RET), and others.

Our new early phase trials continue to include inbuilt novel pharmacodynamic (PD) biomarker studies as well as pharmacokinetic studies. Two new arms of E-SMART include the CDK9/2 inhibitor, CYC065 from Cyclacel, a novel drug which destabilises MYC/MYCN and also targets MCL-1 and MLL, with potential interest in MYCN-driven solid tumours such as neuroblastoma, as well as leukaemia and lymphoma. The PD biomarker work for these arms will be done in the Chesler laboratory at the Institute of Cancer Research (ICR), as is the PD biomarker work for the CRISP phase IB study of Crizotinib (neuroblastoma, rhabdomyosarcoma, ALCL and IMT/other ALK aberrant tumours). The DETERMINE study mentioned above will have a significant translational biology component to it.

Our early phase trial centres are affiliated to laboratories developing and refining techniques for monitoring circulating tumour DNA for early detection of relapse and tracking response to novel treatments. This work is currently underway for neuroblastoma, sarcomas and certain brain tumours (in blood, and where relevant cerebrospinal fluid), and in studies of NTRK, ALK and BRAF/MEK inhibitors). The utility is in non-invasive monitoring (compared to repeat biopsy).

Professor Deborah Tweddle in Newcastle has taken over leadership of the CCLG Tumour Bank, and alongside the appointment of a new manager, has updated standard operating procedures and rejuvenated national biobanking efforts, crucial to providing samples for novel translational studies.

The Newcastle Pharmacology Group led by Professor Gareth Veal remains internationally forefront in supporting early and later phase therapeutic clinical trials, leading pharmacology studies and developing therapeutic drug monitoring for key drugs or special populations (e.g. neonates/infants, patients with renal compromise and others).

Professor Andrew Peet in Birmingham (and others) continue to develop functional imaging biomarker studies for use in response assessment within clinical trials, e.g. the BEACON-Neuroblastoma trial.

Implementation of the successful renewed and expanded Paediatric ECMC network

The Paediatric ECMC Strategy Group (made of theme leads and centre leads) meets regularly to plan and evaluate initiatives across the ECMC themes. Network development has progressed well, with the 11 paediatric ECMC centres working cohesively but also within 4 regional sub-networks, created to facilitate equitable access to clinical trials nationally. Each holds regular regional relapse telephone conferences (weekly-biweekly), whereby data on all relapsed paediatric solid tumour patients can be captured, relevant molecular profiling results discussed and patients whose tumours harbour potentially actionable molecular features considered for early phase clinical trials, or where no trial is open, compassionate/managed access programmes.

Dr Tara McKay has taken over from Dr Sheona Scales as Paediatric ECMC Network co-ordinator and has greatly assisted in driving network activities forward, with Sheona continuing to be involved with the Paediatric Network. The successful establishment of a unified network confidentiality agreement has facilitated a more efficient establishment of new commercial partnerships, allowing industry partners to share details on new studies via the Programme Office, with close co-ordination between the ECMC Network (Chair Dr Guy Makin) and Novel Agents Subgroup allowing rapid assessment, input into study design, efficient expression of interest calls for clinical trial participation and strong encouragement to ensure a good geographic distribution of study sites, ideally with at least one study site within each regional network per study. Multiple companies have made use of this route already (7 enquiries during reporting period) with several of these new studies due to open in 2020/21.

Dr McKay and the ECMC Programme Office have been enormously instrumental in the successful planning and delivery of the Study Start Up Workshop, held in London in November 2019, and sponsored by ECMC Clinical Trial Theme co-leads Professor Kearns and Dr Marshall. This workshop included invited representatives from ECMC centres (medical, research nurse, trial co-ordinators, Research and Development representatives), pharma, regulatory bodies (e.g. the Medicines and Healthcare products Regulatory Agency (MHRA)), ethics committees, funders and consumer/parent/patient groups. The workshop was prefaced by a detailed examination of a sample of early phase trials (adult and paediatric, academic and commercial, geographically spread across the UK) and an industry survey, with the purpose of exploring hurdles to study start up in the UK, and a view to making recommendations for improving efficiency. The outputs from this workshop will be shared with the community in 2020.

The ECMC Trial-Finder (online clinical trials finder to improve awareness of portfolio clinical trials and promote wider access) has been successfully established during this year and continues to be developed further.

Implementation of a UK National "multi-omic" molecular profiling platform and National Molecular Tumour Board

The SMPaeds national molecular profiling programme has successfully launched in 2019 and now includes "multi-omic" techniques (customised NGS panel, WES, RNA Seq, and methylation sequencing), with 116 patients recruited in a year and with low coverage Whole Genome Sequencing (WGS) to follow. It characterises tumours following biopsies performed at relapse. It will dovetail with NHS England/Department of Health genomic medicine initiatives aimed at

offering molecular profiling to all paediatric cancer patients, including at first diagnosis. This NHS England (NHSE) rollout has been delayed from April 2019 but expected in 2020. The objective of all such initiatives is to help stratify patients for precision based clinical trials where available and to drive forward the development and validation of new prognostic and predictive biomarkers, as well as to refine diagnostics. The SMPaeds Molecular Tumour Board runs weekly and has been very successful to date, with defined pathways for the analysis, reporting and rapid communication of results back to referring clinicians, highlighting clinically relevant/potentially actionable molecular aberrations uncovered via the profiling initiatives. Turnaround times are now well within the 28-day set target.

Paediatric Leukaemia Subgroup (Chair, Dr John Moppett)

Open international trials for Ph-pos and infant ALL

EsPhALL 2017/COG AALL1631 (PI Dr Michelle Cummins) was successfully submitted to CRUK for funding in 2019 and aims to open in Q4 2020.

Infant ALL study is under development with plans to open at GOSH as a single site (PI Dr Phil Ancliff).

Contribute to international collaborations in CML and MDS

The European CML registry has regulatory approval and will hopefully open in the UK in Q3 2020 (PI Dr Anupama Rao).

The ongoing NIHR MDS Phenotype/Gentoype study (PI Dr Rao) continues to recruit well.

Agree an international first line ALL trial

The ALLTogether-1 trial (PI Dr Moppett) (CR UK funded 2018) has been HRA approved and is undergoing REC review, with an aim to open in Q3 of 2020. This will be probably the world's largest trial in ALL, recruiting over 2000 patients in the UK and more than 8000 internationally. Amendment 1 will follow shortly in Q4 2020, which opens up the investigational arm (Blinatumumab) in Down syndrome (PI Dr Sujith Samarasinghe). Much progress has also been made on two randomised substudies: CiproPal (PI Dr Bob Phillips), investigating the value of prophylactic antibiotics in induction (currently in 2nd round of NIHR HTA funding call); and ASTA (PI Dr Bradbury), investigating the value of prophylactic Apixiban. An important biomarker substudy, CSF-Flow (PI Dr Christina Halsey) has also been developed and is awaiting submission to the next CRUK funding round (delayed because of COVID).

