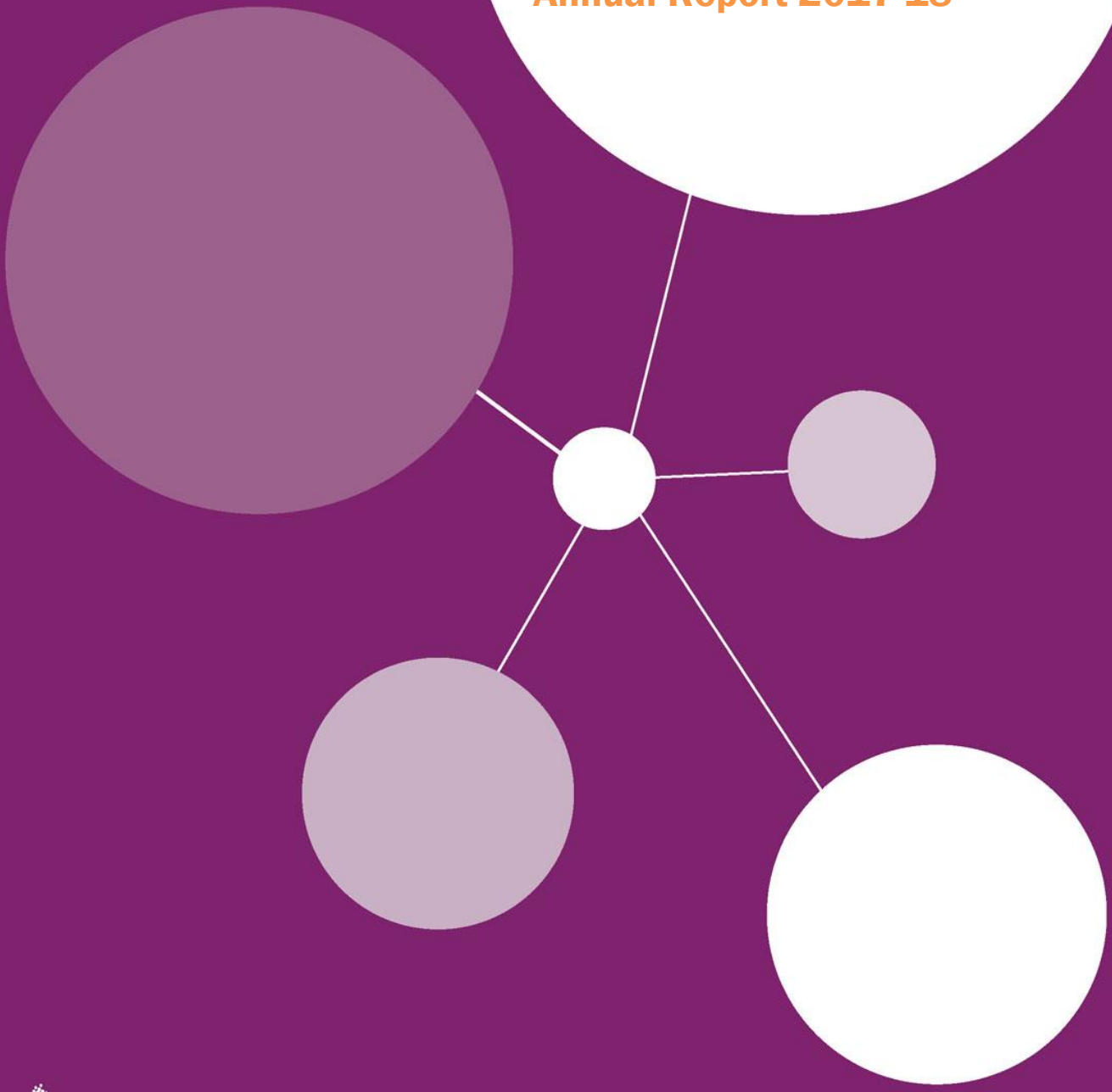
NCRI
National
Cancer
Research
Institute

NCRI Children's Cancer & Leukaemia Clinical Studies Group

Annual Report 2017-18



Partners in cancer research

NCRI Children's Cancer & Leukaemia (CCL) CSG

Annual Report 2017-18

1. Top 3 achievements in the reporting year

Achievement 1

It has been an extremely successful year with eight applications to the Cancer Research UK Clinical Research Committee supported for funding and a further international study invited to submit a full application. This level of funding is unprecedented.

The studies supported address important areas identified in our previous strategy. This includes a significant expansion in the portfolio for targeted therapies and precision medicine through the E-smart and Stratified Medicine Paediatrics (SMPaeds).

The portfolio also includes frontline studies for important diagnostic areas (e.g. rhabdomyosarcoma and germ cell tumours) and phase 2 studies exploring new techniques e.g. sequential intensification treatment in neuroblastoma and new targeted agents in combination with chemotherapy across a number of paediatric malignancies.

Achievement 2

The CSG held highly successful Strategy Day on 1 March 2018, which included involvement from a wide range of external stakeholders and other NCRI groups e.g. NCRI Bone Cancer Subgroup, NCRI TYA & GCT CSG, Bloodwise, Experimental Cancer Medicine Centres (ECMC), and NIHR CRN: Cancer. Key areas for research development were identified (Please see Appendix 2 for the new strategy).

Other important areas were discussed including: addressing gaps in the portfolio, further developing the structure of the CSG and strengthening and widening the portfolio studies e.g. to include long term follow up/late effects.

Achievement 3

The CSG hosted a 5th Annual Trials Meeting (November 2017) which was very well received. There was very good from a broad range of professionals who are participating in clinical trials across the UK. Feedback was largely positive and plans are well underway for the November 2018 meeting.

2. Structure of the Group

The CSG has welcomed a number of new members and strengthened partnerships over the last 12 months. In particular Ms Sheona Scales, ECMC Paediatric Network Manager at Cancer Research UK attended the strategy day and will now attend all future CSG meetings as an observer. This supports the CSG's focus in developing new therapeutic options for patients at the time of relapse and the development of new drugs. This direct link will strengthen the development and implementation of studies in this area.

