NCRI Children's Cancer and Leukaemia (CCL) Group

Annual Report 2020 - 2021

NCRI Partners

NCRI is a UK-wide partnership between research funders working together to maximise the value and benefits of cancer research for the benefit of patients and the public. A key strength of the NCRI is our broad membership with representation across both charity and government funders as well as across all four nations in the United Kingdom.

List of Appendices

NCRI Children's Cancer and Leukaemia Group

Annual Report 2020-21

1. Top achievements in the reporting year (up to three)

Achievement 1

Portfolio development

- The Group has continued to deliver on its wide-reaching portfolio of trials across the full range of paediatric cancer subtypes.
- In the reporting period a number of key frontline (ALLTogether1- acute lymphoblastic leukaemia), overarching (Frontline and Relapse Rhabdomyosarcoma, FaR-RMS) and relapse/refractory (VERITAS) trials have been opened as well as early phase trials enabling access to targeted drugs such as Olaparib, Venotoclax, Ramicirumab, Erbumine, Lenvatinib, Selpercatinib (see Novel Agent Subgroup report). Some trials include not only systemic therapy questions but also surgery/radiotherapy research questions (VERITAS, FaR-RMS).
- Trials funded include the Cipropal, a supportive care substudy of ALLTogether1 and a CRUK supported Cerebrospinal Fluid flow substudy of ALLTogether1 and 2 CRUK endorsed, pharma funded studies (DETERMNE, Low Grade Glioma NF1 study) and the CRUK funded LOGGIC study in low grade glioma.
- Trials developed by the Group and seeking funding currently include GLO-BNHL, and Olaparib with MIBG therapy in relapsed neuroblastoma.

Achievement 2

Genomic/precision medicine

- The next generation sequencing panel developed for our portfolio StratMedPaeds study for relapsed solid tumours has been approved as the paediatric Next Generation Sequencing (NGS) panel for standard NHS use in newly diagnosed patients.
- Numerous industry collaborations for access to targeted agents have been realised both as new arms for the current ESMART portfolio study and as new precision basket trials in solid tumours (DETERMINE, TAPISTRY) and leukaemia (HEM-iSMART)
- Access to a number of targeted therapies through industry sponsored early phase studies in collaboration with the ECMC network (see Novel Agent Subgroup report).
- Opening of an investigator-led study led from Great Ormond Street Hospital ("liquid biopsy study") for monitoring circulating tumour DNA (ctDNA) for early detection of relapse and tracking response to novel treatments.

Achievement 3

Changes in practise arising from the Group's work

Examples include:

- The Liquid cis-retinoic acid study, a UK study, led by D Tweddle tested a new liquid formulation of 13-cis-retinoic acid. 20 patients were recruited in 2018-19, demonstrating good bioavailability and palatability for children unable to swallow capsules (Cancer 2021). The liquid preparation is now available as a standard of care.

- As a result of the Inter – B-NHL high Risk Rituximab trial, B-NHL guidelines have changed. All newly diagnosed high risk NHL patients now are treated with Rituximab plus standard chemotherapy resulting in improved survival (NEJM 2020).
- As a result of StratMedPaeds study, consideration of biopsy at relapse for the purpose of advanced molecular tumour profiling to guide future therapy and clinical trial entry wherever possible has become a new standard of care.

2. Structure of the Group

Between April 2020 and March 2021 there were few changes to the main Children's Research Group owing to the recruitment freeze resulting from the COVID-19 pandemic. For this reason, there has been a vacancy on the Group for the reporting period.

Invited member Dr Amos Burke left the Group in March 2021 when he stepped down from his role as National Institute for Health Research (NIHR) Clinical Research Network (CRN) Cancer National Specialty Lead for Children and Young People's Cancer. His successor, Dr Martin Elliott, is already a member of the Children's Group in his own right.

One of our Consumer members, Angela Polanco stepped down from the Group following our meeting in April 2021 and will be much missed for her energy and contribution. She will be replaced in 2021.

Dr Mark Broughton succeeded Dr Sara Stoneham as Germ Cell Tumour Subgroup Chair and Dr John Moppett succeeded Dr Phil Ancliffe as Leukaemia Subgroup Chair in June 2020.

The freeze on recruitment has affected the Subgroups where formal appointment of new trainees has been on hold. All Subgroups except the Germ Cell Tumour Subgroup have current trainee members and the Germ Cell Tumour Subgroup has identified a junior member to invite informally onto the group as an interim measure pending formal, competitive appointments later in 2021. All the trainees are actively contributing to their respective subgroups.

There are some very good examples of multidisciplinary research. E.g.:

- In the Neuroblastoma Subgroup nursing researcher Helen Pearson is being supported to develop a treatment decision support tool for parents of children with relapsed neuroblastoma
- A study of the pharmacokinetics of a liquid preparation of 13 cis retinoic acid study as a pharmacology/clinical collaboration arising within the Novel Agent Subgroup has led to the availability of the liquid formulation in standard clinical use, important as neuroblastoma is typically a disease of very young patients.
- Within the Novel Agents Subgroup, a preclinical study of the CDK9/2 inhibitor fadraciclb from the Chesler laboratory has now led to the inclusion of the drug in 2 arms of the eSMART study.
- Subgroups include both clinicians and scientists leading to the embedding of biological and biomarker studies into mainstream clinical trials (see Subgroup reports below for highlights).
- See top 5 publications 2020-21.

3. CCL Group & Subgroup strategies

CCL Group (Chair, Dr Julia Chisholm)

It was noted in feedback from the 2019-20 report that the Group's strategy lacks overarching strategic aims. This will be formally addressed at our next strategy review day planned for late 2021 where we will also refresh our consumer involvement strategy.

A James Lind Alliance (JLA) Priority Setting Partnership exercise is ongoing to determine the top 10 priorities to be addressed in children's cancer. The output is expected in 2022. This will inform the Group's strategy and help to focus funding applications.

Our 5 overarching aims can be described as follows, recognising the need for consumer involvement in every aspect of our work (see Appendix 3 for the full current strategy):

1. **Portfolio development to make available world class, cutting edge clinical trials for the major paediatric cancers especially the commonest tumours, high risk tumour types, those with a high unmet medical need, relapsed patients and those where there are unanswered questions.**

Progress

- Opening of Frontline and Relapse Rhabdomyosarcoma Study, ALLTogether Study, VERITAS
- Successful funding applications for the following trials: Cipropal Substudy of ALLTogether study in acute lymphoblastic leukaemia (NIHR HTA); CSF Flow Substudy of ALLTogether1 (CRUK funded); NFI Low Grade Glioma Study (AstraZenica funding, CRUK endorsed); DETERMINE study (relapsed solid tumour platform biomarker-driven study using licensed drugs for unlicensed indications, Roche supporting, CRUK endorsed), LOGGIC study in low grade glioma (CRUK funded).
- Trials in development: there are a number of trials and substudies at various stages of development including some where funding is currently being sought (GLO-BNHL, ALLTogether1 risk stratification substudy, Olaparib in neuroblastoma).

2. **Integration of biological studies and biomarker studies within clinical trials.**

Progress

This is now routinely considered for all frontline and relapsed clinical trials as well as early phase trials. Examples from recently developed late phase trials include:

- Biological substudies for the ALLTogether1 (acute lymphoblastic leukaemia) and MyeChild (acute myeloid leukaemia) studies.
- Frontline and Relapse Rhabdomyosarcoma study: the frontline component includes PET, MRI and molecular biomarker substudies and new randomised phase II/III relapse study evaluating vincristine, irinotecan and regorafenib against standard of care vincristine, irinotecan and temozolomide developed in collaboration with the pharmaceutical company Bayer, will include also include molecular, imaging and circulating tumour DNA biomarker work.
- Within the GLO-BHL ACCELERATE platform study in non Hodgkins lymphoma (funding being sought) an embedded translational project will improve understanding of the biology of relapsed disease.

Please see Subgroup reports for more details of specific translational and biological studies.

3. **Focus on genomic/precision medicine**

Progress

This has been a very major focus and area of success for the Novel Agents Group and is described in detail in its Subgroup report. Highlights include:

- The next generation sequencing panel developed for our portfolio StratMedPaeds study for relapsed solid tumours has been approved as the paediatric Next Generation Sequencing (NGS) panel for NHS use in newly diagnosed patients.
- Numerous industry collaborations for access to targeted agents have been realised as new arms for the current ESMART portfolio study and new precision basket trials in solid tumours (DETERMINE , TAPISTRY) and leukaemia (HEM-iSMART)
- Access to a number of targeted therapies through industry sponsored early phase studies in collaboration with the ECMC network (see Novel Agent Subgroup report).
- Opening of an investigator-led study led from Great Ormond Street Hospital ("liquid biopsy study") for monitoring circulating tumour DNA (ctDNA) for early detection of relapse and tracking response to novel treatment.

4. **Focus on surgery and radiotherapy as well as systemic therapies**

Progress

- A surgical sub-study was published on the HR-NBL-1 trial population, led by Keith Holmes, former member of the Subgroup (Holmes et al JCO 2020), identifying the prognostic role of residual tumour volume post-surgical resection.
- The Neuroblastoma Subgroup (H Gabra) has contributed to the developed of a standardised surgical report form for clinical trials (Annals Surgery 2020).
- Clinical Oncologist Dr H Mandeville has been closely involved in the development of the international SIOPE/QUARTET platform (which went live in early 2021), working with the UK Radiotherapy Trials Quality Assurance group to improve Quality Assurance in paediatric radiotherapy. He is also leading radiotherapy randomisations and an evaluation of the sequencing of surgery and adjuvant radiotherapy as a randomised question within the new FaR-RMS study.

5. **Supportive care questions and Patient Reported Outcome Measures (PROMs) embedded within clinical trials**

Progress

Recent examples include:

- Funding of the Cipropal substudy of the ALLTogether study looking at the role of antibiotic prophylaxis during induction chemotherapy in Acute Lymphoblastic leukaemia
- Embedding Quality of Life questions in both Frontline and Relapse components of the FaR-RMS trial in rhabdomyosarcoma with current development of a validated paediatric sarcoma PROM for future use.

During the COVID-19 pandemic in 2020-21 trial recruitment remained open for all trials except StratMedPaeds, eSMART and PNET 5, all of which subsequently reopened. The response in individual treatment centres varied, with some suspending trial recruitment and others continuing. However, by the autumn of 2020 centres were returning to normal for trial recruitment. As a result of the COVID-19 pandemic, CRUK reviewed all funded trials in a formal portfolio review in July 2020: the Children's Research Group successfully defended all its CRUK-funded ongoing studies, retaining the support of CRUK to continue and complete them. The 2020 CRUK Spring funding awards committees were deferred until November but even at this timepoint no new trials were reviewed. The first CRUK committee to review new trial proposals was in Spring 2021.