Open registries with linked biological sample collection and studies

The Blood Cancer CellBank continues to recruit well. Over 500 samples were released to researchers in 2019, and 17 publications based on CellBank samples have been published in 2019-20. An application to CRUK is underway for funding for a merged CellBank and CCLG Tissue Bank (CCLG Biobank).

Liaise with new agents group to increase portfolio of phase I and II leukaemia trials

There are currently 6 open early phase trials in leukaemia (Bosutinib, Carfilzomib, Daratumumab, Inotuzumab, Seludex, PARC). The accelerate meeting for AML was a very useful forum and several trials are in development from that (Gilteritinib, quizartinib, venetoclax, Enasidenib (ESMART)). Additionally, there are three open CarT trials (one commercial, two academic) with Flotetuzumab (anti-CD123 immunotherapy) and AML CarT in development.

Germ Cell Tumour Subgroup (Chair, Dr Sara Stoneham)

Apply for funding for international collaborative, risk stratified, randomised extra-cranial GCT trial

Completed
Grantee Name: Dr Sara Stoneham
Funding Scheme: Clinical Research Committee - Late Phase Study.
Grant Title: AGCT1531: 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.
Application Reference: C9409/A25632.

Successful application to CRUK for funding to run AGCT1531 – international collaborative, risk stratified, randomised extra-cranial GCT trial.

Understand the role of biological marker's in risk assessment and tracking treatment

Ongoing progress

- A submission to IRAS has been completed to allow the Cambridge research team to gain generic ethical approval, which would cover and include all tissues and circulating biospecimens going forward, as advised by the Birmingham Clinical Trials Unit (CTU) with specific reference to the prospective trial AGCT1531.
- A new application has been submitted to the CCLG Tumour Bank (Dr Owen Burbidge, Tumour Bank manager) for continuation of the highly successful CCLG Biological Study CCLG BS 2002 03, with new aims and objectives.
- In addition, the Cambridge team will work alongside the CCLG Tumour Bank team to provide expert advice regarding acellular biospecimen collection (serum, plasma, urine, Cerebral Spinal Fluid (CSF), pleural fluid, ascites), and assist in making Standard Operating Procedures (SOPs) for this purpose to ensure the Tumour Bank is future-proofed for biological studies, given the increased interest and utility of non-invasive diagnosis.

Publications:

- Murray MJ, Coleman N. Understanding the pathway - MicroRNA dysregulation in malignant germ cell tumours: more than a biomarker? *Journal of Clinical Oncology*, 2019;37:1432-1435
- Amatruda JF, Bagrodia A, Cheng L, Daneshmand S, Murray MJ. Biomarkers in Testicular Germ Cell Tumours. Book Chapter. In: *Molecular Biomarkers in Urologic Oncology*: A Joint WUOF-ICUD International Consultation, 2020, In Press.

Review to investigate the Effectiveness of Chemotherapy Treatments for Paediatric Germ Cell Tumours

This was completed in 2018 with the following publication produced:

- Comparison of carboplatin versus cisplatin in the treatment of paediatric extracranial malignant germ cell tumours: A report of the Malignant Germ Cell International Consortium.

  Frazier AL, Stoneham S, Rodriguez-Galindo C, Dang H, Xia C, Olson TA, Murray MJ, Amatruda JF, Shaikh F, Pashankar F, Billmire D, Krailo M, Stark D, Brougham MFH, Nicholson JC, Hale JP. Eur J Cancer. 2018 Jul;98:30-37. doi: 10.1016/j.ejca.2018.03.004

Secure funding stream to support Patient Reported Outcome Measures (PROMS) alongside AGCT1531 - completed

Included within CRUK grant (grant year 2018-19) and successfully supported as a trial secondary aim.

Complete MaGIC trial database analyses for a) TYA patient outcomes and b) dysgerminoma/seminoma and publish

Completed.
This publication includes trial data from UK paediatric GCT trials: GC1/2/3 and UK Medical Research Council (MRC) Testis cancer trials: TE09, TE13, TE20. The data analysis supports the inclusion of poor risk TYA patients into CRUK funded P3BEP clinical trial – thus we secured agreement with international sponsor to include TYA patients on AGCT1531 trial > 11yrs with poor risk disease.

1. Outcomes of Adolescent Males with Extracranial Metastatic Germ Cell Tumors. A Report from the Malignant Germ Cell Tumour Consortium. Furqan Shaikh, Daniel Stark, Adriana Fonseca, Ha Dang, Caihong Xia, Mark Krailo, Farzana Pashankar, Carlos Rodriguez-Galindo, Thomas A. Olson, James C. Nicholson, Matthew J. Murray, James F. Amatruda, Deborah Billmire, Sara Stoneham, A. Lindsay Frazier. – in submission to Cancer.

This publication includes UK paediatric GCT trial data from GC1/2/3

2. Is carboplatin-based chemotherapy as effective as cisplatin-based chemotherapy in the treatment of advanced-stage dysgerminoma in children, adolescents and young adults? Shah R, Xia C, Krailo M, Amatruda JF, Arul SG, Billmire DF, Brady WE, Covens A,

Gershenson DM, Hale JP, Hurteau J, Murray MJ, Nicholson JC, Olson TA, Pashankar F, Rodriguez-Galindo C, Shaikh F, Stark D, Frazier AL, Stoneham S. Gynecol Oncol. 2018 Aug;150(2):253-260. doi: 10.1016/j.ygyno.2018.05.025.

Analyse and publish outcomes for GC3

Completed

1. Results from the UK Children's Cancer and Leukaemia Group study of extracranial germ cell tumours in children and adolescents (GCIII).Depani S, Stoneham S, Krailo M, Xia C, Nicholson J.Eur J Cancer. 2019 Sep; 118:49-57. doi: 10.1016/j.ejca.2019.05.001

Ongoing

2. Continue to extend links and develop collaboration with current partners in UK and internationally for both intracranial GCT (SIOPe; led by UK) and for extracranial GCT in UK (NCRI TYA and Testis CSG and NCRI Gynae CSG) and internationally with MaGIC, G3 and NOPHO.

