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NCRI Haematological Oncology Clinical Studies Group

Annual Report 2015-16

Partners in cancer research

NCRI Haematological Oncology CSG
Annual Report 2015-16

1. Executive Summary (including top 3 achievements in the year)

The Haematological Oncology CSG is one of the largest and most complex CSGs, with seven disease-specific Subgroups, one Working Group and an overall trial portfolio approaching 100 studies. In addition to contributing to the design of individual study proposals, the CSG plays a crucial cross-cutting role in setting expectations, sharing best practice and addressing common challenges. The CSG also provides a framework for co-ordinating and driving forward research in areas that transcend individual disease areas such as supportive care/late effects, stem-cell transplantation/cellular therapy and TYA. During the last reporting period, the CSG has built on its performance in previous years in terms of trial development, with a high level of success in obtaining funding for new studies. Links with other relevant parties including other CSGs, industry partners, international collaborative groups and LCRN Subspecialty Leads have been further strengthened, and the CSG has continued to engage with local clinical research teams and national patient groups via the Annual Haematological Oncology Trials Review Meeting and disease-specific educational events. The CSG has also had a major impact on clinical practice through the delivery of several pivotal studies and through the contribution of CSG/Subgroup members to numerous NICE appraisals.

The CSG has also faced a number of challenges during the last reporting period. For the first time in several years, trial recruitment has fallen significantly. This is almost certainly due to a gap between the AML17 and AML19 trials for fit patients with AML and underscores the extent to which recruitment into the overall CSG portfolio depends on the availability of a small number of frontline trials in numerically important disease areas such as AML and myeloma. It is therefore crucial that the next frontline myeloma trial is put in place as soon as possible. Another challenge faced by the CSG is to maintain its excellent track record of funding for new studies. This challenge is especially pertinent given that supportive care is now of one of the CSG's new focus areas yet appears to be a low priority area for funding bodies such as Cancer Research UK and NIHR HTA. These challenges are compounded by the recent financial problems encountered by Bloodwise.

2. Structure of the Group

The CSG brings together seven different Subgroups, each focussing on specific disease areas (AML, ALL, CML, CLL, myeloma, MPN, MDS). In addition, a Supportive Care, Transfusion and Late

Effects Working Party has been established. Current CSG members include 14 clinicians, two statisticians, a senior trial co-ordinator, two consumer members, two NCRI Training Fellows and a representative from Bloodwise (formally known as LLR) – the latter providing a crucial link through to the Bloodwise Trials Acceleration Programme (TAP). The CSG currently has representation from most regions in the UK including two of the three devolved nations.

3. CSG & Subgroup strategies

Main CSG

The CSG's scientific strategy is to improve the objective and patient-reported outcome of haematological cancers through the development and evaluation of stratified and/or response-adapted approaches to therapy based on predictive biomarkers and sensitive assessment of residual tumour burden, coupled with the optimisation of supportive care and recognition and management of late effects. At the core of this strategy is the need for innovative trial design, coupled with high-quality biobanking as a platform for cutting edge biomarker discovery/development projects. Engagement with Genomics England Ltd and co-ordination of research endeavours through the Haematological Oncology GeCIP will be a crucial part of this initiative. Operationally, the CSG aims to maintain a balanced and continuously replenishing portfolio of academic and industry studies in all major disease areas, using data from the CSG's early-phase trial programmes (including those funded by LLR and Myeloma UK) to inform on the next generation of phase III studies. International collaboration will be actively sought to accelerate the delivery of trials in small study populations.

In addition, the CSG aims to expand research in supportive care, transfusion and late effects as important cross-cutting themes. This will be achieved through the recently established Working Party. The CSG also aims to apply a more co-ordinated approach to transplant and cellular therapy studies by working more closely with the BSBMT. Finally, the CSG aims to establish closer collaborative links with the CCL and TYA CSGs to ensure an optimally co-ordinated approach for all TYA patients with leukaemia.