Central Nervous System Subgroup (Chair, Professor Simon Bailey)

The CNS Subgroup has wide representation including paediatric neuro oncology, paediatric radiation oncology, paediatric neurosurgery, paediatric neuropathology paediatric neuroradiology, paediatric neuro-pyschology and parent/public representation. The CNS Subgroup has a wide range of trials over many disease types that are open or in planning. All of the Subgroup's trials are European (usually through SIOPE) or worldwide trials due to the rareness of the conditions treated. European level UK researchers, including many CNS Tumour Subgroup members, are involved in the development of the next generation of trials to replace those already open and recruiting. The Subgroup continues to make good progress against its aims:

1. **Increase the number of trials for children with CNS Tumours**

The following interventional phase 3 trials are currently open in the UK:

1) Ependymoma 2 (UK CI Professor Grundy: CRUK funded, 156 recruited in UK), the UK is the highest recruiting country.
2) High Risk medulloblastoma (850 patients over 8 years: European CI Professor Bailey – led by UK and open and in the near future in 16 countries – CRUK funded).
3) International cerebellar mutism study (UK CI - Professor Mallucci) is nearing completion (150 UK patients).
4) PNET5 Standard Risk Medulloblastoma (UK CI – Dr Jorgensen).

There are a number of trials which should open within the next two years. These are:

1) NF1 – Low grade glioma G (European CI Professor Hargrave – funding in place)
2) LOGGIC for children with low grade glioma (UK CI Professor Hargrave) Funding approved by CRUK. 294 patients across Europe – 4.5 years.
3) BIOMEDE 2.0 (UK CI – Professor Hargrave) for diffuse midline gliomas.
4) Atypical Teratoid Rhabdoid tumours (UK CI- Dr Steven Lowis – funding applied for CRUK – 152 patients).
5) Infant medulloblastoma (UK CI – Professor Bailey – funding to be applied for via CRUK- awaiting German funding) 64 patients.

Our clinical trials are also the vehicle for our second strategic aim:

2. **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**

The multidisciplinary nature of the Subgroup has enabled all the aspects of the patient treatment journey to be represented in trial development.

In last year several non-commercial trials have been completed but most not yet formally published. These include:

1) Biomede 1.0 (DIPG)
2) Vinilo (LGG)

There are also a number of early phase studies both having been completed and in progress as well as being planned.

3. **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.**

The CNS Subgroup has pioneered the routine use of molecular stratification especially in medulloblastoma trials and though the central reference system we have been able to incorporate centralised molecular testing via NHS England in a relatively seamless manner.

Germ Cell Tumour Subgroup (Chair, Dr Mark Brougham)

Germ cell tumours are rare in childhood and as such trials require collaboration with multiple countries and other disciplines, particularly colleagues in Adult Testis and Gynaecology groups. We are actively involved in several open and forthcoming trials to meet our strategic objectives for extracranial and intracranial germ cell tumours.

Strategic Objectives

1. **Extracranial Germ Cell Tumours**

AGCT1531 trial
A phase 3 study of active surveillance for low risk and a randomised trial of carboplatin vs cisplatin for standard risk paediatric and adult patients with germ cell tumours. This trial involves surveillance for low risk patients (age 0-50 years) and a randomisation between carboplatin and cisplatin for standard risk patients aged 0-25 years. This trial includes translational biology, toxicity monitoring and Patient Reported Outcome Measures. This is open in other countries with recruitment progressing well. Funding application was successful from CRUK and is due to open in the UK later this year.

UKP3BEP trial
An international, randomised, phase 3 trial of accelerated versus standard BEP (bleomycin, etoposide, cisplatin) for patients aged 11 to 45 years inclusive, with intermediate and poor-risk metastatic germ cell tumours. Recruitment has been progressing well, with around 150 patients recruited internationally thus far, although has been difficult within paediatrics due to the limited sites open and has been affected by COVID-19. Because of these delays, consideration is being given to applying for additional funding. As of March 2021, 42 patients have been recruited in the UK.

TIGER trial
An international, randomised study for patients with relapsed or refractory germ cell tumours. Thus far 345 patients out of a target of 420 have been enrolled, although recruitment in the UK has been challenging, in part due to COVID-19, and the timeline to completion is uncertain at present.

Role of biological markers in risk stratification and response assessment
Whilst AFP and HCG have an essential role in the diagnosis and response assessment of germ cell tumours, the utility of certain microRNA sequences is increasingly recognised. These are both sensitive and specific and can be measured in serum and, for CNS tumours, in CSF. Whilst this is currently a research tool such analysis is embedded into clinical trials. This includes an application to allow formal testing on AGCT1531 samples.

Optimising treatment for metastatic seminoma/ dysgerminoma
In terms of chemotherapy, cisplatin-based options tend to be used in this context. However, there is now good data to support the use of single agent carboplatin, which is associated with good outcomes and less toxicity. Despite this data, there remains a reluctance to use this approach and as such ongoing collaboration and embedding this into future studies is important.

2. **Intracranial Germ Cell Tumours**

GCTII

The European-wide CNS GCTII trial closed to recruitment in 2018 and results are being analysed. However, data thus far have enabled us to recommend a reduction in radiotherapy for patients with pure germinoma who are in complete remission following chemotherapy. Analysis of relapse data for patients with Non-germinomatous Germ Cell Tumour has led to an extension of radiotherapy fields. In addition, dose-intensified chemotherapy may have a role in patients with high risk tumours. The next trial, CNS GCTIII is currently in development and will build on these strategies.

MonoGerm

We are currently developing a new trial for germinoma, MonoGerm, which will be a Phase 2 study looking at the use of single agent chemotherapy, which will be of particular utility for patients with diabetes insipidus as hyperhydration will not be required. The protocol is currently being developed, with carboplatin versus vinblastine monotherapy. The trial will include pharmacokinetic analysis and incorporate biological studies.

Leukaemia Subgroup (Chair, Dr John Moppett)

The Leukaemia Subgroup is a highly active group that is making excellent progress against its strategic priorities:

1. **Open international trials for Philadephia-positive and infant Acute Lymphoblastic Leukaemia (ALL)**

EsPhALL2017 (NCT03007147 PI Cummins) is funded by CRUK. Opening continues to be delayed by contractual issues with the sponsor.

The conceptual structure of Interfant 2021 (PI Bartram) for Infant ALL has been agreed internationally and the UK will participate. A funding application is being developed for the main trial and a funding application for a basic science translational study (SAIL) (PI Bartram) has been submitted to Little Princesses Trust and we have submitted an expression of interest to run a CSF flow cytometry substudy (Goldilocks, PI Halsey) alongside the main trial.

2. **Continue monitoring recruitment to MyeChild01 in Acute Myeloid Leukaemia (AML; PI Gibson)**

Recruitment is progressing well with the opening of several international sites (Australia, New Zealand, Switzerland). UK has recruited 268 patients against a target of 350, whilst the whole trial has recruited 552 against a target of 750. It is estimated that the trial will close to recruitment between March and September 2022 depending on recruitment to the minor (infant) dose finding study. Recruitment to randomisation 1 (R1) (DaunoXome vs Mitoxantrone stopped early due to non-availability of DaunoXome. Recruitment to R2 (1 vs 3 doses Myelotarg) and R3 (Fla vs Ara-C) is progressing well. Recruitment remains challenging for R4 (RIC vs MAC allograft). Plans are being made for the successor trial.

3. **Open ALLTogether1 in Acute Lymphoblastic Leukaemia (PI Moppett)**

The opening of ALLTogether1 (NCT04307576) was held up significantly by a delay in the approval of the SoECAT by NHSE (COVID related). This hurdle has been overcome and the trial has now opened in Bristol (18th May 2021). Two patients have been recruited to date. Opening of other sites is expected in short order. The CSF-Flow substudy of ALLTogether1 is funded and will open in Q4 2021 (PI Halsey). The associated supportive care study CiproPAL (NCT04678869 CI Phillips) is funded and expected to open Q4 2021. A second application to NIHR for an anticoagulation substudy (PI Bradbury) was rejected.

4. **Develop a cohesive strategy for relapsed ALL**

Relapsed ALL remains a very fastmoving area, with two recently published studies showing the benefit of Blinatumomab in high risk relapses. The place of CAR-T therapies and the role of Blinatumomab in lower risk relapses remains to be determined, as does the role of other immunotherapeutics – especially Inotuzumab. The IntReALL consortium has been developing a trial for several years which has iterated over time. We have concerns regarding the trial strategy – especially whether it conflicts with currently open academic CAR-T trials in the UK. However, following the latest iteration we are considering participation in the very high risk arm of IntReALL. Meanwhile there is a comprehensive guideline to guide clinicians – and encouraging recruitment in the relevant early phase trials where appropriate (Delphinus for T-ALL, CARPALL and CATCAR19 for BCP ALL). The Hem-iSMART trial for relapsed T-ALL is being actively progressed (see below) and will help fill a major area of need.

5. **Contribute to international collaborations in Chronic Myeloid Leukaemia (CML) and Myelodysplastic Syndrome (MDS)/ Open registries with linked biological sample collection and studies for Acute Promyelocytic Leukaemia, Downs Syndrome (DS)-AML, CML and MDS**

Ethical approval has been obtained for children with CML to be recruited to the UK CML registry which will in time help us to run a trial of stopping Tyrosine Kinase Inhibitor in good responders. Local site opening is ongoing and recruitment expected to start imminently. Unfortunately at this time ethical approval to share data with the international paediatric CML registry was not given. It is intended to address this in an amendment in due course.

The NIHR MDS study (PI Rao) continues to recruit well (110 cases to date).

We will actively contribute to a retrospective study in relapsed DS-AML (CI Hitzler, Toronto). There is also a proposed European study of CPX-351 in DS-AML – UK PI role being advertised.

6. **Liaise with Novel Agents Subgroup 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.**

Hem-iSMART, a basket trial for relapsed T-ALL is being prepared for a funding application (PI van Delft) and a similar suite of trial in relapsed AML (PeDAL, PI Norton) is being actively developed in collaboration with the North American Children's Oncology Group (COG) and the European Innovative Therapies for Children with Cancer (ITCC) network.

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

B-NHL

1. Ibrutinib – Sparkle international study. Phase I/II randomised trial in relapsed refractory mature paediatric B cell Lymphoma. Study closed.
2. Phase II Inter B-NHL PMBCL Study. Data cleaned and submitted for publication.
3. GLO-BNHL ACCELERATE platform study: Global industry supported, international, academic sponsored study to rapidly assess multiple novel agents relapsed refractory B-NHL. This is an EICNHL-COG-ITCC collaboration with an academic steering committee from all three groups. The GLO-BNHL prioritisation is BiTE, ADC's with standard chemotherapy and CAR-T cells. Ancillary biological studies are planned. Patient recruitment 30 patients/year. Study submitted to CR UK for funding (CI – A Burke, Sponsor Birmingham)
4. Relapsed NHL retrospective International Cohort Study: Data on relapsed NHL patients (excluding ALCL) was submitted to a European international retrospective cohort study and data on 639 patients was collected (Cancers 2021).