Paediatric Non-Hodgkin Lymphoma Subgroup (Chair, Dr Mary Taj)

Ensure successful delivery of Subgroup portfolio especially phase III studies

The B-Cell Non-Hodkin Lymphoma (B-NHL) group has several tumour subgroups – B-NHL, Anaplastic Large Cell Lymphoma (ALCL), Primary mediastinal large B-cell lymphoma (PMLBCL), T cell and B cell Lymphoblastic Leukaemia (LBL) and rare lymphomas. The progress in each of these tumour types is described in the different sections below.

B cell Non-Hodgkin's Lymphoma:

1. The B-NHL Phase III trial on the 'Inter-B-NHL Ritux 2010' was a highly successful international collaboration between the European Intergroup for childhood Non-Hodgkin's Lymphoma (EICNHL) and Children Oncology group (COG). The following manuscript has been accepted for publication in NEJM: Véronique Minard-Colin et al on behalf of the European Intergroup for Childhood Non-Hodgkin's lymphoma (EICNHL) and the Children's Oncology Group (COG). Rituximab in Childhood High-Risk Mature B-NHL.

2. Ibrutinib – Sparkle study: Randomised trial of a small molecule BTK inhibitor in paediatric patients with relapsed refractory mature B cell lymphoma. Phase 1 now published. Randomised part due to complete Q1 2021. Burke GAA et al, Ibrutinib plus CIT for R/R mature B-NHL in children (SPARKLE trial): initial safety, pharmacokinetics, and efficacy. Leukaemia. 2020 Feb 18. doi: 10.1038/s41375-020-0749-5. [Epub ahead of print]

Primary Mediastinal large B Cell Lymphoma (PMLBCL):

The randomised phase II trial looking at the role of addition of Rituximab to DA-EPOCH which was part of 'Inter–B NHL Ritux 2010' trial has been completed and the data are being prepared for publication.

Anaplastic Large cell lymphoma (ALCL):

1. A Phase II trial of nivolumab for paediatric and adult relapsing/refractory ALK+ anaplastic large cell lymphoma, for evaluation of response in patients with progressive disease (Cohort 1) or as consolidative immunotherapy in patients in complete remission after relapse (Cohort 2) was successfully funded as a single centre study in 2019: opening is delayed.

2.CRISP- International study of Crizotinib in ALCL is in set up in UK.

T-lymphoblastic lymphoma trial (T-LBL):

T-LBL patients will be treated on the next leukaemia trial UKALLTogether which is yet to open. The feasibility of a sub-study to look at the role of Positron Emission Tomography-Computed Tomography (PET-CT), biomarkers and MDD as prognostic markers in this disease is being considered.

Rare Lymphomas and collaboration with European Inter-Group for Childhood Non-Hodgkin Lymphoma (EICNHL) group:

Due to small numbers even international studies are not feasible for rare Lymphomas. For this a number of collaborations have been established to collect data (sent to EICNHL) and establish consensus/evidence base for treatment of these tumours.

1. Rare non-Hodgkin lymphoma of childhood and adolescence: a consensus diagnostic and therapeutic approach to pediatric-type follicular lymphoma, marginal zone lymphoma and non-anaplastic peripheral T-cell lymphoma.

   Publication: Andishe Attarbaschi et al on behalf of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Study Group. Rare non-Hodgkin lymphoma of childhood and adolescence: a consensus diagnostic and therapeutic approach to pediatric-type follicular lymphoma, marginal zone lymphoma and non-anaplastic peripheral T-cell lymphoma. Accepted for publication Pediatric Blood & Cancer. (See publication 4 below).
2. Dr Simon Bomken - Second malignancies after mature B-NHL. Mansuscript accepted by leukemia.
3. Dr Taj – Data collected on relapsed refractory NHL – Manuscript sent to Blood.
4. Dr Taj - Data collected on CNS PTLD – Manuscript in preparation.
5. Dr Rebecca Ling – Trainee member – collected national data on 107 patients with PTLD – Manuscript in preparation.

Exploit the increased number of agents available as a result of the legislation around Personal Independence Payments (PIPs)

1. ALCL- Brigatinib studies remain in discussion with TAKEDA.
2. The ACCELERATE platform is progressing, Trial steering committee has been formed and 2 meetings completed– application for funding (for initial platform) to Fighting Kids Cancer submitted with support from pharma companies secured. Novel agents in B-NHL, is one of the main items on the agenda for this platform.
3. Andrew D.J. Pearson et al. ACCELERATE and European Medicine Agency Paediatric Strategy Forum for medicinal product development for mature B-cell malignancies in children. European Journal of Cancer. Volume 110,2019,Pages 74-85,ISSN 0959-8049,https://doi.org/10.1016/j.ejca.2019.01.013.

Prioritise the development of biological studies and engage with SM paeds

The strategy for prioritising biological studies is going apace. Bioscientists Suzanne Turner co-chairs the paediatric NHL subgroup and Dr Simon Bomken is a member. Collaborations with national and international groups are being developed and beginning to show results.

Continue to engage with the Hodgkin's Subgroup

Dr Taj maintains links into the NCRI Lymphoma Research Group and its Hodgkin's Subgroup includes paediatric/TYA membership.

Work with TYA and GCT Research Group

Dr. Ben Carpenter is the TYA representative on the group. We are actively collaborating with him to publish pilot data on PET-CT's in T-LBL patients and extend age of entry in planned T-LBL trial.

3. Task groups/Working parties

The Children's Research Group has had no task groups or working parties during the reporting year.

4. Funding applications in last year

Table 2 Funding submissions in the reporting year

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
Cancer Research UK					
May 2019					
rEECur: International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma	Clinical Trial Award (full)	Dr Martin McCabe	Conditionally supported	Group consulted	£ 613,731.17.
IMAGE-ID: Image-guided Multi-modal Annotation of Genetics and tumour micro-Environment In patients with Diffuse glioma	Experimental Medicine Award (full)	Dr Matthew Grech-Sollars	Not supported	No input	
November 2019					
HR-NBL2: High-Risk Neuroblastoma Study 2 of SIOPEN (the International Society of Paediatric Oncology European Neuroblastoma clinical studies group)	Clinical Trial Award	Dr Martin Elliott	Not Supported	Neuroblastoma subgroup developed application; Group consulted	
EsPhALL 2017/COG AALL1631 International Phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones	Clinical Trial Award	Dr Michelle Cummins	Supported	ALL subgroup developed application , Group consulted	£412,520.40.
Other committees					