ALL Subgroup (Chair, Professor Adele Fielding)

- Obtain maximal grant funding from diverse sources: Obtained a >2.5M CRUK program grant (Co-PI, Fielding and Moorman) "Personalizing therapy for adults with ALL" in collaboration with Sanger Institute to work on aspects of ALL genomics using specimens from the UKALL14 and UKALL60+ trials.
- Work optimally in collaboration with industry: We completed to time and target two large commercial RCT of novel agents in relapsed ALL both of which are likely to be practice changing. UK was a large and significant recruiter to Amgen studies of blinatumomab in relapsed ALL and will be represented on the academic output from these studies.
- Engage collaboratively with adult and paediatric ALL study groups worldwide:
    - We are working well with the Dutch Belgian group HOVON on UKALL60+. We continue to work in good collaboration with the UK paediatric group on ALL studies with specific representatives (Rowntree and Hough) working across the paed/adult divide.
    - We are active members of the European Working Group on ALL.
    - Two of our members were selected to present within the ALL educational sessions at ASCO in the past year (Fielding and Marks). The chair, Fielding, was selected as a plenary introducer at the American Society of Haematology for 2015 which demonstrates the international reach of our work.

AML Subgroup (Chair, Professor Nigel Russell)

The UK has been at the forefront of improving outcome in AML using innovative trial design that asks multiple randomised questions. One of the reasons of the success of these trials is their logical development, with the key findings from the previous trial being incorporated into the design of the following one. Thus AML19 incorporates findings from AML15 and 17 and design of AML18 is heavily influenced by findings from AML16.

Our objectives have evolved over the last few years to include the introduction of selective, molecularly targeted therapies into the existing backbone of chemotherapy, to develop an increasingly personalised approach to therapy, and to utilise MRD assessments and predictive molecular signatures of treatment response that will allow appropriate stratification of therapy. This has most recently been validated in NPM1 +ve AML where MRD assessment can stratify patients into good and poor risk. APL is the obvious success story of targeted therapy on AML. Further targeted interventions may follow with the advent of more potent FLT3 inhibitors, IDH1 and IDH2 inhibitors and MLL-targeting approaches. This increasing complexity of diagnostic sub-stratification in AML and greater recognition of the need for a stratified approach targeting specific subgroups means that collaborations with other European AML Study groups will be increasingly important.

CML Subgroup (Chair, Professor Mhairi Copland)

The CML Subgroup aims to deliver world class clinical research across all phases of CML, contribute to the development of best practice in the management of CML and provide education for healthcare professionals and patients to improve outcomes for all CML patients. SPIRIT2, the largest study comparing first-line imatinib versus dasatinib, continues in follow up and three year data will be reported this year. The SPIRIT2 Biobank continues to be a rich source of translational research articles and presentations. The opening of SPIRIT3 has again been delayed due to the buyout of Ariad's European operations by Incyte. The full implications of this for SPIRIT3 are, as yet, unclear. The first 12 month de-escalation phase of DESTINY and the CHOICES clinical trial will be reported at ASH this year. MATCHPOINT and OPTIC are open and continuing to recruit. This year, we have welcomed a consumer representative. A national education event for CML patients was held in London in November 2015 with internet/social media streaming. Further events for both Healthcare Professionals and Patients/Carers will be held in Manchester in September 2016. Moving forward, our key strategic aim is to open a UK-wide study for newly diagnosed chronic phase CML patients (SPIRIT3 or alternative).

CLL Subgroup (Chair, Professor Peter Hillmen)

The CLL sub-group runs Phase III trials for previously untreated patients with CLL supported by a series of Phase II trials run through the Bloodwise TAP programme studying novel agents and combinations to inform the design of the future Phase III trials. Trial associated translational research is of central importance and depends on samples stored in our UK CLL Trials Biobank. The strategy for the group is to streamline the Phase II trials, translational research and Phase III trials to move rapidly towards logical combinations of agents, to test them quickly, to progress to prolongation of remissions and as quickly as possible to cure.

The Phase III trials test the replacement of chemoimmunotherapy with targeted treatment (ibrutinib plus rituximab in FLAIR), which is the best chemomimmunotherapy in unfit patients (RIAltO) and consolidation therapy for MRD positive patients following conventional therapy (GALACTIC). We are currently adapting FLAIR to add an arm combining ibrutinib plus venetoclax on the basis of data from our Bloodwise TAP CLARITY Trial in relapsed CLL. This will increase the

size of the trial to over 1,400 patients making it the largest Phase III trial ever performed in CLL and has recently been approved by the CRUK.