T Cell Lymphoblastic Lymphoma
T-cell Lymphoblastic lymphoma patients will be recruited to the next ALL trial ALL-Together1 as an observational study. Minimal disseminated disease, biological biomarkers and PET-CT data will be collected to be analysed retrospectively (Lead M Taj).

Anaplastic Large Cell Lymphoma

1. CRISP study: Crizotinib plus Vinblastine closed for ALCL. Unlikely to go forward because of prolonged neutropenia in 2 patients and does not cross the blood brain barrier.
2. Nivolumab study: Open in France (since 2018), Holland and Germany. Has been funded in the UK and is currently in set-up.
3. Briga-ped: Brigatinib (Takeda) phase I/II study to be run by the Prinses Maxima Netherlands. Phase I will look at ALK-positive patients in all paediatric malignancies. Phase II will incorporate Brigatinib plus chemotherapy. The trial will open in Q4 29021 or Q1 2022.
4. Single arm Vinblastine study: Funding obtained in Germany. To be reviewed in the UK.

PTLD

- Rebecca Ling's multicentre cohort of 108 patients is currently being written up.
- EICNHL CNS PTLD study of 25 pts (7 from the UK). Published in BJH in 2021.

Work with the TYA/TCT CSG
Collaborated with TYA & GCT Group to publish pilot data on PET-CT's in T-LBL patients. Also working actively to make sure that the T-LBL sub-study will recruit TYA patients from adult centres. "Utility of 18F-FDG-PET/CT in Lymphoblastic Lymphoma" published leukaemia lymphoma.

Biological Studies

B-NHL

- A patient derived xenograft resource of paediatric B-NHL has been developed (Forde et al., BJH, 2021) from UK patients recruited to the inter-B ritux trial. The adaptability of these PDX to studies of response to therapy and resistance was demonstrated (Cambridge + Newcastle).
- B-NHL genomics study. Study of *TP53* abnormalities in 95 cases of paediatric B-NHL from the CCLG tissue bank. This study identified the strong prognostic effect of *TP53* within Burkitt lymphoma and is currently under review at *Leukemia*. *TP53* will be studied as a biomarker on the B-NHL samples collected on the Inter-Ritux high risk study by the EICNHL group (V Rand and S Bomken).
- Open national CCLG tissue bank study of drivers of relapsed/refractory Burkitt lymphoma, collecting viable patient samples for PDX generation through CCLG tissue bank (PI S Bomken).

ALCL

- A study analysing resistance mechanisms to ALK inhibitors through the conduct of CRISPR/dCas9 screens with validation of findings in patient samples from the MAPYACTS trial in France has been published in Blood. These data propose therapeutic strategies for the treatment of ALK inhibitor relapse disease (Cambridge).
- A new assay has been developed for the detection of ALK autoantibodies in ALCL patients. It is anticipated that the new assay will be retrospectively assessed in the single arm vinblastine study (Cambridge).
- Ongoing QC between labs in Cambridge, Paris, Padua and Hamburg for the detection of MDD/MRD by the detection of ALK transcripts in the blood and/or bone marrow is ongoing. A biological study for the detection of ALK MDD/MRD in UK patients is ongoing in Cambridge.
- A study assessing therapeutic response to ALK inhibitors in patient derived xenografts of CNS-positive ALCL is ongoing in Cambridge.

- Ongoing study to assess the genetic aberrations underlying paediatric ALK-negative ALCL (Cambridge + Newcastle + Barcelona).

Neuroblastoma Subgroup (Chair, Dr Juliet Gray)

The Neuroblastoma Subgroup supports a diverse range of trial activity, with the overall aim of improving risk stratification, treatment and outcome of children with neuroblastoma. In line with our strategic objectives, good progress has been made in many areas over the last 12 months, including:

First line treatment of high risk disease*:* High risk neuroblastoma remains one of the most challenging paediatric cancers, and development of the second SIOPEN high risk neuroblastoma trial (SIOPEN HR-2) began prior to closure of SIOPEN HR-NBL-1 in 2018. Several members of the Subgroup (Gray, Gaze, Burchill) made significant contributions to the trial strategy and design of this pan-European phase 3 randomised study, that seeks to improve upfront treatment by comparing i) 2 different induction chemotherapy regimens ii) intensifying high dose chemotherapy iii) increasing radiotherapy in children with residual disease following surgery. In addition, it is planned to introduce amendments to the trial to test i) the addition of anti-GD2 antibody (dinutuximab beta) to induction chemotherapy and ii) the addition of targeted therapy (lorlatanib) to chemotherapy in patients with ALK-mutated tumours. Funding has been secured to open the trial in the UK (Solving Kids Cancer April 2020) and also to instigate the lorlatanib amendment (Solving Kids Cancer Nov. 2021). All UK regulatory approvals have been achieved within 9 months of funding award and it is expected to open the first UK site in Q2 2021.

Treatment for poor responders*:* 20% of children with high risk neuroblastoma have disease that is refractory to first line treatment. The SIOPEN VERITAS trial aims to improve the outcome of these children in a randomised phase II study of two double high-dose intensification strategies. It is the first randomised trial comparing a molecular radiotherapy-based approach with chemotherapy alone and opened in the UK in January 2021.

Treatment for relapsed disease: Outcome for children with relapsed high risk neuroblastoma is dismal, with < 10% long term survival. The BEACON study opened in 2016, initially aiming to compare different chemotherapy backbones and also to investigate the addition of bevacizumab. Once planned recruitment completed, the study was extended to test the addition of dinutuximab beta (led by Gray), with final completion of recruitment in March 2021 (3 months ahead of target). 9 European countries contributed to the study, with 81/224 patients recruited from the UK. Data from the bevacizumab randomisation was presented at ASCO 2020, and has defined a new standard of care for relapsed disease. A follow on study (BEACON 2, co-led by Gray) is in preparation. In addition a number of early phase studies have been led by the subgroup, including 2 novel immunotherapy studies; i) MINIVAN (led by Gray/Gaze, in collaboration with US/Germany) ii) 1RG CAR-T (led by Anderson/Barone, completed Jan 2020, data published Science Translational Research 2020)

Radiotherapy*:* The IMAT-neuroblastoma trial (led by Gaze), a randomised phase II trial of radiotherapy dose escalation with innovative technology, completed recruitment (50 patients) in 2020, and publication of data is in preparation.

Pharmacology*:* Previous pharmacokinetic studies have shown the unreliable bioavailability of 13-cis-retinoic acid when capsules are opened for children unable to swallow them. A new, tutti-frutti flavoured liquid formulation was developed, and pharmacokinetic evaluation of this (led by Tweddle) completed recruitment in 2019. Results were published in 2021 and the liquid preparation is now available as a standard of care.

Surgery: Data from the SIOPEN HR-1 study been published indicating the "*Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma*" (JCO. 2020) and the

subgroup (Gabra) have contributed to the developed of a standardised surgical report form for clinical trials (Annals Surgery 2020).

Epidemiology: An epidemiological study of survival after relapse, with associated biological data, led by Tweddle, has recruited >200 patients since it opened in 2017, and is offering new insights into the management of relapsed neuroblastoma. In addition the Subgroup (Burchill, Gray) are collaborating with an international study to identify risk factors for 'ultra high risk' disease.

Outreach and dissemination of information: since 2016, the Subgroup has held an annual neuroblastoma clinical trials update day, which attracts a broad attendance from doctors, nurses, pharmacists, charities and parent advocates. In the last year, 3 separate, shorter, virtual meetings, focussing on key areas of research have been held instead. In addition, members of the Subgroup contribute significantly to parent conferences (e.g SKC Global Parent Conference Nov 2020, attended by > 700 people from 46 countries) and also to a regular monthly virtual National Neuroblastoma Advisory Panel, one of the main aims of this is to promote entry into clinical trials.

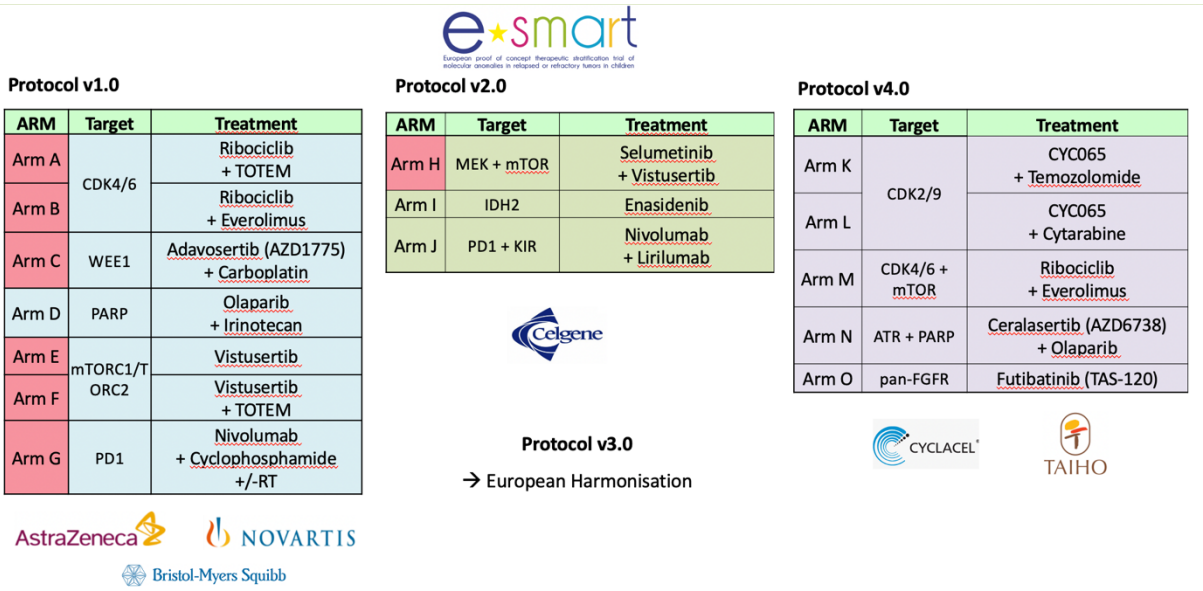
Novel Agents Subgroup (Chair, Dr Lynley Marshall)

The Novel Agents Subgroup and its eleven Paediatric ECMC Network member centres have remained very active over the past year, continuing their work in line with stated key strategic goals:

1. **Developing new trials with academic and industry partners**

Despite the inevitable impact of COVID-19, we have continued to develop, secure, set up and open new trials. We continue to focus on biomarker-driven first-in-child trials, phase Ib combination trials, seamless phase I/II trials and phase II trials in collaboration with the relevant disease specific groups, as well as tumour agnostic trials and multi-arm adaptive platform trials. Our early phase clinical trials activity has remained robust.