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
January 2020					
Cipropal study (substudy of ALLTogether trial)	NIHR HTA committee 1st round	Dr Bob Phillips	Proceed to 2nd round May 2020	Group consulted	
ALCL Nivolumab study	CCLG.Little Princess Trust	Dr Amos Burke	Funding granted	Group consulted	89,882.94
February 2020					
HR-NBL2: High-Risk Neuroblastoma Study 2 of SIOPEN (the International Society of Paediatric Oncology European Neuroblastoma clinical studies group)	Application jointly to Neuroblastoma UK and Solving Kids Cancer	Dr Martin Elliott	Successful	Neuroblastoma Subgroup developed application	£609,762.40 £175,000 from Neurolastoma UK and £434,762.40 from Solving Kids Cancer

5. Consumer involvement

Angela Polanco and Loveday Langton

Consumer members of the children's group have remained very active in their roles through the course of the year. Mrs Loveday Langton and Mrs Angela Polanco have represented the voice of parents and children with cancer within the NCRI portfolio meetings and also through appraisal of funding applications and consultancy roles for professionals in the area of childhood cancer research.

Angela has been a co-applicant in funding bids for Wilm's tumour research and has been an active member of the Renal Tumour Special Interest Group through CCLG. She has also been included in authorship of scientific publications of PPI led research initiatives for early phase trial development and more recently as an author for the international guideline for obstetric care of childhood cancer survivors. Ongoing projects also include the JLA priority setting partnership and close links with CRUK to develop their research strategy and evaluate childhood cancer research funding applications.

Angela currently leads the PPI project 'Wilms tumour link group' which has meetings twice a year and has contributed to prioritisation of patient need and also has led the initiation of a PPI parent's group in Brazil using the format from the UK group. Angela has also been appointed as the lead for the European PPI strategy for childhood cancer research alongside CCI Europe and European Society for Paediatric Oncology (SIOPE) and will continue this project into 2021 to improve the way that childhood cancer research is conducted on an international level. Angela is also part of the WHO childhood cancer strategy, advising in a PPI capacity for the communication of information to those affected.

During the challenging period of COVID-19, Angela has worked closely with CCLG and partnering organisations to repurpose a project piloted by Bethany's Wish to support parents of children with cancer with a psychological intervention called HOPE. This project is part of the larger SHARE study and is currently on its second round and has been positively received by parents. Despite the cancellation of the Childhood Cancer Conference UK this year, Angela continues to jointly plan and deliver this conference aimed at the parents, survivors, researchers and professionals working within childhood cancer research.

Angela and Loveday have worked collaboratively with the NCRI Children's Group members to ensure that a parent/patient focus is paramount to childhood cancer research and so that applications meet unmet needs, highlight potential patient benefit and balance scientific/research questions with practicalities for families enrolling poorly children on to a research study. We will continue to advocate in these uncertain times and promote the need for continuing research and development for children with cancer.

6. Priorities and challenges for the forthcoming year

Priority 1 *Portfolio*: Secure funding for known gaps in available/funded portfolio of trials, especially Low Grade Glioma, relapsed AML: improve recruitment to portfolio trials through opening of funded studies such as ALLTogether and FaR-RMS.
Priority 2 *Membership*: appoint CTRad link and nursing representative to group with next round(s) of appointments; review junior members of subgroups in line with new NCRI policy.
Priority 3 *Quinquennial Review* (QQR) : Prepare for QQR review Nov 2020.
Challenge 1 COVID-19: Potential impact of COVID-19 situation on a number of issues important to the group including ability to meet effectively, trial recruitment, trial development, available funding, function of funding awards committees and ability to work with international colleagues- full impact not yet clear.
Challenge 2 Improve recruitment to portfolio trials back to previously excellent levels – a key part of this is to open pending major trials in ALL, rhabdomyosarcoma, high risk neuroblastoma.
Challenge 3 Promote role of NCRI Children's Group in harnessing the wider portfolio of clinical trials in children's cancer (e.g. supportive care, late effects, epidemiology etc) as NCRI portfolio studies.

7. Collaborative partnership studies with industry

In addition to existing partnerships with industry, particularly via the Novel Agents Group for early phase clinical trials, new commercial phase I/II clinical trials currently in set up within the ECMC Network include studies of Olaparib (AstraZeneca), Idasanutlin (Roche), Alectinib (Roche), Venetoclax (AbbVie), Lenvatinib phase II (Eisai), Ramicirumab (Eli Lilly), Erbumine (Eli Lilly), Abemiciclib (Eli-Lilly), 2 Omburtumab studies (YMabs), 2 Ponatinib studies (Incyte, Takeda), Quizarinib (Daichi Sankyo), LOXO292 (LOXO), and a Niraparib/Dostarlumab combination (Tesaro/GSK). Our investigators are very active as key opinion leaders within international early phase consortia (ITCC) and tumour groups (SIOPE, SIOPEN, EpSSG, ITCC Brain, SIOPE-Wilms, IBFM and others) and are able to build collaborative partnerships via these networks.

8. Appendices

Appendix 1 – Children's Cancer and Leukaemia Group and Subgroup strategies

- A – CCL Group Strategy
- B – Central Nervous System Subgroup Strategy
- C – Germ Cell Tumours Subgroup Strategy
- D – Leukaemia Subgroup Strategy
- E – Paediatric Lymphoma Subgroup Strategy
- F – Neuroblastoma Subgroup Strategy
- G – Novel Agents Subgroup Strategy

Appendix 2 – Top 5 publications in reporting year & Group involvement with NICE appraisals

Dr Julia Chisholm (Children's Cancer and Leukaemia Group Chair)

Appendix 1

Children's Cancer and Leukaemia Group & Subgroup Strategies

A – CCL Group Strategy

Strategic Objective	Action	CSG Lead	Date	Outcomes
Portfolio development: Neuroblastoma	Developing overarching trial for newly diagnosed high risk patients. Further development of portfolio of trials for patients with refractory and relapsed disease Exploring new approaches to neuroblastoma therapy eg MIBG, Nivolumab, Cellular immunotherapy (CAR-T cells).	Martin Elliott Guy Makin Juliet Gray	2019	HRNBL2 funding agreed April 2020 MINIVAN, BEACON 2 trials open. VERITAS to open 2020 BEACON 1/2, MINIVAN open
Portfolio development: Leukaemia	Strengthen representation across the CSG. Development of new frontline Acute Lymphoblastic Leukaemia Trial (Pan European).	Leukaemia subgroup chair John Moppett		JM and PA members, further applications to be encouraged Fully funded. Expected to open Q3 2020