MPN Subgroup (Chair, Professor Claire Harrison)

The MPN Subgroup aims to deliver world-class clinical and translational research. The portfolio is very broad and recruiting well. The MOSAICC pilot has finished recruiting. MAJIC completed recruitment for ET, has completed primary analysis for this group of patients, and has almost completed recruitment for PV. MPD RC112 is recruiting well, as is MPD RC114. The Phazar study opened in the last quarter of the year and has completed recruitment into the first cohort. We anticipate the TAMARIN study will begin recruitment shortly. For commercial studies, the UK has top recruiting sites for the pacritinib studies PERSIST-1 and PERSIST-2, where the global CIs are Subgroup members. The Subgroup continues to generate translational research of the highest calibre. In particular, the flagship "Causes of Clonal Haemopoiesis" project has led to the discovery of a prevalent mutation in the calreticulin gene (NEJM 2013), the elucidation of the clinical importance of the sequence in which multiple mutations are acquired in MPNs (NEJM 2015), and the identification of factors that predispose to MPNs. Partnership with patient representation and charities is strong. Two national education events for clinicians and patients, respectively, were held in November 2015 together with six regional patient advocacy meetings.

MDS Subgroup (Chair, Dr Dominic Culligan)

During the last 12 months, the MDS Subgroup has continued the Phase II ELASTIC study of azacitidine and eltrombopag in high risk MDS which has just received approval to open Cohort 3, and a joint study with the National Blood authority; REDDS, which has recruited well. The Subgroup has received funding from LLR for a phase II study in CMML with the drug Terfinostat and the last twelve months has led to ethical and MHRA approval. The contracts are to be signed and the trial will hopefully open in the third quarter, 2016. There is less good news on our lead Phase III approach to develop a randomised, Phase III, placebo controlled trial of antibiotic prophylaxis. The trial; RAPRIMA, was declined for funding by HTA as it did not fit into their current portfolio. However, a submission for funding was made to Bloodwise in July 2015 and following an invited resubmission in February 2016, with appropriate modifications and clarifications, the Bloodwise clinical trials group recommended that the trial be funded. However, the Trustees of Bloodwise declined this recommendation because of financial difficulties at the Charity. This has been more than two years of work for the Subgroup and is incredibly disappointing. We have recently started work on a potential randomised phase II study of the novel regimen VBaP for anaemic low risk MDS patients.

The Subgroup has engaged with a number of Companies with the aim of developing a portfolio of Phase I, II and III studies. The commercial portfolio contains five open studies. We have added to the portfolio over the last year with four interesting therapies including Rigosertib for high risk disease (Open) and Luspatercept, (ACE-536) for sideroblastic anaemia, opening quarter 3, 2016.

Myeloma Subgroup (Chair, Professor Gordon Cook)

The Myeloma Subgroup continues to oversees a large trial portfolio, (phase I-IIIb), incorporating the accelerated therapy Clinical Trials Network (Myeloma UK CTN). The portfolio incorporates both academic and commercial studies, with outputs contributing significantly contributing to clinical practice both in the UK and internationally. For example, following from the publication of the first manuscript from Myeloma X trial, the results have now been incorporated into the International Myeloma Working Group Guidelines on relapsed disease management. The current front-line phase III study, Myeloma XI/XI+ is nearing recruitment target, so planning is underway

for a replacement studies: Myeloma XIV and XV. Our frontline supportive care study, TEAMM, nears completion of the recruitment target and will contribute in an impactful way to the international management guidelines for myeloma. We completed recruitment to the phase II allogeneic stem cell transplantation trial, LenaRIC, and whilst we continue in the follow-up phase, an abstract to ASH this year will be based on immune biomarkers. The Myeloma UK CTN continues to expand its accelerated trial portfolio, with four studies completed, three studies actively recruiting and four in the planning stage. The portfolio continues to be attractive to commercial collaborators and now includes systemic immunotherapy studies.