The CRUK-sponsored ITCC ESMART phase I/II adaptively designed molecularly enriched platform trial opened in the UK in December 2019 (UK CI: L Marshall). Study entry is based on multi-omic molecular tumour profiling conducted on biopsy at relapse and processed via the CRUK-sponsored Stratified Medicines Paediatrics (StratMed-Paediatrics) study (CI: L Chesler). ESMART has been developed collaboratively within the ITCC European early phase trials consortium with significant UK investigator input. In partnership with multiple industry partners the trial originated with seven arms, with a further three subsequently added, and a further substantial amendment opened in France in late Q1 2021 and in set up in the UK will add a further five arms, making it a fifteen-arm trial since inception. There are single agent and combination arms, including some first-in-child arms. Six arms have been written and led by UK investigators (L Marshall - four arms; S Gatz - two arms) with preclinical and translational aspects conducted in UK laboratories (Chesler lab, ICR). The CDK2/9 inhibitor Fadraciclib was actually discovered and developed at The Institute of Cancer Research and then licensed to Cyclacel, who then partnered with Novel Agents Subgroup investigators and the ITCC to put it into ESMART. ESMART tests classes of drugs of significant interest to the paediatric/TYA cancer population but many not previously readily accessible. ESMART arms to date are shown below:



New commercial phase I/II clinical trials which have opened within the Network in this reporting period include: Olaparib (AstraZeneca) in solid tumours with a 'BRCAness' signature; Idasanutlin (Roche) in solid tumours and acute leukaemias, expanding in combination with venetoclax or chemotherapy in neuroblastoma, ALL and AML; Venetoclax (AbbVie) in acute leukaemia and solid tumours; two Ramicirumab studies(Eli Lilly) – in synovial sarcoma and desmoplastic small round cell tumour; Ponatinib (Incyte) in solid tumours, acute leukaemia and CML; Erbumine (Eli Lilly) in solid tumours and with chemotherapy in neuroblastoma; Lenvatinib (Eisai) in combination with chemotherapy in osteosarcoma. The adult study of the RET inhibitor Selpercatinib (LOXO Oncology) has opened as a randomised phase III study which allows patient enrolment from the age of 12 years, providing access to this highly targeted agent which has to date been available in the UK only on a named patient programme for children; the paediatric phase I/II study which will include younger children is in set up.

Other ongoing commercial phase I/II trials in this period include: Pembrolizumab (Merck), Regorafenib (Bayer), Larotrectinib (LOXO Oncology), Entrectinib (Roche), Durvalumab/Tremelimumab (AstraZeneca), Dabrafenib/Trametinib rollover (Novartis), Eribulin (Eisai), Selumetinib (AstraZeneca), Erdafitinib (Janssen), Avelumab (AstraZeneca), Daratumumab (Janssen), Carfilzomib (Amgen). Other ongoing academic phase I/II trials include: Lorlatinib (NANT/Pfizer), PARC (CRUK), Bosutinib (Erasmus/Pfizer), Inotuzumab (Erasmus/Pfizer), Seludex (CRUK/AstraZeneca), BEACON-Neuroblastoma (CRUK), rEECur (CRUK), VERITAS (CRUK).

New commercial phase I/II clinical trials in set up within the Network include studies of Alectinib (Roche) in ALK fusion positive tumours; Ponatinib (Takeda) in Ph+ leukaemia; Bempegaldesleukin + Nivolumab (BMS) in solid tumours; a Niraparib/Dostarlumab combination (GSK) in solid tumours expanding in neuroblastoma and osteosarcoma,;9-ING-41 GSK3B inhibitor (Actuate Therapeutics) in neuroblastoma; FIREFLY, a study of the pan-RAF inhibitor DAY101 (Day One Therapeutics) and the Roche-sponsored multi-arm platform study TAPISTRY (akin to the academic-sponsored DETERMINE study described below, but testing unlicensed drugs in unlicensed indications, in a tumour agnostic and age-agnostic trial that includes adult, TYA and paediatric patients).

Several other new academic trials are in set up to open in 2021/22. This includes the DETERMINE Study, sponsored by the CRUK Centre for Drug Development (CDD), which received CRUK Clinical Research Committee endorsement in December 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: M Krebs; Paediatric Lead: L 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 seven drugs and considerable financial support for the study already committed by Roche (Vemurafenib, Cobimetinib, Atezolizumab,

Alectinib, Entrectinib, Trastuzumab and Pertuzumab). Louis Chesler has had significant input into the translational packages for the trial.

A transatlantic academic investigator-initiated phase I trial of the combination of MIBG/olaparib in relapsed/refractory neuroblastoma expanding for patients with mutations deemed 'PARPable' eg ATRX mutations, is currently in set-up, based on preclinical work conducted by Sally George (CI) at The ICR. It will be sponsored by the Birmingham CR-CTU and is currently under funding submission with the charity Solving Kid's Cancer.

A three continent (UK + EU, North America and Australia) academic investigator-initiated phase I trial of the cassette combination AMXT1501/DFMO with chemotherapy in neuroblastoma is in development based on preclinical work done in the Haber/Chesler laboratories, and in partnership with colleagues in Sydney and the NANT North American consortium (UK/EU leads Marshall/Chesler)

The academic-sponsored CRISP phase IB study in tumours with ALK/ROS1/MET aberrations has just received UK regulatory and ethical approval of a substantial amendment and will open in the UK in Q3 2021.

2. Novel agents for poor prognosis tumours at diagnosis and relapse

Our Novel Agents clinical trial portfolio has continued to include novel therapeutic options for paediatric/TYA patients across the age and disease spectrum: relapsed/refractory/poor prognosis CNS and non-CNS solid tumours and leukaemias/lymphomas; disease-specific, target-specific (tumour agnostic) and broader eligibility trials, at the time of relapse but also, where relevant, in earlier lines of treatment.

For 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 L Moreno - new arms including the anti-GD2 antibody Dinutuximab beta recruited ahead of target and closed in Q1 2021); rEEcur for Ewing sarcoma – CI: M McCabe – a new novel combination arm including a CDK4/6 inhibitor is in set-up; Frontline and Relapse Rhabdomyosarcoma study (Far-RMS) – CI: M Jenney; Relapse Study Lead Dr Chisholm, will provide novel options for rhabdomyosarcoma patients particularly at relapse, with Regorafenib from Bayer now secured as the first novel drug in the Far-RMS study, on the basis of the commercial phase I and phase IB studies (UK CI Marshall), run across our Network.

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 in ALK-mutant neuroblastoma (Lorlatinib will now be tested upfront in a transatlantic phase III study sponsored by Solving Kids Cancer and currently in development within the Neuroblastoma group), NRTK inhibitors in infantile fibrosarcoma and infant high grade glioma).

3. Develop and deliver biomarker and pharmacokinetic studies

The CRUK-funded Stratified Medicine Paediatrics (StratMed-Paediatrics) national molecular profiling programme started enrolment in April 2019. Via this programme, patients undergoing tumour biopsy and advanced molecular profiling (NGS panel sequencing, RNA fusion panel sequencing, methylation profiling and whole exome sequencing) at disease relapse can be considered for more predictive biomarker-based clinical trials of novel agents. StratMed-Paediatrics has recruited 305 patients in just over 2 years since opening, recruiting ahead of target.

Alongside this programme, we have continued to drive forward molecular enrichment/biomarker-driven studies e.g. ESMART (multiple targets and pathways, including new arms, as above), CRISP (Crizotinib – ALK/ROS/MET in combination), Lorlatinib (ALK) and Alectinib (ALK/ROS),

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 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 including the generation of patient-derived xenograft models, and we have been in discussions with Roche about extending the immune-related biomarker aspects of this work.

Our early phase trial centres are affiliated to laboratories developing and refining techniques for monitoring circulating tumour DNA (ctDNA) 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). This is being extended across other tumour types and an investigator-initiated 'Liquid biopsy' study sponsored by GOSH (CI: J Anderson) opened at GOSH and the Royal Marsden in Q1 2021.

Professor Deborah Tweddle in Newcastle has taken over leadership of the CCLG Tumour Bank and 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). A liquid cisretinoic acid formulation for young children with neuroblastoma has just been validated for wider use off the back of this group's work.

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, the ALK-functional imaging trial.

4. Implementation of the successful renewed and expanded Paediatric ECMC network

The Paediatric ECMC Strategy Group (theme leads and centre leads) meets regularly to plan and evaluate initiatives across the ECMC themes. Network collaboration has continued to grow, with the eleven paediatric ECMC centres working cohesively but also within four regional sub-networks, created to facilitate equitable access to clinical trials nationally. Each holds regular regional relapse discussion panel 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 as Paediatric ECMC Network co-ordinator has greatly assisted in driving network activities forward and 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. Despite COVID-19, this industry-related activity has increased in 2020-21.

Dr McKay and the ECMC Programme Office have continued to work on the outputs from the successful Study Start Up Workshop, held in London in November 2019, and sponsored by ECMC Clinical Trial Theme co-leads Professor Pam Kearns and Dr Lynley Marshall. This workshop included invited representatives from ECMC centres, pharma, regulatory bodies (including the MHRA), ethics committees, funders and consumer/parent/patient groups and 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 and keeping the UK attractive for commercial sponsors in a post-BREXIT environment. Outputs have included a pilot piece of work on 'standard of care' disease assessments (piloted by Dr Juliet Gray in Neuroblastoma) with a view to standardising contract and costing negotiations; attendance at HRA workshops; a survey of investigator experience of ethics committees, amongst others. Further recommendations will be made in this area.

A new focus of ECMC work commencing in 2021 and underway is a focus on access to clinical trials for TYA patients, led by Caroline Huxley from the ECMC Programme Office and in line with the ACCELERATE international multistakeholder 'Fostering Age Inclusive Research' (FAIR Trials) initiative. A workshop is planned for later in 2021.

The ECMC's EC Trial-Finder (online clinical trials finder to improve awareness of portfolio clinical trials and promote wider access) which is up and running has continued to be further developed and refined in this year.

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

The StratMed-Paeds programme opened in April 2019, is open in all 20 UK centres and is recruiting ahead of target, with turnaround of results within the planned 28 days. It characterises tumours following biopsies performed at relapse. It will dovetail with NHS genomic medicine initiatives aimed at offering molecular profiling to all paediatric cancer patients, including at first diagnosis. Indeed, the laboratories conducting the StratMed-Paediatrics profiling (GOSH and Royal Marsden/ICR) form part of the North London Genomics Hub. This NHS England (NHSE) rollout was repeatedly delayed from April 2019, but rollout is beginning in mid-2021. 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 StratMed-Paediatrics 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 across the UK (who are invited to dial into the discussion), highlighting clinically relevant/potentially actionable molecular aberrations uncovered via the profiling initiatives.