A number of members were reappointed to the CSG this year: Dr Lisa Howell, Dr Martin Elliott, Dr John Moppett and Mr Ian Kamaly-Asl, and continue to support important areas of work (renal tumours, neuroblastoma, leukaemia and surgery, respectively).

Dr Darren Hargrave stepped down as Chair of the Novel Agents Subgroup. Dr Hargrave has contributed enormously to the development of this important research area. He will be succeeded by Dr Lynley Marshall. Professor Keith Wheatley has also rotated off after a very significant contribution to the Group over six years. Dr Veronica Moroz has taken over the role of statistical lead for the CSG.

During the Strategy Day, the lack of a paediatric pathology member on the CSG was highlighted and we plan to address this in the coming year.

3. CSG & Subgroup strategies

Main CSG

The CSG Strategy has been refreshed following the Strategy Day on 1 March 2017. The draft Strategy document is attached in Appendix 2.
An update on the previous strategy is given below.

Portfolio development This has been strengthened significantly by the large number of studies funded this year. There are some gaps in frontline studies e.g. osteosarcoma and the need to develop studies for patients who relapse or for those who have rare tumours with poor outcomes. This is an ongoing challenge and will require new study design and novel approaches to address this unmet need, given the low number of patients in each diagnostic group.
Increasing early phase activity and participation The CSG continues to work closely in partnership with other European groups, specifically to develop trials for rare tumours and increasing early phase research activity and participation. This includes funding of the E-smart study: European proof of concept therapeutic stratification of trial of molecular anomalies in relapsed or refractory tumours, and Stratified Medicine Paediatrics (SMPaeds). Genomic characterisation of relapsed paediatric cancers for diagnostics and stratified therapy will strongly strengthen the ability for patients across the UK to participate in early phase studies. Both studies were developed through the Novel Agents Subgroup.

These research programmes, together with the development of ECMC Paediatric Network will facilitate the entry of patients from centres across the UK. This is a step change in infrastructure, enabling improved access for children, particularly at the time of relapse

There remains a focus on rarer disease where unanswered questions remain.

Successful delivery of clinical trials

The CSG continues to work closely with the local clinical research networks for England and the devolved nations. It has become clear that coordination could be improved through more direct contact between the CSG and the CLRNs and therefore the minutes of the CSG meetings are made available to the speciality leads. The CSG is addressing important issues in delivery including excess treatment costs and the development of research questions relating to the delivery of radiotherapy. There has been a challenge in delays in opening radiotherapy trials because of the RTTQA process. Members or the CSG are working with CT Rad and across the network to improve trial opening.

UK wide and international links

The process for the prioritisation of international clinical trials has been clarified. The UK now hosts a number of international clinical trials through the CRCTU in Birmingham. There have also been successful bids for EU funding (e.g. Horizon 2020) which has supported the international study in hepatoblastoma (PHITT).

CSG structure and function

The CSG has completed the developments that were identified at the previous quinquennial review. The Germ Cell Tumour Subgroup continues to thrive and although the subgroups for renal and hepatobiliary tumours were stood down, studies in these areas are ongoing and comprise an important part of the portfolio.

Consumer involvement and impact

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

Raising Profile

The CSG continues to work for strong links with national and international groups. The Chair presents an update from the CSG annually at the national professional group meeting (Children's Cancer and Leukaemia Group) and there are now strong working links between the CSG subgroups and the CCLG Special Interest Groups where back to back meetings are held wherever possible to optimise professional interaction and trial development.

The Annual Trials Meeting continues to be highly successful. Representatives from all principle treatment centres and many shared care units attend the meeting, thus enabling trial development to be disseminated across the UK.

Central Nervous System Subgroup (Chair, Prof Simon Bailey)

Improve Event Free and Overall Survival

Children with CNS tumours have a variable prognosis with some tumours such as DIPG having a dismal outcome and some such a low grade gliomas a relatively good one. A major aim is to develop trials that sequentially improve the event free and overall survival for all CNS tumour types. With more trails planned this aim is more likely to be realised. In addition, early diagnosis and education via such programmes such as Headsmart in making the public and primary care doctors more aware of brain tumours in children this is gradually improving.

Better identify prognostic and predictive biomarkers and implement their usage

Given the profound consequences of CNS tumours and their treatment for many young people it is important to be able to identify which children may need less intensive treatment and those that need either more intensive treatment or novel therapies. This is best achieved by looking for prognostic and predictive biomarkers based on trial cohorts and then applied as part of subsequent trials. The first CNS trial using this approach is PNET 5 and it will also form part of the stratification in the upcoming high risk medulloblastoma trial. There is a plan that biological stratification will be tested and used in the majority of CNS trials in the future.

Increase the number of clinical trials for children with CNS tumours

Over the last year there have been an increase in the number of clinical trials in children's CNS tumours, given the relative rarity of CNS tumours in childhood it is necessary to run multinational trials usually as part of SIOP Europe. We currently have trials open for low grade glioma, standard risk medulloblastoma, ependymoma and DIPG. In the next year a high risk medulloblastoma trial led by the UK will open and other trials such as infant medulloblastoma, low grade glioma (LOGGIC), high grade glioma and ATRT are in advance stages of development. The aspiration is to have a clinical trial open for each type of CNS tumour.

Application of molecular diagnostics to routine clinical practice

Over molecular diagnostics play an important part in the management of children with CNS tumours. These are now incorporated in a number of clinical trials and in trials to come. In addition, medulloblastoma patients are now able to access free of charge up to date molecular diagnostics and central review irrespective of whether the young person is eligible for a trial or not. It is planned that this sort of service will be offered for children with all tumour types in the future.