4. Task groups/Working parties

Supportive Care, Transfusion & Late Effects Working Party (Chair, Professor John Snowden)

The SCTLE WP was approved in 2015 to assess the feasibility of studies of blood transfusion, late effects and survivorship, palliative care and psychosocial aspects over a two year period. Membership includes representatives from relevant Haem Onc CSG Subgroups, NHSBT, Supportive and Palliative Care CSG, Psychosocial Oncology and Survivorship CSG, TYA CSG and patient representatives.

The current portfolio includes a number of fully recruited and open studies covering late effects (TRYMS: Testosterone Replacement in Young Male cancer Survivors), palliative medicine (factors associated with place of care and place of death); transfusion studies (TOPPS, INCITE, TREATT, HLA Epitope, RING, REDDS and REDEEM). Work has also commenced in five further agreed projects:

1. Intravenous immunoglobulin as infection prophylaxis in haemato-oncology and HSCT.
2. Cardiometabolic risk factors and late effects in survivors of haematological cancer and HSCT.
3. Fertility and pregnancy following intensive (non-transplant) treatment for acute leukaemia.
4. Psycho-social impact of watchful-waiting strategies in chronic haematological malignancies.
5. Rehabilitation strategies post-intensive chemotherapy for acute leukaemia and autologous HSCT for myeloma. The WP continues to meet regularly via teleconferences to progress these projects with a view to completion of systematic reviews and grant applications by summer 2017.

5. Patient recruitment summary for last 5 years

The Haematological Oncology CSG has enjoyed a year-on-year increase in patient recruitment to both interventional and non-interventional studies over the last three years. However, recruitment figures from 2015/2016 shown a significant downturn. This likely reflects the fact that for much of the reporting period there was no trial for younger patients with AML following the closure of AML17 in Dec 2014. Thus AML trials account for a large proportion of the CSG overall recruitment figures (AML17 recruited >3500 patients from >100 centres). A successor to AML17 (AML19) was launched in November 2015 and will hopefully restore overall recruitment figures to their previous levels during the next reporting period. These trends illustrate the importance of maintaining continuity wherever possible between one trial and the next, especially in high-recruiting areas such as AML and myeloma.

In the overall Haematological Oncology CSG portfolio, 28 trials closed to recruitment and 30 opened during the reporting period indicating that the portfolio is in steady state with respect to the number of studies.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2011/2012	2910	2757	2807	2757	26.4	25.9

Table 2 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
2012/2013	2708	3109	2572	3099	19.5	23.5
2013/2014	2925	3027	2818	3027	21.4	23.0
2014/2015	3132	3320	2972	3320	22.5	25.2
2015/2016	3068	2705	3064	2704	23.23	20.5

6. Links to other CSGs, international groups and network subspecialty leads

- A trial for high-risk solitary plasmacytoma (IDRIS) has been developed in collaboration with CTRad.
- The CSG has representation on SPED via the Myeloma Subgroup.
- It has been agreed with the NCRI Lymphoma CSG that there should be a single, joined-up approach to CLL, ALL and Waldenstrom's macroglobulinaemia, as well as lymphoma transplant studies.
- It has been agreed with the Children's Cancer and Leukaemia CSG that patients with ALL up to 24 years of age should enter UKALL2011 (rather than UKALL14).
- The MDS and MPN Subgroups have worked with the Palliative and Supportive Care CSG to develop red-cell transfusion studies.
- The Danish, Irish and Dutch/Belgian HOVON groups are recruiting into UKALL60+.
- Australia and New Zealand have expressed an interest in joining UKALL14.
- The CLL Subgroup has links with the German CLL Study Group through reciprocal membership of DMCs.
- Australia, New Zealand, France and the Mayo Clinic are recruiting into PT1.
- A new study is being developed for PV with the French and Nordic groups.
- CSG and Subgroup members are active contributors to the European Working Group on ALL (EWALL), the European Research Initiative in CLL (ERIC) and the CML Working Group.

7. Funding applications in last year

Details of submissions to funding bodies other than Cancer Research UK were received from the Myeloma Subgroup only.