4. Cross-cutting research

The CRUK-funded Stratified Medicine Paediatrics (StratMed-Paediatrics) national molecular profiling programme described in the Novel Agent Subgroup report is a key piece of cross cutting work that has implications for all patients with relapsed solid tumours and is key to accessing relevant targeted agents within the eSMART trial, other upcoming biomarker driven basket trials, specific early phase trials of targeted agents and compassionate access to drugs through extended access programmes.

Following on from StratMed-Paediatrics, translational clinician scientist Prof Louis Chesler from the Novel Agents Subgroup (and chief investigator of StratMedPaediatrics) with Dr Mike Hubank, clinical genomics lead at The Institute of Cancer Research and lead for the North London Genomics Hub, with support from the parent-led charity Christopher's Smile succeeded in advancing the ICR-developed next generation sequencing panel (piloted in a previous portfolio Next Generation Sequencing Study and which forms the basis of the StratMedPaediatrics study) as an approved Next Generation Sequencing (NGS) panel for NHS use in 2020.

Dr Henry Mandeville, working with the UK Radiotherapy Trials Quality Assurance group, has been one of the key European leads for the development of the SIOPE/QUARTET platform to improve Quality Assurance in paediatric radiotherapy trials. QUARTET went live in early 2021 and is now being used for Radiotherapy Quality Assurance in the Frontline and Relapse Rhabdomyosarcoma Study, for which Children's Group members Dr Mandeville and Dr Chisholm are among the joint international leads.

5. Funding applications in last year

Table 1 Funding submissions in the reporting year

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
Cancer Research UK*					
March 2021					
LOGGIC	Full Application		Supported	Discussion in CNS Tumour Subgroup and Children's Group	£2, 029, 609
Long term health outcomes, following childhood cancer	Stage 1		Not supported	Discussed with Children's Group	
December 2020					
CCLG Biobank renewal	Sample Collection Award New Professor Deborah Anne Tweddle		Not supported Resubmission invited		
DETERMINE (aDvancing gEnomically maTchEd tReatMents IN rare cancErs)	Endorsement New	Dr Matthew Krebs	Roche supporting CRUK sponsored (CDD)	Novel Agents Subgroup members contributed to developmen t; feedback from Children's Group. Paediatric Study lead is Novel Agents Group Chair	
ACNS1831 COG SIOPE NF1 (NF1) A Phase 3 Randomized Study of Selumetinib (IND # TBD) versus Carboplatin/Vincristine in Newly	Clinical Trial Award (May 2020)	Professor Darren Hargrave	AstraZeneca supporting CRUK endorsed	Discussed within CNS Tumour Subgroup	

Diagnosed or Previously Untreated Neurofibromatosis Type 1 (NF1) associated Low-Grade Glioma (LGG)				and Children's Group. International leadership by Brain Tumour Subgroup member	
Phase 2 study of the efficacy and safety of Fludarabine in combination with Vyxeos, a liposomal complex of daunorubicin and cytarabine, in children with refractory / relapsed AML.	Clinical Trial Award - Outline (May 2020)	Professor Brenda Elizabeth Simpson Gibson	Full application not invited. European funding being sought	Discussed in Leukaemia Subgroup	
Global Study of Novel Agents in Relapsed and Refractory B-cell non-Hodgkin lymphoma (Glo-BNHL)	Clinical Trial Award - Outline New	Dr Amos Burke	Full application invited	Developed collaboratively between Paediatric Non-Hodgkin Lymphoma Subgroup and Novel Agents Subgroup with UK international leadership	
Other committees**					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of Group input**	**Funding amount**
Cipropal Substudy of ALLTogether	NIHR HTA Full application	Dr Bob Phillips	Successful	Developed with Leukaemia Subgroup, Discussed and	£1,400,000

				supported in Children's Group	
Solving Kids Cancer	Charity Funding Awards Committee	Dr Sally George	Under discussion	Developed in Neuroblastoma and Novel Agent Subgroups, discussed and supported in Children's Group	
CSF Flow Substudy of UK ALLTogether Trial	CCLG, Little Princess Trust Full Application	Dr Halsey	Supported	Developed within Leukaemia Subgroup	£247, 415

**CRUK CRC applications for table 1 completed by NCRI Executive.*
***Other applications in the table to be completed by Group Chair*

6. Consumer involvement

Loveday Langton

Loveday Langton has represented the interests and experiences of children with cancer and their families in Children's Group meetings and has been an active member of the NCRI Consumer Forum. Loveday is a member of the steering group for the JLA Priority Setting Partnership for children's cancer, including the subgroup looking at creative ways of engaging children in the survey. She is co-presenting an overview of this project at the upcoming NCRI Children's Group webinar. Loveday is co-author, along with her son, of a study into the impact of a cancer diagnosis on children's education, funded by CCLG. Loveday and her son are also members of the "expert panel" advising on the development of an app (Xploro) to support and empower children in hospital. Loveday is a member of the Paediatric Oncology Reference Team, a group of parents who review trial literature. She has recently joined the Clinical Advisory Group for a study into follow-up for paediatric acute leukaemias, which is applying for funding.

Dr Chisholm and Loveday have discussed consumer involvement in the NCRI Children's Group, and this was a discussion topic in the most recent Group meeting. Subgroup chairs commented on the great value that Consumer representatives bring to the Subgroups, explaining that their involvement is intrinsic to the functioning of the groups. There are some Subgroups which are currently actively seeking to appoint Consumer members. Future actions agreed in these discussions include building links between Consumer members across the Group and beyond, including the TYA & GCT Group.

Angela Polanca

Angela Polanca has been an active and extremely highly valued member of the Children's Group for a number of years, and has sadly now stepped down due to work commitments. The NCRI is actively recruiting a new consumer member for the main group.

In the past year, Angela has continued to make a very significant impact in paediatric cancer research. Angela co-authored a number of papers, including an onco-fertility white paper being published by COG group and 'Unmet needs for relapsed and refractory Wilms tumour', submitted to EJC. She was co-applicant for a renal tumour trial data linkage project and was invited to contribute to a special issue of Primer for Nature Reviews on Wilms Tumour. She is an active member of a number of groups nationally and internationally, including the Wilms Tumour Link Group, where she is PPI Lead; BENCHISTA - PPIE lead; SIOP RTSG Epidemiology, Genetics and Clinical Outcomes committee member; steering group member Child Cancer Smart ; CCI PPIE lead and steering group member for the JLA Childhood cancer priority setting. She was co-author for CRUK's clinical research studies and impact of COVID-19 report from NCRI consumer members.

Angela is closely involved with the CCLG, including running the Bethany's Wish Named Fund, contributing to booklets about renal cancer and as a member of CCLG Research Advisory group, RTSG and the CCLG Late Effects Group. She is a Cancer POINTE member and HRA Public Involvement network member, and participated in SIOPE Valencia (European PPI strategy work. This year Angela also submitted her PhD exploring communication of future reproductive risk for female childhood cancer survivors and has been appointed Public Engagement Lead for Our Future Health.

7. Collaborative partnership studies with industry

Historically the strongest links with industry have come through the Novel Agent Subgroup. However, tumour specific groups are increasingly linking with pharma to include new targeted agents in frontline (for example planned new Ewings study, Glo-BNHL in Non Hodgkin's lymphoma, lorlatinib (ALK 23inhibitor) upfront in HR-NBL2; LOGGIC, an international phase III trial which includes a randomisation upfront between a MEK inhibitor and either vincristine/carboplatin or vinblastine in newly diagnosed low grade glioma) and the relapse component of newly opened Frontline and Relapse Rhabdomyosarcoma Study (regorafenib). Some of these have built upon concepts, links with pharma and phase I trials originating within or conducted via the Novel Agents Subgroup but then moving forward once promising activity has been demonstrated.

The ITCC eSMART phase I/II platform trial is an example of an international trial where investigator initiated trial arms have been supported by close industry partnerships, with UK investigators playing a key role in both the preclinical and translational biomarker work underpinning some trial arms, and their writing/design/clinical delivery. A similar European trial is being planned in acute leukaemia (HEM-iSMART) with close involvement of the Leukaemia Subgroup.

The CRUK-sponsored DETERMINE Phase II platform trial under development for adult, TYA and paediatric rare cancers will test licensed drugs in unlicensed rare indications. It is supported by industry, with the first pharma partner Roche giving seven drugs for inclusion in the trial (Vemurafenib, Cobimetinib, Atezolizumab, Alectinib, Entrectinib, Trastuzumab and Pertuzumab). Dr Lynley Marshall is the Paediatric lead for the study (adult medical oncologist Dr Matthew Krebs is CI) and Prof Louis Chesler has been heavily involved in the design of the translational package. The protocol is in the late stages of writing and the study will be submitted to UK regulators in Q3 2021.

The Roche-sponsored TAPISTRY study is the commercially sponsored 'sister study' to DETERMINE and is a phase II platform study testing unlicensed drugs in unlicensed indications. It is in set up in the UK at present, expected to open Q2/3 2021.

There are close links and productive interaction/partnerships with the following industry partners, to name but some: Abbott, Amgen, Astellas, AtraZeneca, Bayer, Bristol-Myers-Squibb (BMS), Boehringer-Ingelheim, Celgene, Cyclacel, Epizyme, Eisai, Glaxo Smith Kline (GSK), Incyte, Janssen, LOXO oncology Merck, Novartis, Pfizer, Roche, Takeda, Tesaro and others (mainly initiated via investigators in the Novel Agents Subgroup).

8. Priorities and challenges for the forthcoming year

Priority A key priority is to refresh and streamline the main Children's Group and Subgroup strategies in the light of the findings of the Quinquennial Review planned for May 2021, ensuring that we have a clear overarching strategy and that our strategy for consumer involvement is further developed. This will be achieved through a Children's Group strategy day later in 2021 and, review by Subgroups of each Subgroup Strategy.
Challenge 1 A key challenge is to maintain our high-performing, international profile as a paediatric cancer research community post BREXIT. Many of our strongest collaborations are with

European colleagues and it may be harder to lead on European collaborations and access European funding in the post BREXIT era. We are developing stronger links outside Europe but it is essential that we maintain close European collaboration and continue to lead innovation through involvement in our European working groups and consortia.
Challenge 2 A further challenge is to ensure that in the post-COVID-19 funding climate, trials in preparation which are supported by the Children's Group are able to find sources of funding. This will be achieved by: continued dialogue with the CRCTU in Birmingham which acts as international or UK partner organisation for most of our investigator-led, non-commercial trials and as sponsor is key in supporting funding applications; continued dialogue with CRUK and other significant funding charity bodies; further developing existing links with smaller charity funding partners such as Little Princess Trust, Solving Kids Cancer; raising awareness of the need for more central government funding streams for children's cancer research including NIHR funding, and continuing to develop our partnerships with industry.