Germ Cell Tumour Subgroup (Chair, Dr Sara Stoneham)

Apply for funding for international collaborative, risk stratified, randomised extra-cranial GCT trial CRUK funding obtained February 2018.
Understand the role of biological marker's in risk assessment and tracking treatment Validation and translation into clinical practice as part of AGCT1531 and P3BEP CRUK funded studies.
Review to investigate the Effectiveness of Chemotherapy Treatments for Paediatric Germ Cell Tumours Lancet Oncol. 2016 Apr;17(4):e149-e162. doi: 10.1016/S1470-2045(15)00545-8. Epub 2016 Mar 29. Review.
Secure funding stream to support PROMS alongside AGCT1531/GC4 Secured as part of AGCT1531.
Complete MaGIC trial database analyses for a) TYA patient outcomes and b) dysgerminoma/seminoma and publish a) In final stages of write -up b) Gynecol Oncol. 2018 Jun 5. pii: S0090-8258(18)30921-1. doi: 10.1016/j.ygyno.2018.05.025
Analyse and publish outcomes for GC3 Analysed and in final stages of write up.

Leukaemia Subgroup (Chair, Dr Phil Ancliff)

Open international trials for Ph-pos and infant ALL Ph+ ALL study (EsPhALL2017/COG1631) to be submitted to CRUK for funding next year. International pilot for blinatumomab plus Interfant 06 chemotherapy in set-up at GOS – patients to receive blinatumomab only at GOS, remainder of chemotheraphy at referring centre. UK CSG was the largest national recruiter to Interfant 06.
Contribute to international collaborations in CML and MDS UK accepted in to EWOG-MDS group June 2018. Ongoing efforts to enable anonymous entry of UK CML patients to an international registry.
Agree an international first line ALL trial Agreed. Submitted for funding to CRUK in May. ALL2011 to close end 2018. Aim to pilot 2019 and open early 2020.
Open registries with linked biological sample collection and studies CellBank remains funded at present. Good links to trial patients. Banking on-going as part of MyeChild.
Liaise with new agents group to increase portfolio of phase I and II leukaemia trials Daratumumab (anti CD38 – all lymphoblastic leukaemias) to open over the summer. Innotuzumab (anti CD22 – just B-cell disease) – protracted wrangling between CRTU and Netherlands. CPX 351 – discussions over potential AML relapse protocol. CART programme continues strongly with 3-4 studies open for ALL. CD123 CART (for AML) programme in development, aiming to open Q2 2019. Licensing of Novartis CTL019 (Q3 2018) will pose new challenges with regards to investigational studies.

Neuroblastoma Subgroup (Chair, Dr Mark Gaze)

Diagnosis, staging and risk stratification

The members of the Neuroblastoma Subgroup are also active members of SIOPEN, the International Society of Paediatric Oncology European Neuroblastoma clinical trials organisation. As part of SIOPEN's work, in conjunction with North American colleagues, Subgroup members have contributed to the development of recently published Revisions to the International Neuroblastoma Response Criteria. We have also supported international collaborations on the scoring of mIBG scans, essential for accurate staging, risk stratification and response assessment in high-risk neuroblastoma. Work on circulating biomarkers of disease extent at diagnosis and for monitoring of minimal residual disease continues, and evidence of the association between the levels of circulating neuroblastoma mRNAs at diagnosis and survival in infants and toddlers has been published.

Define molecular targets in NBL

There is a large portfolio of early phase clinical trials of new treatments aimed at novel molecular targets in neuroblastoma. An example is the LuDO trial of molecular radiotherapy with 177-Lutetium DOTATATE which targets the somatostatin receptor subtype 2, which has now completed recruitment. Results should be published in the coming year. A second example is the new trial, MINIVAN, which is being developed together with colleagues in Germany and the USA for relapsed and refractory neuroblastoma, and should open later in 2018. This brings together the molecular radiotherapy with 131-Iodine mIBG which targets the noradrenaline transporter molecule, Together with immunotherapy using the anti-PD1 compound Nivolumab, and the anti-GD2 monoclonal antibody, Dinutuximab Beta.

High Risk NBL

The biggest achievement this year has been the closure to recruitment of the SIOPEN High-Risk trial which has been running since 2002, recruiting over 3,000 patients in total. The UK has been one of the major contributors to this study, consistently recruiting above the target. There have been five randomised comparisons in this trial, which have defined various components of standard treatment for this disease. The R1 randomisation published this year has confirmed BuMel as being better than the American comparator high-dose chemotherapy schedule both in terms of survival and also reduced toxicity. The R4 randomisation has confirmed the European COJEC schedule as equivalent to the American Comparator schedule in terms of response rate, but with significantly lower toxicity. Members of the Neuroblastoma Subgroup have been actively involved in the design of the successor study, the SIOPEN High-Risk 2 trial, which will be the subject of a funding application in the coming year.

Low and Intermediate Risk NBL

Unfortunately, the UK has not been able to participate in recruitment of patients to the SIOPEN LINES trial for low and intermediate risk neuroblastoma, although Subgroup members are committed individuals on the LINES trial committee, and are helping to shape the design of the

next LINES study. The UK has been a good contributor to the Opsoclonus-Myoclonus international trial.

Novel Agents Subgroup (Chair, Professor Darren Hargrave, outgoing)

Developing new trials with academic and industry partners

There are currently 20 open early phase trials; 14 dose finding (phase I/II) and 6 later phase II trials. 75% are industry sponsored. The portfolio concentrates in biologically targeted therapies and immunotherapy with 3 immune checkpoint studies open during 2017; pembrolizumab, atezolizumab and combination studies with nivolumab and ipilimumab in relapsed/ refractory childhood tumours. In addition, there are trials of CAR-T therapies in both neuroblastoma and leukaemia. There are 3 academic studies funded and approved CRISP, eSMART and PARC which will open in 2018. Increasingly studies of both novel: chemotherapy and Novel: Novel combinations are coming onto the protocol a major goal for the group.

Novel agents for poor prognosis tumours at diagnosis and relapse

The portfolio covers CNS, tumours, relapsed leukaemia, neuroblastoma and sarcomas which account for over 50% of deaths from childhood/ Teenage and Young Adults (TYA) cancers but there remain gaps due to rarity and lack of targets for some tumours. Due to this, the group are linking with academic basic translational groups to consider how to target these. At the last NAG meeting we had a discussion on targeting *MYC* as a strategy to target several paediatric tumour types.