Table 3 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
May 2015 (Bloodwise)			
Assessment of the Mechanism of Action of Venetoclax (ABT-199) in combination with Ibrutinib (PCI-32765) in relapsed/refractory Chronic Lymphocytic Leukaemia (CLARITY)	Bloodwise TAP Programme Application	Professor Peter Hillmen	Funded
July 2015 (CTAAC)			
SPIRIT 3: a phase 3 randomised trial to evaluate the most effective way to use imatinib, nilotinib, dasatinib and ponatinib in newly-diagnosed chronic phase CML	Full application *Amendment*	Professor Stephen O'Brien	Approved (no cost)
December 2015 (Bloodwise)			
Core support for biobanking as part of NCRI trials in CLL and lymphoma	Extension of funding	Professor Andrew Pettitt	Funded
LCK as a predictive biomarker of in-vivo BCR engagement and therapy response in chronic lymphocytic leukaemia	Feasibility application	Dr Joseph Slupsky & Dr Ke Lin	Not funded
May 2016			
FLAIR: Front-Line therapy in CLL: Assessment of Ibrutinib + Rituximab (previously known as CLL10): Amendment to add two additional arms – ibrutinib monotherapy and ibrutinib plus ventoclax	Full application *Amendment*	Professor Peter Hillmen	Recommended for Support
A phase 3 trial to assess a novel triplet IRDa versus CRDa in patients with newly diagnosed Multiple myeloma not suitable for a stem cell transplant with randomisation according to frailty between standard therapy and dose adjusted therapy.	Full application	Professor Graham Jackson & Professor Gordon Cook	Funded
Identification of the pathogenetic genomic signature that predicts for dysplastic and leukaemic transformation in severe aplastic anaemia following treatment with eltrombopag	Full application	Professor Ghulam Mufti	Funded
CRUK/12/043: AML 18 - A trial for older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome	Full application	Dr Robert Hills	Recommended for Support
CRUKE/10/052: RIAltO: A Randomised Investigation of Alternative Ofatumumab-based regimens for less fit patients with CLL	Full application	Professor Andrew Pettitt	Recommended for Support
Other committees			
Study	**Committee & application type**	**CI**	**Outcome**
Phase 1B Trial grant for BUBBLE study	LLR TAP	Professor Kwee Yong	Funded
Phase 1B Immune biomarker discovery in VIRel trial (MUK11). £189, 969	Celgene	Professor Gordon Cook	Funded
Non-interventional study of exercise in multipe myeloma (MASCOT study). £40,000	Celgene	Professor Kwee Yong	Funded
Supportive grant for Phase III Myeloma XII trial. £453,434.08.	Takeda Oncology	Professor Gordon Cook	Funded

8. Collaborative partnership studies with industry

The CSG continues to enjoy strong links with industry partners in terms of the large number of industry-led studies on the portfolio plus industry support in the form of free drug and/or central running costs for academic studies. Commericial studies account for approximately one third of trials on the CSG portfolio. Companies with which the CSG collaborates include: Abbvie, Acerta Pharma, Amgen, Ariad/Incyte, Bristol-Myers Squibb, Celgene, Genentech, Gilead, Janssen, Novartis/GSK, Pharmacyclics, ProStrakan, Roche, Sigma Tau. New commercial trials are often (although not always) discussed with the CSG prior to implementation. Such an arrangement is mutually beneficial as it allows a structured approach to portfolio management and minimises competition for small patient groups. One important event that may impact on the CSG portfolio is the recent takeover by Incyte of Ariad who had agreed to fund the SPIRIT3 trial in CML.

9. Impact of CSG activities

UKALL12 changed practice in ALL therapy through routine monitoring of MRD, deployment of stem-cell transplantation, international cytogenetic risk classification and the use of imatinib in Ph+ ALL. In addition, the UK played a leading role the international BITE trial which resulted in the recent FDA approval of blinatumomab for relapsed ALL. The results achieved with Mylotarg in AML15 and AML16 led to it being commissioned as part of AML18 and AML19 despite as yet being unlicensed. Likewise, AML17 is supporting an EMEA licence extension application for arsenic trioxide as first-line therapy for APL and has led to the introduction of MRD monitoring as standard of care in NPM1 +ve AML (NEJM 2016;374:422-33). The frontline COMPLEMENT-1 trial led to the NICE approval of chlorambucil plus ofatumumab in less fit patients with CLL.