	Focus on patients with less curable disease key).	John Moppett		Arms of ALLTogether specifically focus in this area (Abl-class, Down syndrome, high level measurable disease). See also CarT below
	Reducing toxicity and deescalating treatment for patients with excellent survival.	Bob Phillips		Cipropal study submitted for NIHR HTA funding Jan 2020. ASTA trial (Apixiban prophylaxis) under development
	Work towards new study with Philadelphia positive disease.	Michelle Cummins		EsPhALL study funded 2019
	Work with Adult CSG to explore where it is possible to development joint strategy and trials.			ongoing
	Develop strategy for relapsed AML.	Phil Ancliff		Relapsed AML trial Vitality (CPX-351 & Fludarabine) developed and submitted for funding April 2020: PI Gibson
	Continue the implementation of CAR-T cell therapy for ALL / lymphoma.	Persis Amrolia		Cassiopeia (industry sponsored CD19 CarT in high risk de novo ALL), CARPALL (dual CD19/22 CarT in relapsed/refractory ALL) and TT52CAR19 (CRISPR-CAR genome edited allo-CAR in relapsed refractory ALL)

	Establish a CAR-T programme for AML Integrate GE testing into routine care			In pre-clinical development (W Qasim GOSH) GE WGS for acute leukaemia go live date 07/09/2020. Work ongoing to link to trials and cellbank
Portfolio development: Germ Cell	Maintain links with key external stakeholders for international trial design: UK – NCRI TYA and GCT CSG; Gynae CSG; International: MaGIC; G3; EORTC – Develop stronger links with European colleagues via SIOPe GCT	Sara Stoneham Matt Murray/Sara Stoneham/ James Nicholson/Mark Brougham Anthony Penn, James Hayden, Matt Murray, James Nicholson, Mark Brougham, sara Stoneham		AGCT1531 P3BEP MaGIC Clinical Trial design group – co-

	Build on Malignant Germ cell tumour International Collaborative (MaGIC)= UK and US paediatric oncology initiative to create a large trial database that has enabled development of a new risk stratification for extracranial GCT and a frame work for new trial design internationally. For extra cranial:, Low risk: explore opportunities for reducing therapy (e.g. role of biomarkers) e.g. Stage 1 testis cancer > 11yrs High risk, explore new trial design e.g. MAMS Embed biology in all trial design. Engage with TYA CSG to strengthen interface with medical oncologists and paediatric oncologists on subgroup. Publishing joint analyses from MaGIC.			chairs: Sara Stoneham and Dr Robert Huddart A) Immature teratoma consensus conference (Sept 2020) and de-escalation of therapy on AGCT1531 B) Relapsed/refractory paediatric disease – umbrella/ phase 1 consortium - ongoing international discussion C) Poor risk TYA/adult GCT – follow on study from P3BEP in development

	For intracranial – continue SIOPe collaborative Extend links with US/Asia to align language/risk stratification and marker thresholds internationally Embedding biology into all trial design			Joint publications from MaGIC using MRC data (TYA outcomes) and TYA CSG +GCT members to develop national consensus guidelines IC GCTIII in development with SIOpe Joint publications from MaGIC completed Establishment of a GCT 'data commons' Funding and ethical approvals obtained to facilitate collection storage and study.
Strategic Objective		**CSG Lead**	**Date**	**Outcomes**
Portfolio development: Bone Tumour	Continue development of Ewing Studies. Osteosarcoma remains a major gap in the portfolio and a strategic aim will need to collaborate internationally.	YOSS Subgroup Chair / Chairs CCL and Sarcoma CSGs		ICONIC study funded and opened 2019

	Improve strategic relationship with sarcoma CSG to ensure access of sarcoma studies to paediatric patients. Focus on survivorship, patients routinely disabled. Local therapy questions (radiotherapy) for next Euro Ewing's Study. Formalise reporting from bone sub group to CCL CSG (similar to YOSS)	CTRad Link		Included in trial design
Portfolio Development: CNS tumours	Trials available for all tumour groups			Progress in 2019-20; number of trials expected to open in next year and more in planning including UK led high risk medulloblastoma study within Europe

	Molecular diagnostics informing all trials To be European leader in brain tumour trials To run biological studies to identify those patients whose treatment can be reduces, and those for whom novel treatment strategies are available Note Gaps in portfolio (e.g. embryonal)			(on hold until COVID crisis over but ready to open) In place for a number of tumour types and will be integrated with genomic hubs. SMP paeds open and recruiting for determining targets for relapsed tumours Genomics England and SMPaeds UK leading new high risk medulloblastoma study within Europe These are in place for a number of tumour groups and continue to inform stratification of both current and trials planned in the future.
Portfolio Development: Novel Agents Group	Consider structure, size and succession planning within Novel Agents Subgroup.	Chair Novel Agent subgroup	May 2018 Oct/Nov 2018	Dr Lynley Marshall appointed as incoming Novel Agents Subgroup chair

	Following the paediatric ECMC renewal and launch of SMPaeds and of ESMART, further development of novel agent trials and longitudinal sampling studies		Nov 2019 Ongoing	Two new paediatric oncology national grid trainees appointed to group (Dr Charlotte Burns & Dr Vijal Parmar) New consumer representative appointment to the group, pending acceptance and confirmation. Ongoing collaboration with a former consumer representative, Chris Copland, in his capacity as co-chair of the ACCELERATE FAIR Trials Group (Fostering Age-Inclusive Research). Dr Marshall & Chris Copland co-chair the UK FAIR Trials Group, with support via the NIHR (Sub-Specialty Lead Dr Amos Burke, Dr Shamaila Anwar) Decision to continue wider Novel Agents Network Subgroup meeting attendance in addition to the NCRI Core Novel Agents Subgroup,