Develop and deliver biomarker and pharmacokinetic studies

Final confirmation and awarding from CRUK of the Stratified Medicine Paediatrics (SMPaeds) molecular profiling programme has now provided a national platform for rapid sequencing of relapsed childhood solid tumours. This linked with the Department of Health genomic medicine plans provides a robust mechanism to be stratify patients for precision based clinical trials and also to provide data for analysis to identify, develop and validate new prognostic and predictive biomarkers. The Newcastle Cancer Centre Pharmacology Group led by Dr Gareth Veal remains a valuable national centre supporting clinical trials and leading pharmacology studies.

Implementation of the successful renewed and expanded Paediatric ECMC network The paediatric ECMC network has a dedicated coordinator, Ms Sheona Scales and the Paediatric ECMC strategy group has met twice in 2017-18. Plans to develop 4 regional groups which cover the UK population and pilot regular meetings have already started with the aim of ensuing better coordination, more equitable access and better accrual to patients for early phase trials plus act as a link with the SMPaeds programme. An online clinical trials finder database is being developed by the ECMC network with input from the paediatric group.
Implementation of a UK National "multi-omic" molecular profiling platform and National Molecular Tumour Board The final protocol for the SMPaeds national multi-omic (customised NGS panel, WES, RNASeq, low coverage WGS and methylation sequencing) is almost near completion with an expectation of opening in late 2018. At the same time a system to interpret, report and feedback on clinically relevant (including eligible clinical trials) has been developed which will use a National Molecular Tumour board. Discussions are ongoing to see how this will dovetail with the emerging National Health Service Genome Tumour Advisory Boards.

4. Task groups/Working parties

The CCL CSG have had no task groups or working parties during the reporting year.

5. Funding applications in last year

Table 2 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)				
Study	**Application type**	**CI**	**Outcome**	**Level of CSG input**
May 2017				
E-SMART: European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumours in children	Full application	Dr Lynley Marshall	Supported	Subgroup developed CSG consulted
Stratified Medicine Paediatrics - SMPaeds: Genomic Characterisation of Relapsed Paediatric Cancers for Diagnostics and Stratified Therapy	Full application	Professor Louis Chesler	Supported	Subgroup developed CSG consulted
FaR-RMS: A multiarm-multistage study for children and adults with localised and metastatic Frontline and Relapsed RhabdoMyoSarcoma	Full application	Dr Meriel Jenney	Supported	Subgroup developed CSG consulted
PARC: A Phase II study evaluating the activity of Pegylated recombinant human Arginase (BCT-100)	Full application	Dr Francis Mussai	Supported	CSG consulted
HR-MB: An international High-Risk Medulloblastoma trial	Outline application	Professor Simon Bailey	Invited to full	Subgroup developed CSG consulted
November 2017				
CRISP: A phase Ib of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies (Study ITCC 053)	Full application	Dr Lynley Marshall	Supported	Subgroup developed CSG consulted

VERITAS: An international multicentre phase II randomised trial evaluating and comparing two intensification treatment strategies for metastatic neuroblastoma patients with a poor response to induction chemotherapy	Full application	Dr Guy Makin	Supported	Subgroup developed CSG consulted
AGCT1531: A Phase 3 Study of Active Surveillance for Low Risk and a Randomized Trial of Carboplatin vs. Cisplatin for Standard Risk Paediatric and Adult Patients with Germ Cell Tumours	Full application	Dr Sara Stoneham	Supported	Subgroup developed Led by CCL CSG with input fromGynaecological Cancer CSG and TYA & GCT CSG
HR-MB: An international High-Risk Medulloblastoma trial	Full application	Professor Simon Bailey	Supported	Subgroup developed CSG consulted
Other committees				
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**
None				

6. Consumer involvement

Consumer members of the CSG have remained very active in their roles throughout the course of the year. In addition to their participation in core CSG activities, Mrs Angela Polanco has been a member of the Novel Agents Subgroup and Mr Nick Bird a member of the Neuroblastoma Subgroup.

Through being tuned into the wider parent community, Angela and Nick have been able to bring important issues to the attention of the CSG for discussion, highlighting the need to address gaps in the portfolio and bring a research focus to areas of need identified by patients and those affected by childhood cancer. This has led to positive and actionable responses from researchers with new trial applications and strategy setting based upon this feedback. Other examples of consumer involvement include instigating important discussions around petitions to governing bodies and subsequent parliamentary debates – in particular regarding the treatment of neuroblastoma and DIPG where the UK research community has been directly challenged, and meeting with leading childhood cancer organisations to initiate priority setting partnerships with consumer involvement.

Angela's involvement with PORT (Paediatric Oncology Reference Team) has afforded her the opportunity to contribute to multiple childhood cancer trial information resources to ensure legibility and appropriateness. She has also been involved in an international working group (SIOPE) around improving access to innovative medicines for children with cancer and continues to work closely with key stakeholders. Angela also presented at the NCRI CCL CSG Annual Trials Meeting in November on the importance of PPI in the design and development of clinical trials, providing tangible examples of where consumer involvement at an earlier stage would have been of real benefit. The take home message being that the right kind of PPI is an activity to enhance clinical trial design and development, not merely a tick box activity.

Throughout the year Angela and Nick have provided input at all CSG meetings and contributed to the core work of the group – reviewing and providing feedback on trial proposals and applications for funding. Their insightful analysis brings a parent/patient focus to bear; burden of treatment, meeting unmet needs, potential patient benefit, and the balancing of scientific/research requirements with attractiveness to, and impact on, families enrolling often quite poorly children on studies.

As part of their wider roles within the paediatric cancer community, Angela has been responsible for organising the Childhood Cancer Conference UK alongside CCLG, and Nick has been heavily involved with the work of Solving Kids' Cancer including establishing a new dedicated Senior Trials Coordinator for neuroblastoma within the CRCTU at Birmingham – something that evolved directly as a result of his involvement at CSG meetings. The new post is intended to speed up delivery of trials, particularly those that are international in nature, in neuroblastoma as well as increasing general overall capacity within the team. Both members also attend scientific meetings and conferences as time permits. The insight, experience and knowledge gained from these wider activities helps to engender more meaningful engagement with scientific members of the CSG.