Dr Julia Chisholm, (CCL Group Chair)

Appendix 1

Membership of the CCL Group

Name	Specialism	Location
Dr Henry Mandeville	Clinical Oncologist	London
Mr. Mark Davies	Medical Oncologist	Swansea
Dr Mary Taj	Paediatric Haematological Oncologist	London
Dr John Moppett	Paediatric Haematological Oncologist	Bristol
Dr Phil Ancliff	Paediatric Haematological Oncologist	London
Dr Julia Chisholm (Chair)	Paediatric Medical Oncologist	London
Dr Bob Phillips	Paediatric Medical Oncologist	York
Dr Mark Brougham	Paediatric Medical Oncologist	Edinburgh
Prof. Bruce Morland	Paediatric Medical Oncologist	Birmingham
Prof. Deborah Tweddle	Paediatric Medical Oncologist	Newcastle
Dr Lisa Howell	Paediatric Medical Oncologist	Liverpool
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Dr Juliet Gray	Paediatric Medical Oncologist	Southampton
Dr Lynley Marshall	Paediatric Medical Oncologist	London
Dr John Paul Kilday	Paediatric Neuro-Oncologist	Manchester
Prof. Simon Bailey	Paediatric Neuro-Oncologist	Newcastle
Dr Edmund Cheesman	Pathologist	Manchester
Prof. Simon Gates	Statistician	Birmingham
Mr. Hany Gabra	Surgeon	Newcastle
Mr Ian Kamaly-Asl	Surgeon	Manchester

Consumer Representation

Name	Location
Loveday Langton	London
Angela Polanco	Warwick, UK

Membership of the Subgroups

Central Nervous System Subgroup		
Name	**Specialism**	**Location**
Dr Nicky Thorp	Clinical Oncologist	Liverpool
Dr Thankamma Ajithkumar	Clinical Oncologist	Cambridge
Dr Jenny Adamski	Neuro-Oncologist	Birmingham
Sophie Thomas	Neuropsychologist	Chesterfield
Prof. Rob Dineen	Neuroradiologist	Nottingham
Dr David Jenkinson**	Oncologist	Fleet
Dr Julia Cockle*	Paediatric Medical Oncology Trainee	London
Prof. Simon Bailey	Paediatric Neuro-Oncologist	Newcastle
Prof. Darren Hargrave**	Paediatric Neuro-Oncologist	London

Prof. Richard Grundy**	Paediatric Neuro-Oncologist	Nottingham
Dr John Paul Kilday	Paediatric Neuro-Oncologist	Manchester
Mr. Conor Mallucci	Paediatric Neurosurgeon	Liverpool
Dr Mette Jorgensen	Paediatric Oncologist	London
Prof. Steve Clifford	Paediatric Oncologist	Newcastle
Dr Tom Jacques**	Pathologist	London
Dr Kim Bull	Psychologist	Southampton

Germ Cell Tumour Subgroup		
Name	**Specialism**	**Location**
Dr Thankamma Ajithkumar	Clinical Oncologist	Cambridge
Dr Alex Freeman	Histopathologist	London
Dr Matthew Murray	Medical Oncologist	Cambridge
Dr Dan Stark	Medical Oncologist	Leeds
Dr Mark Brougham	Paediatric Medical Oncologist	Edinburgh
Dr Anthony Penn	Paediatric Medical Oncologist	Manchester
Dr James Hayden	Paediatric Medical Oncologist	Liverpool
Dr James Nicholson	Paediatric Medical Oncologist	Cambridge
Shaun Wilson	Paediatric Oncologist	Oxford
Mr Suren Arul	Surgeon	Birmingham

Leukaemia Subgroup		
Name	**Specialism**	**Location**
Mr Neil Ranasinghe	Consumer	London
Dr Anthony Moorman	Epidemiologist	Newcastle
Dr Anupama Rao**	Paediatric Haematologist	London
Dr Brenda Gibson	Paediatric Haematologist	Glasgow
Dr Chris Halsey	Paediatric Haematologist	Glasgow
Dr Denise Bonney	Paediatric Haematologist	Manchester
Dr Michelle Cummins	Paediatric Haematologist	Bristol
Dr Vesna Pavasovic	Paediatric Haematologist	London
Dr Sara Ghorashian	Paediatric Haematologist	London
Dr Phil Ancliff	Paediatric Haematologist	London
Dr Sujith Samarasinghe**	Paediatric Haematologist	London
Dr Alice Norton	Paediatric Haematologist	Birmingham
Dr Beki James	Paediatric Haematologist	Leeds
Dr David O'Connor	Paediatric Haematologist	London
Dr John Moppett	Paediatric Haematologist/Medical Oncologist	Bristol
Dr Rosanna Ghinai	Paediatric Haematology Trainee	Birmingham
Dr Donna Lancaster**	Paediatric Medical Oncologist	London
Prof. Josef Vormoor	Paediatric Medical Oncologist	Newcastle
Dr Fredrick van Delft	Paediatric Medical Oncologist	Newcastle
Dr Amy Kirkwood	Statistician	London
Dr Rachael Hough**	TYA Haematologist	London
Dr Anna Castleton	TYA Haematologist	Manchester

Paediatric Non-Hodgkin Lymphoma Subgroup		
Name	**Specialism**	**Location**
Dr Andrew Wotherspoon	Consultant Histopathologist	London
Dr Ben Carpenter	Haematologist	London
Dr Mary Taj	Paediatric Haematological Oncologist	London
Dr Simon Bomken	Paediatric Medical Oncologist	Newcastle
Dr Amos Burke	Paediatric Medical Oncologist	Cambridge
Dr Suzanne Turner	Pathologist	Cambridge
Prof. Keith Wheatley	Statistician	London
Dr Rebecca Ling*	Trainee	London
Dr Emma Seaford	Trainee	London

Neuroblastoma Subgroup		
Name	**Specialism**	**Location**
Dr Mark N Gaze	Clinical Oncologist	London
Mr Nicholas Bird	Consumer	Epsom
Prof. Louis Chesler**	Medical Oncologist	London
Dr Juliet Gray	Paediatric Medical Oncologist	Southampton
Prof. Deborah Tweddle	Paediatric Medical Oncologist	Newcastle
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Prof. John Anderson**	Paediatric Medical Oncologist	London
Dr Kate Wheeler	Paediatric Medical Oncologist	Oxford
Dr Sarah Brown	Paediatric Medical Oncologist	Southampton
Dr Sally George	Paediatric Medical Oncologist	London
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Dr Ramya Ramanujachar	Paediatric Medical Oncologist	Southampton
Dr Guiseppe Barone**	Paediatric Medical Oncologist	London
Dr Simon Wan	Radiologist	London
Prof. Susan Burchill	Scientist	Leeds
Mr. Hany Gabra	Surgeon	Newcastle

Novel Agents Subgroup		
Name	**Specialism**	**Location**
Dr Lynley Marshall	Paediatric Medical Oncologist	London
Dr Donna Lancaster	Paediatric Medical Oncologist	London
Prof. Bruce Morland	Paediatric Medical Oncologist	Birmingham
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Prof Darren Hargrave	Paediatric Medical Oncologist	London
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Prof. Pamela Kearns	Paediatric Medical Oncologist	Birmingham
Prof. Steve Clifford	Paediatric Medical Oncologist	Newcastle
Dr Andrew Peet	Paediatric Neuro-Oncologist	London
Dr Charlotte Burns*	Paediatric Oncology Trainee	Cambridge
Dr Vijal Parmer	Paediatric Oncology Trainee	London
Dr Gareth Veal	Pharmacologist	Newcastle

The Novel Agents Subgroup also has a wider ‘network’ Subgroup membership to allow wider attendance beyond the core membership, of members from the 11 centres forming the Paediatric ECMC network, and additional clinician scientists with core expertise in the field.

* denotes trainee member
**denotes non-core member

Appendix 2

Children's Cancer and Leukaemia (CCL) Group & Subgroup Strategies

A – CCL Group Strategy 2018-2021

Strategic Objective	Action	RG 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. UK approvals in place. BEACON trial (2016-2021); data presented ASCO 2019,20. MINIVAN (Opened 2018), 1RG CAR-T (Anderson et al Science Translational Research 2020) VERITAS UK 2021 BEACON 2 in preparation MINIVAN (Opened 2018), 1RG CAR-T (Anderson et al Science Translational Research 2020) LUDO trial (Gaze et al European Journal Nuclear Medicine and Molecular Imaging 2020), LUDO-N follow on trial in development
Portfolio development: Leukaemia	Strengthen representation across the RG. 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 2021

Strategic Objective	Action	RG Lead	Date	Outcomes
	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 and rAML below
	Reducing toxicity and deescalating treatment for patients with excellent survival.	Bob Phillips		Cipropal study awarded NIHR HTA funding 2020. ASTA trial (Apixiban prophylaxis) under development EsPhALL study funded 2019 Age 18-29 included within ALLTogether
	Work towards new study with Philadelphia positive disease.	Michelle Cummins		
	Work with Adult RG to explore where it is possible to development joint strategy and trials.	John Moppett		Relapsed AML trial Vitality (CPX-351 & Fludarabine) developed and submitted for funding April 2020: PI Gibson
	Develop strategy for relapsed AML.	Sara Ghorashian		PeDAL early phase trial strategy to deliver 1st in child and other early phase studies in rAML
	Continue the implementation of CAR-T cell therapy for ALL / lymphoma.	Sara Ghorashian		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)

Strategic Objective	Action	RG Lead	Date	Outcomes
	Establish a CAR-T programme for AML	John Moppett/Anthony Moorman		In pre-clinical development (W Qasim GOSH) GE WGS for acute leukaemia go live date 07/09/2020.
	Integrate GE testing into routine care			Work ongoing to link to trials and cellbank
Portfolio development: Germ Cell	Extracranial GCT Maintain links with key external stakeholders for international trial design: UK – NCRI TYA and GCT RG; Gynae RG; International: MaGIC; G3; EORTC –	Sara Stoneham Matt Murray/Sara Stoneham/ James Nicholson/ Mark Brougham		AGCT1531 P3BEP TIGER
	Develop stronger links with European colleagues via SIOPe GCT	Anthony Penn, James Hayden, Matt Murray, James Nicholson, Mark Brougham, Sara Stoneham		Develop links with European colleagues, particularly those currently less involved with MaGIC