	Increase links with tumour site groups – leading early phase studies (in collaboration with site specific groups) Ensure good links with science as well as clinical communities Build capacity in preclinical research (eg via membership of translational programmes eg the 3 centre INSTINCT Brain Tumour Consortium) Build expertise in area of epigenetic			to ensure adequate centre, disease type (solid, CNS, haematological malignancies), and professional group representation (paediatric/TYA medical oncologist, research nurse, clinician scientist, translational/ laboratory scientists/trainees) to maximise opportunities to broaden the Novel Agents clinical trial and biomarker portfolio across areas of unmet medical need. Outcome = new trials/trial arms. Close co-ordination between Novel Agents Subgroup Chair/Subgroup and Paediatric ECMC Programme Office/Co-ordinator, using ECMC network confidentiality agreement to facilitate rapid expert review of proposed new pharma-sponsored early phase trials and quick, co-ordinated responses to

	targeting (membership attendance at ACCELERATE paediatric Strategy Forum on Epigenetic Modifiers, Philadelphia, January 2020)			expression of interest calls for trial participation. This will help develop and select the best possible studies for UK patients and make the UK attractive to sponsors for setting up and conducting studies efficiently. Outcome will be UK participation +/- leadership on new commercial trials Development of new academic trials/trial arms within basket/adaptively designed trials with sponsors inside and outside of the UK, by ensuring UK clinical and biology experts are embedded within European and other international consortia, both tumour-specific groups and more generic biology and early phase trial consortia (eg ITCC, SIOPEN, SIOPE, EpSSG, IBFM and others). Outcome will be UK participation +/- leadership on new

				academic investigator-initiated trials. Build network collaboration and optimise use of preclinical resources by facilitating joint posts and/or projects across translational laboratories and centres affiliated to the Subgroup eg via clinical/research fellowships, joint grant proposals etc. Outcome = more clinical trials/arms/biomarker studies originating from UK centres. Translational outputs within clinical trials via links with Subgroup-affiliated laboratories; clinical trials/trial arms of agents targeting epigenetic mechanisms of action as these become increasingly better understood, preclinical data supports and clinical compounds become available.

Portfolio development: Radiotherapy	Increased number of radiotherapy trials (eg IMAT/HRNBL2/FaR-RMS)) Consider development of trials in Proton Beam Radiotherapy Maintain direct links with CTRad Work with European colleagues on the SIOPE/QUARTET platform to enhance radiotherapy quality assurance in paediatric trials	Henry Mandeville NB Subgroup Chair		More trials with randomised radiotherapy questions open and recruiting. Recruitment of patients treated with protons in radiotherapy trials. Study day with CTRad and TYA CSG planned Far-RMS HRNBL2 PNET V
Portfolio development (Systemic Anti-cancer Therapy)	Explore opportunities to use non-conventional chemotherapy e.g. immunotherapy.	Juliet Gray Deborah Tweddle		MINIVAN

	Develop pharmacokinectic studies e.g. liquid 13 Cis-retinoic acid.			
General Trial Delivery	Working in partnership with European Trials (particularly when not led in UK) Ensuring adequate clinician time for contribution to clinical research and paediatric oncology. Managing complex external research approaches e.g. CED and Mexico (DIPG) Need to work with partners outside of the NHS (where evidence base exists).	CRCTU NIHR lead Chair Novel Agents ALL CSG Chair and NCRI lead		Included in ACGT153/GC4 trials (germ cell)

	PROMs to be considered in clinical trial design across paediatric trial portfolio. Work with NIHR to ensure appropriate mapping of funding for the radiotherapy component of multicentre trials			
Personalised medicine/genomic strategy	Seek opportunity for genomic sequencing within paediatric cancers e.g. full genomic sequencing for patients with ALL. Focus on rarer diseases where unanswered questions remain e.g. APL, Downs, Leukaemia. Consider clinical leads for each tumour site to	Chair Novel Agents Subgroup Chairs PPI leads		Genome England due to come on board 2020 Ongoing

	coordinate GEL Work. Ensure PPI involvement in genomic and SMP Studies (e.g. Ethics and Biopsy). Maintain direct links with paediatric ECMC network			

Strategic Objective	Action	CSG Lead	Date	Outcomes
Relapse	Maintain focus regarding research questions at time of relapse across all paediatric cancers			
Survivorship and Long Term Follow Up	Strengthen the portfolio of studies in the area of LTFU/Late Effects. Invite Chair of Late Effects SIG to CSG. Identify lead for late effects and long term follow up studies	CSG Chair NCRI support		

	Focus on patients with bone tumours in whom the majority have a disability following therapy.			
Consumer involvement	Identify points where consumers can support trial development outside the CCL CSG process (e.g. lowering age limits in adult site specific trials and liaising with other CSGs and wider trial development. Develop role in genomics (e.g. ethical approaches to tumour biopsy) Development of long term follow up studies Collaboration with TYA CSG about transition from paediatric to TYA care	Consumer representatives CSG Chair with TYA lead		
Pathology	Appointment paediatric pathologist to CSG.	NCRI support		Completed March 2019

	Maintain directs links with CMPath Recognition of pathology and radiology timeline in grant applications. Need to link with Biological Studies Steering Group within CCLG tumour bank. Strongly support TYA biological studies and strengthen interface with TYA Group.			
CSG Structure and Function	Ensure appropriate succession planning across the CSG. Encourage next generation of researchers Identify routes by which UK can participate in NCI Studies and collaborate with	CSG Chair All CRCTU and all members		Annual review Trainee scheme ongoing

	International Groups. Work with CRUK to ensure data collection within ECMC Paediatric Network is joined up Explore interface with NIHR (e.g. Just In Time initiative) and other funders. Work with partners (e.g. CCLG and CRCTU) in ensuring dissemination of key results from research. Review annual Clinical Trials Study day; closer collaboration with CCLG	NIHR lead and CSG chair CSG chair		CCLG/NCRI Annual Trials Meeting brought together in 2020

B – Central Nervous System Subgroup Strategy

Strategic aims

- Improve Event Free and Overall Survival for all patients CNS tumours with a poor prognosis and reduce morbidity and long-term toxicity in those with good risk CNS tumours.
- To better identify prognostic and predictive biomarkers and to implement their use in clinical trials using routine real time molecular diagnostics for all CNS tumour types.
- Increase the number of trials for children with CNS Tumours
- Better Identify prognostic and predictive biomarkers and implement their usage.

Improve Event Free and Overall Survival for all patients CNS tumours with a poor prognosis and reduce morbidity and long-term toxicity in those with good risk CNS tumours.

This is being achieved by the introduction of new trials which stratify patients using clinical and molecular biomarkers (eg treatment reduction in PNET 5 for very good risk children with medulloblastoma and intensification of treatment or novel treatments in those with a poor outcome). More detailed molecular testing and the development of new biomarkers further enhances this. Detailed quality of life and neurocognitive outcomes are mandatory in all new trials to document changes in these parameters.

Biomarkers.
Development and discovery of new biomarkers are being discovered and subsequently tested in prospective clinical trials for a number of CNS tumours. Proven molecular biomarkers have been introduced into routine clinical practice after development in research laboratories. Real time molecular testing is routine for some tumour types and will become more widespread with the opening of the genomic hubs. Molecular guided therapy at relapse is becoming more commonplace with the opening of SM-Paeds and its associated E-smart early phase trials programme.