7. Priorities and challenges for the forthcoming year

Priority 1 To continue to the development of clinical trials where there remains a gap in the portfolio. Of note, the current frontline study in Acute Lymphoblastic Leukaemia is due to close and a follow-on study will be required. The next international study in ALL is ready for submission for funding later this year. A strategy for relapsed AML is also an important gap in the portfolio.
Priority 2 To develop a focus on the area of long term follow up/late effects. This will include inviting the Chair of the CCLG Late Effects Special Interest Group to the CSG and identify leads for late effects studies within the CSG.
Priority 3 Ensure a good balance of membership within the CSG. This will include the appointment of a paediatric pathologist to the CSG as this was identified as a priority in the recent strategy day. There is also a need to strengthen the surgical input to align with important developments in paediatric radiotherapy.
Challenge 1 Improve recruitment. Recruitment overall has fallen over the last 12-18 months but it is anticipated that this will steadily improve with the opening of the many studies that have recently been funded. However, it will be important to maintain momentum. Given the very large number of studies due to open across all Principle Treatment Centres in paediatric oncology. The CSG will need to work with the local research networks to prioritise and optimise study opening.
Challenge 2 Further development of 'personalised medicine' research. The CSG will need to seek opportunities for genomic sequencing within paediatric cancers (e.g. full genomic sequencing for patients with ALL) and development new strategies for patients with rarer disease where unanswered questions remain e.g. APL Downs.
Challenge 3 Structure and function of the CSG – there needs to be a focus on succession planning across the CSG and a review of the subgroups, ensuring they are fit for purpose and working efficiently alongside the CCLG and other key strategic partners.

8. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies

- A – Main CSG Strategy
- B – Central Nervous System Subgroup Strategy
- C – Germ Cell Tumours Subgroup Strategy
- D – Neuroblastoma Subgroup Strategy
- E – Novel Agents Subgroup Strategy
- F – Leukaemia Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 – Top 5 publications in reporting year

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

Dr Meriel Jenney (Children's Cancer & Leukaemia CCL CSG Chair)

Appendix 1

Membership of the Children's Cancer & Leukaemia CSG

Name	Specialism	Location
Dr Mark Gaze	Clinical Oncologist	London
Dr Henry Mandeville	Clinical Oncologist	Sutton
Dr Phil Ancliff	Paediatric Haematological Oncologist	London
Dr John Moppett	Paediatric Haematological Oncologist	Bristol
Mrs Angela Polanco	Consumer	Warwick
Mr Nicholas Bird	Consumer	Epsom
Dr Amos Burke*	Paediatric Medical Oncologist	Cambridge
Dr Julia Chisholm	Paediatric Medical Oncologist	Sutton
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Dr Juliet Gray	Paediatric Medical Oncologist	Southampton
Dr Lisa Howell	Paediatric Medical Oncologist	Liverpool
Dr Meriel Jenney (Chair)	Paediatric Medical Oncologist	Cardiff
Professor Pam Kearns*	Paediatric Medical Oncologist	Birmingham
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Professor Bruce Morland	Paediatric Medical Oncologist	Birmingham
Dr James Nicholson*	Paediatric Medical Oncologist	Cambridge
Dr Sara Stoneham	Paediatric Medical Oncologist	London
Professor Deborah Tweddle	Paediatric Medical Oncologist	Newcastle
Professor Simon Bailey	Paediatric Neuro-Oncologist	Newcastle
Professor Darren Hargrave	Paediatric Neuro-Oncologist	London
Professor Andy Hall	Pathologist	Cardiff
Mrs. Julie Evans	Research Nurse	Leeds
Ms Veronica Moroz	Statistician	Birmingham
Mr Ian Kamaly-Asl	Surgeon	Manchester

* denotes ex-officio member

Membership of the Subgroups

Central Nervous System Subgroup		
Name	**Specialism**	**Location**
Dr Phil Hexley**	Brain Tumour Charity rep	Farnborough
Dr Nicky Thorp	Clinical Oncologist	Liverpool
Professor Barry Pizer	Paediatric Medical Oncologist	Liverpool
Professor Steve Clifford	Paediatric Molecular Oncologist	Newcastle upon Tyne
Dr Jenny Adamski	Paediatric Neuro-Oncologist	Birmingham
Professor Simon Bailey (Chair)	Paediatric Neuro-Oncologist	Newcastle upon Tyne
Professor Richard Grundy	Paediatric Neuro-Oncologist	Nottingham
Professor Darren Hargrave**	Paediatric Neuro-Oncologist	London
Dr Andrew Peet	Paediatric Neuro-Oncologist	Birmingham
Dr Sue Picton	Paediatric Neuro-Oncologist	Leeds
Dr Julia Cockle*	Paediatric Oncology Trainee	Leeds
Dr Rebecca Hill*	Paediatric Oncology Trainee	Newcastle upon Tyne
Dr Tom Jacques**	Pathologist	London
Dr Kim Bull	Psychologist	Southampton
Mr Conor Mallucci	Surgeon	Liverpool

Germ Cell Tumour Subgroup		
Name	**Specialism**	**Location**
Dr Gail Horan	Clinical Oncologist	Cambridge
Dr Liz Hook	Histopathologist	Cambridge
Dr Mark Brougham	Paediatric Medical Oncologist	Edinburgh
Dr Juliet Hale	Paediatric Medical Oncologist	Newcastle upon Tyne
Dr James Hayden	Paediatric Medical Oncologist	Liverpool
Dr James Nicholson	Paediatric Medical Oncologist	Cambridge
Dr Anthony Penn	Paediatric Medical Oncologist	Manchester
Dr Sara Stoneham (Chair)	Paediatric Medical Oncologist	London
Dr Sarita Depani*	Paediatric Oncology Trainee	London
Dr Claire Thornton	Pathologist	Belfast
Dr Mathew Murray	Medical Oncologist	Cambridge
Dr Dan Stark	Medical Oncologist	Leeds
Mr Suren Arul	Surgeon	Birmingham