Strategic Objective	Action	RG Lead	Date	Outcomes
	Build on Malignant Germ cell tumour International Collaborative (MaGIC) UK and US paediatric oncology groups combined datathat has enabled development of a new risk stratification for extracranial GCT and a frame work for new trial design internationally. This has expanded to several other countries and includes an international Data Commons. *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 RG to strengthen interface with medical oncologists and paediatric oncologists on Subgroup. Publishing joint analyses from MaGIC.	As above		MaGIC Clinical Trial design group – co- 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 Joint publications from MaGIC using MRC data (TYA outcomes) and TYA RG +GCT members to develop national consensus guidelines Joint publications from MaGIC completed Establishment of a GCT 'data commons' Development of MonoGerm Phase 2 study

Strategic Objective	Action	RG Lead	Date	Outcomes
	Intracranial GCT Continue SIOPe collaborative Extend links with US/Asia to align language/risk stratification and marker thresholds internationally Embedding biology into all trial design			Funding and ethical approvals obtained to facilitate collection storage and study.
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. Improve strategic relationship with sarcoma RG 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 Subgroup to CCL RG (similar to YOSS)	Chair of Sarcoma Research Group and its bone tumour Subgroup		Advanced plans for new multistage Ewings study including phase Ib in metastatic Ewings and RT question ICONIC study funded and opened 2019 Included in Ewings study design

Strategic Objective	Action	RG Lead	Date	Outcomes
Portfolio Development: CNS tumours	Trials available for all tumour groups To be European leader in brain tumour trials Molecular diagnostics informing all trials To run biological studies to identify those patients whose treatment can be reduced, and those for whom novel treatment strategies are available Note Gaps in portfolio (e.g. embryonal tumours, craniopharyngioma, rare tumours such as ETMR)			Number of trials expected to open in next year (LOGGIC, NF1 LGG, ATRT, BIOMEDE 2.0) HRMB opened in 2021 (16 country trial led by UK) In place for a number of tumour types and will be integrated with genomic hubs. Genomics England for newly diagnosed tumours and SMP paeds open and recruiting for determining targets for relapsed tumours 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 Nov 2019	Dr Lynley Marshall appointed as incoming Novel Agents Subgroup chair 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. Delays owing to COVID-19. To be prioritised in 2021

Strategic Objective	Action	RG Lead	Date	Outcomes
			Ongoing	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 DrMartin Elliott, Dr Clare Shaw) Decision to continue wider Novel Agents Network Subgroup meeting attendance in addition to the NCRI Core Novel Agents Subgroup, 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.
	Following the Paediatric ECMC renewal and launch of StratMedPaeds and of eSMART, further development of novel agent trials and longitudinal sampling studies			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 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
	Increase links with tumour site groups – leading early phase studies (in collaboration with site specific groups)			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

Strategic Objective	Action	RG Lead	Date	Outcomes
	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 targeting (membership attendance at ACCELERATE paediatric Strategy Forum on Epigenetic Modifiers, Philadelphia, January 2020)			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 (eg FaR-RMS) Maintain direct links with CTRad Work with European colleagues on the SIOPE/QUARTET platform and UK RTTQA Group to enhance radiotherapy	Dr Henry Mandeville		More trials with randomised radiotherapy questions open and recruiting. Recruitment of patients treated with protons in radiotherapy trials. Study day with CTRad and TYA RG 2019 FaR-RMS HRNBL2 HRMB PNET5 Ependymoma 2 IMAT

Strategic Objective	Action	RG Lead	Date	Outcomes
	quality assurance in paediatric trials			Euronet pHL C2
Portfolio development (Systemic Anti-cancer Therapy)	Explore opportunities to use non-conventional chemotherapy e.g. immunotherapy. Develop pharmacokinectic studies e.g. liquid 13 Cis-retinoic acid.	Juliet Gray Deborah Tweddle		MINIVAN
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 RG Chair and NCRI lead		Strong leadership from Birmingham CRCTU in relation to BREXIT changes. Included in ACGT153/GC4 trials (germ cell) CED trial- concluded not to support Nov 2020.

Strategic Objective	Action	RG Lead	Date	Outcomes
	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			SAM Paeds under development (sarcoma).
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 coordinate GEL Work.	Chair Novel Agents Subgroup Chairs PPI leads		Through NHS England, genomic sequencing for all newly diagnosed paediatric cancer patients now available. StratMedPaeds facilitates advanced molecular profiling for all patients with solid tumours undergoing biopsy at relapse. Now plans to also include advanced profiling for leukaemia patients using StratMedPaeds platform/technologiy 2021 to enhance access to profiling and trials for leukaemia pts in UK; links to international initiatives eg hem-iSMART & others. Efficient use of funding/resouces; harmonisation. Ongoing

Strategic Objective	Action	RG Lead	Date	Outcomes
	Ensure PPI involvement in genomic and StratMedPaediatrics Studies (e.g. Ethics and Biopsy). Maintain direct links with paediatric ECMC network			Ongoing

Strategic Objective	Action	RG Lead	Date	Outcomes
Relapse	Maintain focus regarding research questions at time of relapse across all paediatric cancers. Discuss clinical trial options for each patient at each relapse, via disease-specific national advisory panels and ECMC regional relapse panels	Subgroup chairs		
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 RG. Identify lead for late effects and long term follow up studies Focus on patients with bone tumours in whom the majority have a disability following therapy.	RG Chair NCRI support		To be actioned
Consumer involvement	Identify points where consumers can support trial development outside the CCL RG process (e.g. lowering age limits in adult site specific trials and liaising with other RGs and wider trial development). Develop role in genomics (e.g. ethical approaches to tumour biopsy)	Consumer representatives RG Chair with TYA lead		

Strategic Objective	Action	RG Lead	Date	Outcomes
	Development of long term follow up studies Collaboration with TYA RG about transition from paediatric to TYA care			
Pathology	Appointment paediatric pathologist to RG. 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.	NCRI support		Completed March 2019 Representation on TYA biological studies Group since 2019
RG Structure and Function	Ensure appropriate succession planning across the RG. Encourage next generation of researchers Identify routes by which UK can participate in NCI Studies and collaborate with 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.	RG Chair All CRCTU and all members NIHR lead and RG chair RG chair		Annual review Trainee scheme ongoing

Strategic Objective	Action	RG Lead	Date	Outcomes
	Review annual Clinical Trials Study day; closer collaboration with CCLG			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 (e.g. 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 StratMedPaeds and its associated eSMART 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
- VINILO for low grade glioma
- High Risk Medulloblastoma, funded by CRUK/Brain Tumour Charity (2018), UK led pan European SIOPE study run by CRCTU (Birmingham),

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

- LOGGIC – SIOPE study for children with low grade gliomas, open in Germany 2019, planned in UK for 2021/22, funding application with CRUK.
- ATRT - SIOPE study for children with ATRT, funding application in UK 2021.
- Infant medulloblastoma –SIOPE study for children with children under 3 with medulloblastoma in mid development, funding to be sought 2021.
- BIOMEDE 2 for Diffuse intrinsic pontine glioma

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 – definition of CR, radiotherapy field in bifocal disease

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 RG
- 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 Novel Agents Subgroup 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 Non-Hodgkin Lymphoma Subgroup Strategy

Strategic aims over last 7 years:

- Ensure successful delivery of Subgroup portfolio especially phase III studies.
- Finalise the next T-lymphoblastic lymphoma trial.
- Work with the TYA/TCT RG.
- Exploit the increased number of agents available as a result of the legislation around PIPs.
- Prioritise the development of biological studies.
- Open ALCL Nivolumab trial.
- Briga-ped trial?
- Accelerate trial
- ALCL-vinblastine?
- Engage with SM-Paediatrics (Children's Group).

- Work closely with EICNHL and ITCC groups.
- Work closely with biological lead ST to ensure maximal and optimal conduct of biological studies within trials.
- Work closely with CCLG tissue bank in the development of resources for PDX/organoids and liquid biopsies
- Work collaboratively with Hodgkin SG.
- Work with the team to set up a paediatric lymphoma advisory panel.

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 Novel Agents Subgroup.

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.
4. 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 (StratMedPaeds), the implementation of a National molecular platform of advanced tumour profiling to genomically characterise relapsed solid paediatric cancers and a National Molecular Tumour Board (the StratMedPaeds Molecular Tumour Board) to interpret "actionable mutations" and facilitate precision medicine trials by triaging patients based on biology. StratMedPaeds is now open in the 20 planned UK tertiary paediatric oncology units with 305 patients recruited in just over 2 years, since opening to recruitment in April 2019 ahead of target). The StratMedPaeds molecular tumour boards run weekly. With an additional CRUK funding award to develop and rollout advanced molecular tumour profiling for leukaemia patients in addition to solid tumour patients, there are strategic plans underway to harmonise these efforts by utilising the StratMedPaeds platform and infrastructure to benefit patients with haematological malignancies too.
- The Paediatric ECMC Network will continue to build on the work of the 4 regional ECMC Subgroups covering the whole of the UK, which have been successfully developed to allow coordination and discussion of paediatric relapse cases to consider clinical trials and link with the StratMedPaeds programme and National (StratMedPaeds) Molecular Tumour Board.
- To work with the ECMC Network to develop an online clinical trials finder to improve awareness of portfolio clinical trials and promote wider access. This initiative has advanced well and the EC Trialfinder is now, in 2021, being rolled out in its second more advanced phase.
- To link with more academic groups working in basic/ translational science at an early stage with the Novel Agents Subgroup to help define and develop promising new targets/ therapies along with colleagues in the ECMC combinations alliance and CRUK Centre for Drug Development.

Appendix 3

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. Enshaei A, O'Connor D, Bartram J, et al. A validated novel continuous prognostic index to deliver stratified medicine in pediatric acute lymphoblastic leukemia. Blood. 2020;135(17):1438-1446	The authors used retrospective trial data to develop and validate a patient-specific prognostic risk index including white cell count at diagnosis, pretreatment cytogenetics, and end-of-induction minimal residual disease that outperforms existing risk algorithms and can be used in future trials in acute lymphoblastic leukaemia	Senior author Anthony Moorman, member of the Leukaemia Subgroup; the studyinvolved several members of the Subgroup
2. Veal GJ, Tweddle DA, Visser J, Errington J, Buck H, Marange J, Moss J, Joseph S, Mulla H. Pharmacokinetics and Safety of a Novel Oral Liquid Formulation of 13-cis Retinoic Acid in Children with Neuroblastoma: A Randomized Crossover Clinical Trial Cancers (Basel). 2021 Apr 14;13(8):1868.	13-cis-retinoic acid (13-CRA) is a key component of neuroblastoma treatment protocols. This randomized crossover study compares the pharmacokinetics (PK), safety and palatability of a novel oral liquid formulation to the current method of extracting 13-CRA and has led to the (pending) availability of a liquid forumulation of 13-CRA	Conceived and led by members of the NCRI Children's Group & Neuroblastoma Subgroup
3. Ladenstein R, Pötschger U, ValteauCouanet D, Luksch R, Castel V, Ash S, Laureys G, Brock P, Michon JM, Owens C, Trahair T, Chi Fung Chan G, Ruud E, Schroeder H, Beck-Popovic M, Schreier G, Loibner H, Ambros P, Holmes K, Castellani MR, Gaze MN, Garaventa A, Pearson ADJ, Lode HN. Investigation of the Role of Dinutuximab Beta-Based Immunotherapy in the SIOPEN HighRisk Neuroblastoma 1 Trial (HR-NBL1). Cancers (Basel). 2020 Jan 28;12(2):309	This study demonstrated improved outcome for patients receiving dinotuximab immunotherapy within the HR-NBL1/SIOPEN trial, supporting its role in standard therapy for High Risk Neuroblastoma	Several UK coauthors; UK contributed many patients to this study.