Trials
The number of clinical trials for children with CNS tumours needs to be increased. This will be done at a European level due to the rarity of the diseases. There are a number of trials in development as well as some diseases for which there are no planned trials and alternative strategies need to be developed.

The following trials are open in the UK (all pan European)

- Ependymoma 2 for all children and young people with ependymoma,
- PNET 5 for standard risk medulloblastoma
- BIOMEDE for Diffuse intrinsic pontine glioma
- VINILO for low grade glioma

The following are in late stages of development and have been through the CNS subgroup.

- High Risk Medulloblastoma, funded by CRUK/Brain Tumour Charity (2018), UK led pan European SIOPE study run by CRCTU (Birmingham), will be open in June 2019.
- LOGGIC – SIOPE study for children with low grade gliomas, open in Germany 2019, planned in UK for 2020, funding application to be submitted in 2019.

- ATRT - SIOPE study for children with ATRT, funding application in UK 2019.
- Infant medulloblastoma –SIOPE study for children with children under 3 with medulloblastoma in mid development, potentially funding to be sought 2020.
- CED – convection enhanced delivery of chemotherapy in children with diffuse Intrinsic pontine glioma run by the Sarah Cannon Research Institute in Harley Street. This is awaiting approval by the main CSG and is in late development.
- NIVIGlio for High grade glioma is open in France and funding will be sought in the UK in the near future.

These trials are all underpinned by real time central pathology and radiology review as well as the QUARTET radiotherapy quality assurance initiative for all upcoming and some current trials. Many of the trials have molecular biomarkers in order to stratify treatment. In addition, the majority of trials have a mandatory quality of survival studies built in.

Application of molecular diagnostics to routine clinical practice

The development of funded centralised routine molecular diagnostics and pathology review for all children with CNS tumours is in development via regional hubs and should be live by mid-2019. This is already in place however for all children with medulloblastoma including for the PNET5 trial and the upcoming high risk and infant trials. This process for other CNS tumour types are in earlier stages of development although a central review process is in place for ependymoma with a weekly national MDT.

C – Germ Cell Tumour Subgroup Strategy

Key aim

To improve overall survival and quality of survival for all patients diagnosed with a GCT.

Strategic aims

Intracranial

- SIOPe CNS GCT collaborative
- Extend links with US and Asia
- Trial Development in IC GCT

- Continue pan-European collaboration with SIOPe; led by UK
- Align language – risk stratifications, marker thresholds etc with COG
- View to aligning next trial design based on ACNS 1123 COG and SIOP CNS GCT II
- Embedding CSF/serum microRNA into trial development
- Under consideration:
  - NGGCT – high risk – intensification, role of HDT
  - Germinoma

- Chemo de-escalation randomisation
- RT de-escalation randomisation

Extra-cranial

- Maintain and develop links with external stakeholders:

- UK
  - NCRI Teenage & Young Adults and Germ Cell Tumour CSG
  - NCRI Testis
  - NCRI Gynae
- International
  - MaGIC
  - G3
  - EORTC via IRCI

Trial development in EC GCT

- Develop common language between stakeholders
  - for staging
  - for risk grouping
  - For surgical approach
- Find shared questions important to answer for stakeholders
  - e.g. role of HDT in relapse
  - role of microRNA in disease; role of biomarkers of toxicity across all trial design
  - PROMs the same between male and female, TYA and adults.

More specifically:

- Low risk
  - More surveillance. Less chemotherapy. More use of biomarkers.
- Standard risk
  - Less overall dose of chemotherapy. Less toxic chemotherapy.
- High risk
  - Earlier identification of these patients. MAMS trial design- against winner of P3BEP.
- Relapse
  - Son of TIGER - Randomised induction and HDT regimens – international
  - Paediatric – Umbrella trial vs. basket trial options

D – Leukaemia Subgroup Strategy

Strategic aims

- Open international trials for Ph-positive and infant ALL.
- Continue monitoring recruitment to MyeChild01.
- Open ALLTogether
- Develop a cohesive strategy for relapsed ALL.
- Contribute to international collaborations in CML and MDS.
- Open registries with linked biological sample collection and studies for APL, DS-AML, CML and MDS.
- Liaise with new agents group to increase portfolio of phase I and II leukaemia trials testing antibody and cellular therapy and targeted agents, especially for T-cell and AML where there is an unmet need.

E – Paediatric Lymphoma Subgroup Strategy

Paediatric NHL Subgroup (MT) • Ensure successful delivery of Subgroup portfolio especially phase III studies • Finalise the next T-lymphoblastic lymphoma trial • Work with the TYA/GCT CSG • Exploit the increased number of agents available as a result of the legislation around PIPs • Prioritise the development of biological studies • Open ALCL Nivolumab trail • Continue to engage with the Hodgkin's SG • Engage with SM-Paeds (CCL CSG)	• Finalise the next T-lymphoblastic lymphoma trial • Work with the TYA/GCT CSG • Work closely with EICNHL and ITCC groups • Work closely with biological lead ST • Currently going through funding process • Work collaboratively with Hodgkin SG • Work with the team to set up paeds lymphoma panel	MT and SG members SG members SG members SG members SG members SG members MT and SG members	Q1 2020 Q2 2020 Q2 2020 Q2 2020 Q2 2020 Q1 annually Q1 annually

F – Neuroblastoma Subgroup Strategy

Strategic aims

1. Improve Event Free and Overall Survival for all Neuroblastoma patients.
2. Diagnosis, staging and risk stratification: Refine the prognostic significance of tissue and imaging biological markers and integrate them into stratification of treatment groups in clinical trials.
    - Finalise analysis in current HR study of data linking biological markers and radiology, specifically mIBG scans 2016.
    - Evaluate FDG PET and mIBG PET.
    - Undertake an international retrospective study of ALK mutation testing and next generation sequencing for selected genes from banked DNA samples from patients treated on the high-risk Neuroblastoma trial.
3. Define molecular targets in NBL: Introduce molecular targeted treatments upfront into ultra-high risk and relapsed patient studies.
    - Continue to increase the portfolio of molecularly driven early phase trials for patients with relapsed neuroblastoma in conjunction with the NCRI New Agents Subgroup.
4. High Risk NBL
    - Continue to enrol all eligible UK patients in the SIOPEN HR trial.
    - Work with the European group to develop the next high-risk trial for 2017.
        - Induction chemotherapy: Continue enrolling into R3 to evaluate the best induction regimen.
        - Local therapy: Establish evidence for current local therapy in HR NBL, radiotherapy dose and extent of field and timing and extent of surgical excision of primary tumour.