Leukaemia Subgroup		
Name	**Specialism**	**Location**
Dr Rachael Hough**	Clinical Oncologist	London
Mr Neil Ranasinghe	Consumer	London
Dr Anthony Moorman	Genetic Epidemiologist	Newcastle upon Tyne
Dr Brenda Gibson	Haematologist	Edinburgh
Dr Clare Rowntree	Haematologist	Cardiff
Dr Phil Ancliff (Chair)	Paediatric Haematological Oncologist	London
Dr Denise Bonney	Paediatric Haematological Oncologist	Manchester
Dr Michelle Cummins	Paediatric Haematological Oncologist	Bristol
Dr John Moppett	Paediatric Haematological Oncologist	Bristol
Professor Owen Smith	Paediatric Haematological Oncologist	Dublin
Dr Sujith Samarasinghe**	Paediatric Haematological Oncologist	London
Dr Anupama Rao**	Paediatric Haematological Oncologist	London
Dr Donna Lancaster**	Paediatric Medical Oncologist	Sutton
Professor Josef Vormoor	Paediatric Medical Oncologist	Newcastle upon Tyne

Neuroblastoma Subgroup		
Name	**Specialism**	**Location**
Dr Mark Gaze (Chair)	Clinical Oncologist	London
Mr Nicholas Bird	Consumer	Epsom
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Professor John Anderson**	Paediatric Medical Oncologist	London
Dr Guiseppe Barone**	Paediatric Medical Oncologist	London
Professor Louis Chesler**	Paediatric Medical Oncologist	Sutton
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Dr Juliet Gray	Paediatric Medical Oncologist	Southampton
Professor Andrew Pearson**	Paediatric Medical Oncologist	London
Dr Ramya Ramanujachar	Paediatric Medical Oncologist	Southampton
Professor Deborah Tweddle	Paediatric Medical Oncologist	Newcastle
Dr Kate Wheeler	Paediatric Medical Oncologist	Oxford
Dr Elwira Szychot*	Paediatric Oncology Trainee	London
Professor Sue Burchill	Radiologist	Leeds
Dr Simon Wan	Radiologist	London

Professor Keith Wheatley	Statistician	Birmingham
Mr Hany Gabra	Surgeon	Newcastle upon Tyne

Novel Agents Subgroup		
Name	**Specialism**	**Location**
Dr Lynley Marshall (Incoming Chair)	Consultant in Paediatric and Adolescent Oncology Drug Development	London
Mrs Angela Polanco	Consumer	Warwick
Dr Sam Behjati*	Geneticist	Cambridge
Professor Steve Clifford	Paediatric Haematological Oncologist	Newcastle upon Tyne
Professor Ajay Vora	Paediatric Haematological Oncologist	London
Dr Martin Elliott	Paediatric Medical Oncologist	Leeds
Professor Pamela Kearns	Paediatric Medical Oncologist	Birmingham
Dr Guy Makin	Paediatric Medical Oncologist	Manchester
Professor Bruce Morland	Paediatric Medical Oncologist	Birmingham
Professor Josef Vormoor	Paediatric Medical Oncologist	Newcastle
Professor Darren Hargrave (Outgoing Chair)	Paediatric Neuro-Oncologist	London
Dr Andrew Peet	Paediatric Neuro-Oncologist	Birmingham
Dr Gareth Veal	Pharmacologist	Newcastle

* denotes trainee member
**denotes non-core member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

Please note that the below is a draft version of the 2018-2021 CCL CSG Strategy.

Strategic Objective	Action	CSG Lead	Date	Outcomes
Portfolio development: Neuroblastoma	Developing overarching trial for newly diagnosed high risk patients. Further development of portfolio of trials for patients with refractory and relapsed disease Exploring new approaches to neuroblastoma therapy eg MIBG, Nivolumab, Cellular immunotherapy (CAR-T cells).	Martin Elliott Guy Makin Juliet Gray		HRNBL2 in development VERITAS, MINIVAN, BEACON 2 BEACON 1/2, MINIVAN
Portfolio development: Leukaemia	Strengthen representation across the CSG. Development of new frontline Acute Lymphoblastic Leukaemia Trial (Pan European). Focus on patients with incurable disease (Genomics is key).	John Moppett	Submission June 2018	

	Reducing toxicity and deescalating treatment for patients with excellent survival. Work towards new study with Philadelphia positive disease. Work with Adult CSG to explore where it is possible to development joint strategy and trials. Develop strategy for relapsed AML.	Leukaemia Subgroup Chair		
Portfolio development: Germ Cell	Build on International Collaborative Group. (MaGiC) a large database which has enabled re-stratification of the risk groups and an excellent basis for new studies. For extra cranial, low risk, explore opportunities for reducing therapy (role of biomarkers), high risk, explore new trial design e.g. MAMS Engage with TYA to strengthen interface with medical oncologists and paediatric oncologists on subgroup. Publishing joint analyses.	Sara Stoneham		

Strategic Objective	***Action***	**CSG Lead**	**Date**	**Outcomes**
Portfolio development: Bone Tumour	Continue development of Ewing Studies. Osteosarcoma remains a major gap in the portfolio and a strategic aim will need to collaborate internationally. Improve strategic relationship with sarcoma CSG to ensure access of sarcoma studies to paediatric patients. Focus on survivorship, patients routinely disabled. Local therapy questions (radiotherapy) for next Euro Ewing's Study. Formalise reporting from bone sub group to CCL CSG (similar to YOSS)	YOSS Subgroup Chair / Chairs CCL and Sarcoma CSGs CTRad Link		
Portfolio Development: CNS tumours	Trials available for all tumour groups Molecular diagnostics informing all trials To be European leader in brain tumour trials			

	To run biological studies to identify those patients whose treatment can be reduces, and those for whom novel treatment strategies are available Note Gaps in portfolio (e.g. embryonal)			
Portfolio Development: New Agents Group	Consider structure, size and succession planning within Novel Agents Subgroup. Following the launch of ESMART, paediatric ECMC renewal and SMPaeds further development of novel agent trials and longitudinal sampling studies Build expertise in area of epigenetic targeting Increase links with tumour site groups – leading early phase studies (in collaboration with site specific groups) Build capacity in preclinical research Ensure good links with science as well as clinical communities	Chair Novel Agent subgroup		
Portfolio development: Radiotherapy	Increased number of radiotherapy trials (eg IMAT/HRNBL2/FaR-RMS))	Henry Mandeville NB Subgroup Chair		More trials with randomised radiotherapy questions open and recruiting.