4. Minard-Colin V, Aupérin A, Pillon M, Burke GAA, Barkauskas DA, Wheatley K, Delgado RF, Alexander S, Uyttebroeck A, Bollard CM, Zsiros J, Csoka M, Kazanowska B, Chiang AK, Miles RR, Wotherspoon A, Adamson PC, Vassal G, Patte C, Gross TG. Rituximab This study resulted in the addition of rituximab to chemotherapy becoming standard of care in High Risk BNHL in children. 2 NCRI Group members are coauthors on this paper: UK centres contributed patients 89for High-Risk, Mature B-Cell NonHodgkin's Lymphoma in Children. N Engl J Med. 2020 Jun 4;382(23):2207- 2219.	This study resulted in the addition of rituximab to chemotherapy becoming standard of care in High Risk BNHL in children.	2 NCRI Group members are co-authors on this paper: UK centres contributed patients
5. Evon Poon, Tong Liang, Yann Jamin, Susanne Walz, Colin Kwok, Anne Hakkert, Karen Barker, Zuzanna Urban, Khin Thway, Rhamy Zeid, Albert Hallsworth, Gary Box, Marli E. Ebus, Marco P. Licciardello, Yordan Sbirkov, Glori Lazaro, Elizabeth Calton, Barbara M. Costa, Melanie Valenti, Alexis De Haven Brandon, Hannah Webber, Nicolas Tardif, Gilberto S. Almeida, Rossitza Christova, Gunther Boysen, Mark W. Richards, Giuseppe Barone, Anthony Ford, Richard Bayliss, Paul A. Clarke, Johann De Bono, Nathanael S. Gray, Julian Blagg, Simon P. Robinson, Suzanne A. Eccles, Daniella Zheleva, James E. Bradner, Jan Molenaar, Igor Vivanco, Martin Eilers, Paul Workman, Charles Y. Lin, Louis Chesler	The drug tested in this study is fadraciclib. On the basis of this publication it is now included in 2 arms of the eSMART study that are led by Dr Marshall, Chair of the Novel Agents Subgroup with the Chesler lab leading on the PD biomarker work.	Senior author is NCRI Neuroblastoma Subgroup member; work being taken forward with leadership from Novel Agents Subgroup.

Orally bioavailable CDK9/2 inhibitor shows mechanism-based therapeutic potential in MYCN-driven neuroblastoma. J Clin Invest. 2020 Nov 2; 130(11): 5875–5892. Published online 2020 Oct 5. doi: 10.1172/JCI134132		

Appendix 4

Recruitment to the NIHR portfolio

Summary of patient recruitment by Interventional/Non-interventional and number of studies opened/closed.

Year	All participants		Cancer patients only*		Number of studies	
	Non-interventional	Interventional	Non-interventional	Interventional	Opened	Closed
2016/17	1319	765	1319	765	10	13
2017/18	967	821	952	821	12	10
2018/19	580	794	580	794	12	16
2019/20	457	497	457	497	11	10
2020/21	567	425	567	425	10	7

*This data is based on a proxy from CPMS (the NIHR database used to collect patient recruitment data) and includes diagnostics, screening and prevention patients.

Appendix 5

Annual report feedback 2019-20

Dear Julia

Re: NCRI Children's Group Annual Report 2019-20

Thank you for submitting an annual report for the Children's Group for 2019/20, especially given the challenges with the ongoing COVID-19 pandemic which will have impacted on both the Group and the report itself.

All the Group's annual reports were reviewed at a two-day meeting on the 12th and 13th October 2020 by a panel consisting of some former NCRI Group Chairs, NCRI CMPath Chair, former NCRI CTRad and the current NCRI Strategic Advisory Group (SAG) Chair, NCRI Head of Research Groups and representatives from the NIHR Cancer Coordinator Centre, NHS Cancer Alliances, epidemiology, CTU/basic science, allied health profession, NCRI Consumer Forum and the Canadian Cancer Clinical Trials Network.

We are writing to you now with a summary of the feedback which is based on the information provided in the report. It was noted that there is likely to be more activity taking place within the Group than is documented.

Please share the contents of this letter with your members for discussion at the next Group meeting.

Generic feedback for all the Groups

Strategic objectives and the impact of COVID 19

- Due to the research funding challenges and restrictions on NHS resources resulting from COVID 19, the Panel recommended the Groups evaluate their strategic objectives and focus on the most important priorities or questions that need to be answered as it would not be feasible for the Groups to be doing everything they planned or continue to "plug in the gaps." Additionally, the Panel suggested looking for more cost-efficient methods of working where they can.
- The Panel felt that the strategic objectives for most Groups were too broad especially in the current climate. The Groups were asked to provide specific, measurable aims for their strategic objective and attach timelines/metrics to them.

Multidisciplinary approach to research and membership

- The Panel noted the importance of collaborative and multidisciplinary working, especially in the current climate, and would encourage all Groups to continue to reach out to other relevant NCRI Groups and consider the NCRI strategic priorities where appropriate.

Linking with the wider research community

- The Groups were asked to link with the wider research community and engage with relevant networks, in particular, with researchers who are developing or are running large national platform studies when there is one available in the disease site e.g. PrecisionPanc (Upper GI Group) and TRACERx (Lung Group). The NCRI recognised that there is a role for them to play in promoting collaboration and will be working with the partners to encourage greater interaction between the Groups and the networks in future.

Funding opportunities

- Given the potential decrease in funding opportunities, the Groups are encouraged to explore alternative funding sources and collaborations e.g. with industry, government funders, NHS Cancer Alliances etc.

Consumers involvement:

- The Panel encouraged Groups to integrate public and patient involvement (PPI) in all aspects of the Group's activities e.g. study design, proposal development, prioritisation of strategic areas etc.
- The Panel wanted to ensure that the consumer activity was captured throughout the report and not just in the consumer section, especially where the consumer reports are missing.

Specific feedback for the Children's Group

Areas of strength:

- The Panel commended the Group on the successful development of a new international standard of care in high- grade neuroblastoma resulting from the HR1 SIOPEN study and the establishment of Stratified Medicine Paediatric (SMPaeds) platform and the link to the eSMART study.
- The Panel was impressed with the significant increase in number of smaller trials open for children, for example, in CNS tumours.
- The Group was commended for their excellent links with the international children's community.
- High success rate with funding application submissions.
- The Panel was impressed with the active consumer involvement in the Group, with strong links to European groups and the WHO Childhood Cancer Global Initiative.
- The addition of the Paediatric NHL Subgroup (which was previously led by the Lymphoma Group) was welcomed by the Panel, as it will allow researchers with the relevant expertise and knowledge in paediatric oncology to have oversight of and input into the Subgroup.

Areas which the Group need to consider:

- The Panel lauded the Group's strategy to have a trial open for all paediatric cancer patients but urged the Group to prioritise their objectives given the funding challenges ahead and limit on NHS resources resulting from COVID-19.
- The Panel noted that while each of the Subgroups had wide ranging strategic objectives, the over-arching Group strategy is limited. The Group were asked to consider developing an "over-arching" strategy.
- The Panel recommended the Group to incorporate pre-clinical science in their strategy.

- With regards to consumer involvement, the Panel would be interested in hearing more about the James Lind Alliance (JLA) Priority Setting Partnership and their involvement with CRUK strategy on developing their research strategy on childhood cancers i.e. when these were completing and how consumer representative in question would feed into these initiatives.

Congratulations to you and your members for all your hard work and achievements in 2019/20.

If you have any comments on this year's process, please send them to Nanita Dalal (Nanita.Dalal@ncri.org.uk) for collation.

Best wishes,

Professor Tim Maughan
NCRI Strategic Advisory Group Chair
Professor of Clinical Oncology
University of Oxford

Dr Gillian Rosenberg
NCRI Head of Research Groups

Appendix 6

Quinquennial review feedback - 2021

Strengths

- The panel commended the Group for providing children with cancer with numerous options for trials in the UK, with the exception of some rare cancers such as Juvenile Myelomonocytic Leukaemia (JMML).
- The panel agreed that the Group's trial portfolio was broad and comprehensive.
- Great consideration and inclusion of Patient and Public Involvement (PPI) in the work of the Group was noted by the panel. As the parent voice is growing, the panel suggested that it may be worth exploring the opportunities for working more closely with parent groups surrounding clinical trial access and delivery. The panel suggested that the Group could further improve their PPI activity by collaborating more with other RG's consumers, such as Teenage and Young Adult & Germ Cell Tumour (TYA&GCT) Group, as well as external organisations such as the Children's Cancer and Leukaemia Group (CCLG).
- The Group has been networking well with other Groups within the NCRI as well as external organisations.
- The report demonstrates the high number of UK investigators that are active in European committees.

Areas for consideration

- The panel noted that there was a lack of translational scientists on the main Group and Subgroups, with this work being heavily reliant on just two Subgroup members.
- The panel recommended for the next Group strategy setting a smaller number of more focussed objectives with specific metrics and timelines, whilst encouraging the Group to ensure that cross-cutting themes are embedded and prioritised.
- The panel recommended for the future Children's Group strategy to consider carefully the area of precision medicine.
- It was not clear from report how UK researchers are influencing trials developed in the EU and how this is measurable.
- The panel recommended that the Group should explore opportunities for collaborating more with the Living With and Beyond Cancer (LWBC) Group, particularly the Late Consequences Group.

Issues for the NCRI to consider:

- NCRI should include an organogram in future QQR information packs to give external panel members an understanding of the structure and function of the NCRI in the UK cancer research landscape.
- Groups of significance to childrens cancer are partially described in the portfolio but not included in the report, such as Hodgkin's Lymphoma, Sarcomas and Wilms tumour.
- The NCRI to consider what is within our remit to address the issues posed by Brexit.

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