- Immunotherapy: Define and refine immunotherapy administration to maximise effectiveness and minimise toxicity.
  - Get the R4 in HR NBL 1 open in the UK and in all centres by 2015 Q3.
  - Open the Phase 1b trial of zoledronate and IL-2 combined with ch14.18 anti-GD2 antibody 2015.
  - Facilitate data collection and analysis regarding immunotherapy in HR study and LTI study 2017.
- Surveillance: Monitor off treatment HR patients with imaging and molecular monitoring and link with clinical data to better understand patterns of relapse.
  - Set up a randomised maintenance treatment study with biomarker monitoring alongside maybe including DFMO 2016.
- Refractory disease
  - Get SIOPEN Veritas clinical trial open in the UK by 2016.
- Relapsed disease: To better understand the biology and clinical characteristics of relapsed Neuroblastoma.
  - Continue recruitment into BEACON study and get amendment through UK regulatory process for additional third randomisation with TOTEM 2015.
  - Await outcome of a grant application for a national retrospective genetic and Epidemiological study of relapsed Neuroblastoma 2015.

5. Low and Intermediate Risk NBL: Facilitate registration and collection of toxicity and outcome data for these Neuroblastoma patients who are not currently treated within a clinical trial as unable to get the SIOPEN LINES trial open in the UK in 2012.
   - Participate in the PICORET study, a Horizon 2020 project that is comparing outcome in comparable patients treated within and without a clinical trial. Await grant application 2015 Q4 and, if favourable, participate.
   - Achieve UK participation in the SIOPEN spinal cord compression study 2015/16.
   - Plan for involvement in next low and intermediate risk NBL trial if it involves further randomisations.

G – Novel Agents Subgroup Strategy

Strategic aims

- To continue to develop and deliver novel agent studies for children and TYA across the cancer spectrum in partnership with academic and industry partners, with a focus on more combination studies.
- To focus on novel agents for poor prognosis tumours at diagnosis and relapse in collaboration with tumour specific subgroups.
- To develop and deliver biomarker and pharmacokinetic studies.
- Following successful CRUK funding of the Stratified Medicine Paediatrics (SMPaeds), the implementation of a National molecular platform to genomically characterise relapsed solid paediatric cancers and a National Molecular Tumour Board to interpret “actionable mutations” and facilitate precision medicine trials by triaging patients based on biology.
- The Paediatric ECMC Network will develop 4 regional groups covering the whole of the UK to allow coordination and discussion of paediatric relapse cases to consider clinical trials and link with the SMPaeds programme and National Molecular Tumour Board.
- Work with ECMC Network to develop an online clinical trials finder to improve awareness of portfolio clinical trials and promote wider access.
- To link with more academic groups working in basic/ translational science at an early stage with the Novel Agents group to help define and develop promising new targets/ therapies along with colleagues in ECMC combinations alliance and CRUK Centre for Drug Development.

Appendix 2

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	Group involvement in the trial
1. NGS pilot study George S et al A tailored molecular profiling programme for children with cancer to identify clinically actionable genetic alterations European Journal of Cancer 121 (2019) 224-235	This was the national Next Generation Sequencing Pilot study which has led to the successful funding and opening of the SMPaeds study, the UK national molecular profiling platform for relapsed paediatric tumours.	Directly developed by Novel Agents Group members.
2. Interfant 06 study Pieters R, et al. Outcome of Infants Younger Than 1 Year With Acute Lymphoblastic Leukemia Treated With the Interfant-06 Protocol: Results From an International Phase III Randomized Study. J Clin Oncol. 2019 Sep1;37(25):2246-2256. doi: 0.1200/JCO.19.00261. Epub 2019 Jul 8. PMID: 31283407	This was the first international randomised trial in infant acute lymphoblastic leukemia (ALL) which is characterized by *KMT2A* (*MLL*) gene rearrangements and coexpression of myeloid markers. The study, tested whether myeloid-style consolidation chemotherapy is superior to lymphoid style, the role of stem-cell transplantation (SCT), and which factors had independent prognostic value. The trial found that early intensification with postinduction myeloid-type chemotherapy courses did not significantly improve outcome for infant ALL compared with the lymphoid-type course treatment.	The trial was developed internationally and endorsed at national level by the leukaemia subgroup of the Children's Research Group. A new UK only Infant ALL trial is under development by the subgroup.
3. UK GC III study (predating NCRI)	Confirmed that carboplatin-based chemotherapy as part of a risk-stratified approach leads to	Manuscript prepared by GCT subgroup members

Depani et al Results from the UK Children's Cancer and Leukaemia Group study of extracranial germ cell tumours in children and adolescents (GCIII). Eur J Cancer. 2019 Sep; 118:49-57. doi: 10.1016/j.ejca.2019.05.001	excellent survival in paediatric MGCTs, minimising potential burden of long-term effects.	Data form the basis of the successful funding application to CRUK for the AGCT1531 study which will include a comparision of cisplatin v carboplatin in Standard Risk Paediatric and Adult Patients with Germ Cell Tumours .
4. Ludo Study (molecular radiotherapy in neuroblastoma) Gains et al. A phase IIa trial of molecular radiotherapy with 177-lutetium DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma. Eur J Nucl Med Mol Imaging. 2020 Mar 11. doi: 10.1007/s00259-020-04741-x	This was a CRUK -funded single-centre, single-arm, two-stage clinical trial to evaluate the safety and activity of 177-lutetium DOTATATE (LuDO) molecular radiotherapy in neuroblastoma. Although there were no objective responses this study demonstrated the ability of the UK to conduct molecular radiotherapy studies in neuroblastoma, now being realised again in the VERITAS study which is due to open shortly	Developed and led by Dr Mark Gaze, previous Children's Group member and neuroblastoma subgroup Chair
5 Oral Dabrafenib In Children and Adolescents Hargrave DR, et al Efficacy and Safety of Dabrafenib in Pediatric Patients with *BRAF* V600 Mutation-Positive Relapsed or Refractory Low-Grade Glioma: Results from a Phase I/IIa Study. Clin Cancer Res. 2019	Dabrafenib demonstrated meaningful clinical activity and acceptable tolerability in patients with *BRAF* V600-mutant pLGG. These efficacy data have informed the design of a trial in BRAF-mutated low grade glioma, currently submitted to CRUK for consideration of funding.	Group members directly involved in trial design and international trial leadership (Dr Hargrave)

Dec 15;25(24):7303-7311. doi: 10.1158/1078-0432.CCR-19-2177.		