	Consider development of trials in Proton Beam Radiotherapy Maintain direct links with CTRad Work with European colleagues on the SIOPE/QUARTET platform to enhance radiotherapy quality assurance in paediatric trials			Recruitment of patients treated with protons in radiotherapy trials Far-RMS HRNBL2 PNET V
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.	CRCTU NIHR lead		

	Managing complex external research approaches e.g. CED and Mexico (DIPG) Need to work with partners outside of the NHS (where evidence base exists). 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	Chair Novel Agents ALL CSG Chair and NCRI lead		
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		

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

Strategic Objective	**Action**	**CSG Lead**	**Date**	**Outcomes**
Relapse	Maintain focus regarding research questions at time of relapse across all paediatric cancers			
Survivorship and Long Term Follow Up	Strengthen the portfolio of studies in the area of LTFU/Late Effects. Invite Chair of Late Effects SIG to CSG. Identify lead for late effects and long term follow up studies Focus on patients with bone tumours in whom the majority have a disability following therapy.	CSG Chair NCRI support		
Consumer involvement	Identify points where consumers can support trial development outside the CCL CSG process (e.g. lowering age limits in adult site specific trials and liaising with other CSGs and wider trial development.	Consumer representatives		

	Develop role in genomics (e.g. ethical approaches to tumour biopsy Development of long term follow up studies Collaboration with TYA CSG about transition from paediatric to TYA care	 CSG Chair with TYA lead		
Pathology	Appointment paediatric pathologist to CSG. 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		
CSG Structure and Function	Ensure appropriate succession planning across the CSG. Encourage next generation of researchers	Sara Stoneham All		Trainee scheme ongoing

	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.	CRCTU and all members NIHR lead and CSG chair CSG Chair		

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.

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.

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. This is in place for the PNET5 trial and is in late development for high risk and infant medulloblastoma as well as other embryonal tumours. This process for other CNS tumour types are in earlier stages of development although a central review process is in place for ependymoma with a weekly national MDT.

C – Germ Cell Tumour Subgroup Strategy

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

Strategic aims

Intracranial

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

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

Extra-cranial

- Maintain and develop links with external stakeholders:

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

Trial development in EC GCT

- Develop common language between stakeholders
  - for staging
  - for risk grouping
  - For surgical approach
- Find shared questions important to answer for stakeholders

- e.g. role of HDT in relapse
- role of microRNA in disease; role of biomarkers of toxicity across all trial design
- PROMs the same between male and female, TYA and adults.

More specifically:

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

D – Leukaemia Subgroup Strategy

Strategic aims

- Open international trials for Ph-pos and infant ALL.
- Continue monitoring recruitment to UKALL 2011, MyeChild01 and InteReALL.
- Contribute to international collaborations in CML and MDS.
- Agree an international first line ALL trial.
- Open registries with linked biological sample collection and studies for APL, DS-AML, CML and MDS.
- Liaise with new agents group to increase portfolio of phase I and II leukaemia trials testing antibody and cellular therapy and targeted agents, especially for T-cell and AML where there is an unmet need.

E – Neuroblastoma Subgroup Strategy

Strategic aims

1. Improve Event Free and Overall Survival for all Neuroblastoma patients.
2. Diagnosis, staging and risk stratification: Refine the prognostic significance of tissue and imaging biological markers and integrate them into stratification of treatment groups in clinical trials.
    - Finalise analysis in current HR study of data linking biological markers and radiology, specifically mIBG scans 2016.
    - Evaluate FDG PET and mIBG PET.
    - Undertake an international retrospective study of ALK mutation testing and next generation sequencing for selected genes from banked DNA samples from patients treated on the high-risk Neuroblastoma trial.
3. Define molecular targets in NBL: Introduce molecular targeted treatments upfront into ultra-high risk and relapsed patient studies.
    - Continue to increase the portfolio of molecularly driven early phase trials for patients with relapsed neuroblastoma in conjunction with the NCRI New Agents Subgroup.
4. High Risk NBL
    - Continue to enrol all eligible UK patients in the SIOPEN HR trial.
    - Work with the European group to develop the next high-risk trial for 2017.
        - Induction chemotherapy: Continue enrolling into R3 to evaluate the best induction regimen.
        - Local therapy: Establish evidence for current local therapy in HR NBL, radiotherapy dose and extent of field and timing and extent of surgical excision of primary tumour.
        - Immunotherapy: Define and refine immunotherapy administration to maximise effectiveness and minimise toxicity.
            - Get the R4 in HR NBL 1 open in the UK and in all centres by 2015 Q3.
            - Open the Phase 1b trial of zoledronate and IL-2 combined with ch14.18 anti-GD2 antibody 2015.
            - Facilitate data collection and analysis regarding immunotherapy in HR study and LTI study 2017.
        - Surveillance: Monitor off treatment HR patients with imaging and molecular monitoring and link with clinical data to better understand patterns of relapse.
            - Set up a randomised maintenance treatment study with biomarker monitoring alongside maybe including DFMO 2016.
        - Refractory disease
            - Get SIOPEN Veritas clinical trial open in the UK by 2016.
        - Relapsed disease: To better understand the biology and clinical characteristics of relapsed Neuroblastoma.
            - Continue recruitment into BEACON study and get amendment through UK regulatory process for additional third randomisation with TOTEM 2015.
            - Await outcome of a grant application for a national retrospective genetic and Epidemiological study of relapsed Neuroblastoma 2015.
5. Low and Intermediate Risk NBL: Facilitate registration and collection of toxicity and outcome data for these Neuroblastoma patients who are not currently treated within a clinical trial as unable to get the SIOPEN LINES trial open in the UK in 2012.

- Participate in the PICORET study, a Horizon 2020 project that is comparing outcome in comparable patients treated within and without a clinical trial. Await grant application 2015 Q4 and, if favourable, participate.
- Achieve UK participation in the SIOPEN spinal cord compression study 2015/16.
- Plan for involvement in next low and intermediate risk NBL trial if it involves further randomisations.

F – Novel Agents Subgroup Strategy

Strategic aims

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

Appendix 3

Portfolio maps

NCRI portfolio maps

Children's Cancer and Leukaemia

Map B – Leukaemia, lymphoma, all cancers

Click ↓ below to reset map

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

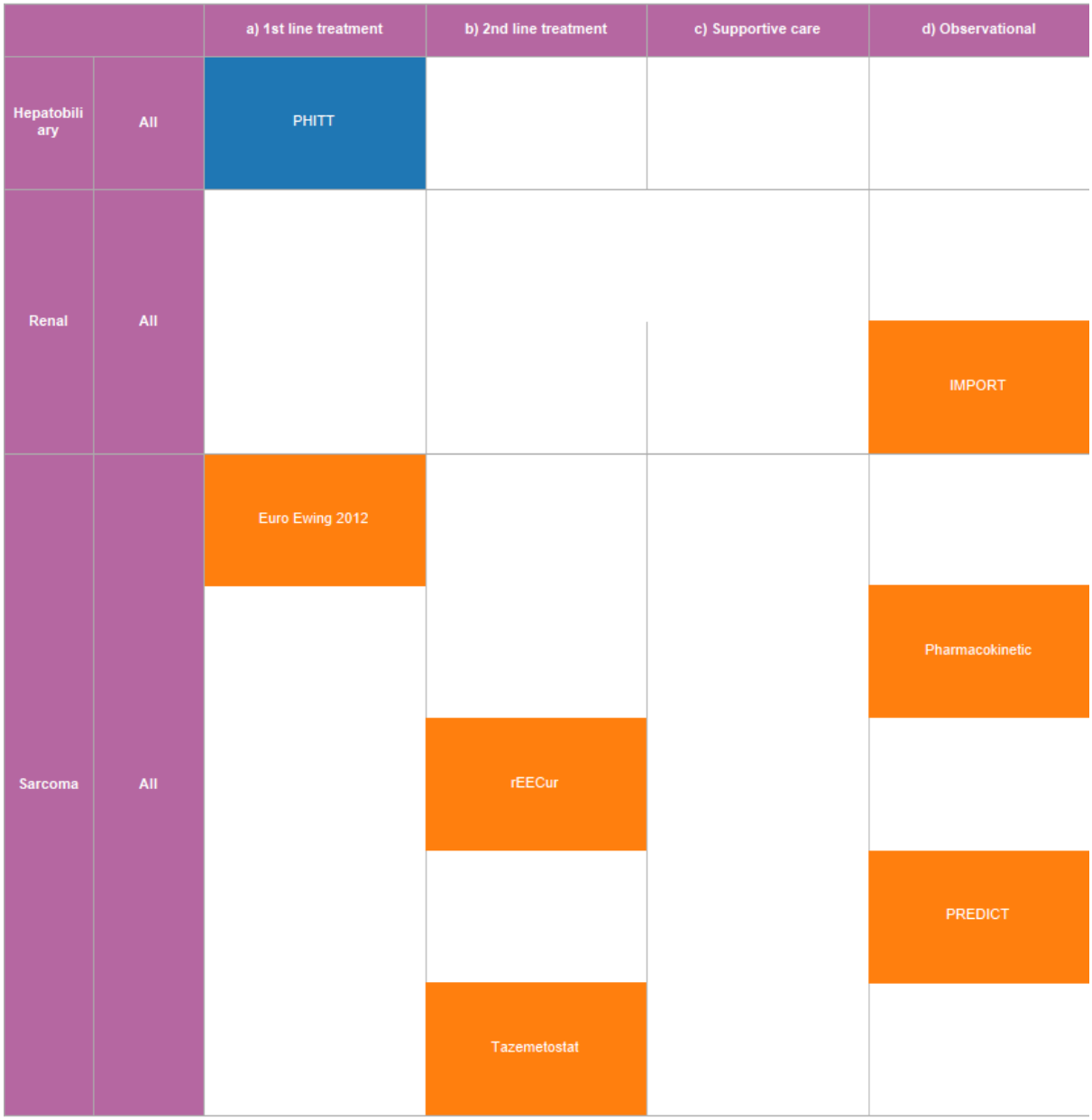
Null | In Setup / single re.. | Open / single rese..
In Setup / multi res.. | Open / multi resea.. | Suspended / singl..

NCRI portfolio maps

Children's Cancer and Leukaemia

Map C – Renal, sarcoma, melanoma, hepatobiliary

Click ↓ below to reset map



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

Open / single rese..
Open / multi resea..

NCRI portfolio maps

Children's Cancer and Leukaemia

Map D – Novel agents

Click ↓ below to reset map

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

Open / single rese..

Appendix 4

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia. O'Connor D, Moorman AV et al, J Clin Oncol. 2018 Jan 1;36(1):34-43	Direct impact on patient care as stratification is now a key part of patient management.	CSG supported
2. Use of Minimal Residual Disease Assessment to Redefine Induction Failure in Pediatric Acute Lymphoblastic Leukemia. O'Connor D, Moorman AV et al J Clin Oncol. 2017 Feb 20;35(6):660-667.	Direct impact on patient care as stratification is a key part of patient management.	CSG supported
3. Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. Park JR et al, J Clin Oncol. 2017 Aug 1;35(22):2580-2587.	Direct impact on patient care.	CSG supported

4. Topotecan-Vincristine-Doxorubicin in Stage 4 High-Risk Neuroblastoma Patients Failing to Achieve a Complete Metastatic Response to Rapid COJEC: A SIOPEN Study. Amoroso L et al, Cancer Res Treat. 2018 Jan;50(1):148-155.	Direct impact on patient care	CSG supported
5. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Ladenstein R et al, Lancet Oncol. 2017 Apr;18(4):500-514.	Defined standard of care in frontline therapy	CSG supported

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Children's Cancer & Leukaemia CSG portfolio, 15 trials closed to recruitment and 8 opened.

Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2013/2014	1419	625	751	625	-	-
2014/2015	1605	643	795	643	-	-
2015/2016	1412	715	749	715	-	-
2016/2017	1228	630	594	630	-	-
2017/2018	914	698	468	698	-	-