In addition, NIHR-adopted industry trials (RESONATE and Gilead 0116) led to the EMA approval of ibrutinib and idelalisib, respectively, for relapsed/refractory CLL. The SPIRIT trial of CML demonstrated that interferon was poorly tolerated in newly diagnosed patients, whereas SPIRIT2 enabled patients to obtain access to dasatinib as first-line treatment. The LEN-5 and CMML201 trials cast doubt on the perceived benefit of azacitidine in CMML and of lenalidomide in high risk MDS with del(5q). The PT1 trial in MPN has saved the NHS ~£20M pa in drug acquisition costs by showing that anagrelide does not offer any advantages over hydroxycarbamide in the frontline setting. Myeloma IX demonstrated that zoledronic acid improves overall survival benefit and changed practice worldwide, while the recently published results from Myeloma X have now been incorporated into the International Myeloma Working Group Guidelines on transplantation in relapsed disease.

10. Consumer involvement

The two CSG consumer members have continued to play an active and valuable role in CSG activities as well as those of the Myeloma Subgroup and the newly-formed Supportive Care, Transfusion and Late-Effects Working Party, and also with Trial Management Groups / Steering Committees. Consumer input and comments were made to numerous CTAAC applications and Patient Information Sheets. The seven Subgroups now all have trained, motivated and active consumer representatives, better able to provide more consistent involvement in all aspects of clinical trials. In addition to the direct links to the Myeloma Subgroup and Supportive Care Working Party provided by the CSG consumer members, a strong relationship with the consumer representative on the ALL Subgroup (John Reeve), has been maintained, and strengthening the

links between all of the Subgroup consumer representatives and the CSG consumer members is a key objective for the coming period to enhance involvement across all groups.

One consumer representative (Lesley Roberts) was a member of the NICE Myeloma Guideline Development Group, the guideline was published in February 2016. She is also on two Trial Management Committees, one for PROMS and also ACCORD. She serves on the main board of INVOLVE and is involved in local PPI representation. In her initial year of membership, the new consumer member (Gillian Murphy) has received excellent guidance from her appointed mentors (fellow CSG consumer member, Lesley Roberts and scientific mentor, Professor Adele Fielding) and is developing her role as an NIHR Patient Research Ambassador for her local Trust. Working with patient support groups and blood cancer charities (e.g. Bloodwise/ Anthony Nolan patient experience programmes), and harnessing social media continues to be an effective way of engaging more patients in clinical trials and supporting the development of new trials and treatments.

11. Open meetings/annual trials days/strategy days

The CSG holds an Annual Trials Review Meeting every summer which is organised by the Birmingham CTU and paid for by pharma sponsorship. Feedback obtained from the 2015 meeting was highly positive. In addition, disease-specific meetings bring together interested clinicians, scientists and patients. For example, the UK CLL Forum and UK Myeloma Forum hold twice yearly meetings, while the UK MDS Forum holds a similar annual meeting. The MPN Subgroup runs a biennial two day national update event for clinical staff and patients plus seven regional patient fora in partnership with the patient advocacy group MPN voice. The most recent event was attended by >160 clinicians and >250 patients and included updates on MDS and CML. In addition there is usually a joint CML/MPN day on alternate years. The AML Subgroup held Roadshows in the North West and South West targeting investigators and research nurses to publicise AML Trials.

12. Priorities and challenges for the forthcoming year

Priorities:

- Frontline phase III trials for all disease areas
  It is one of the CSG's aims to ensure that flagship phase III trials are in place across all disease areas, especially high-recruiting areas such as AML and myeloma, and that wherever possible one trial flows seamlessly into the next. Although the recent gap in the AML portfolio has now been plugged, putting in place a new frontline trial for myeloma remains a matter of top priority. Other areas that lack flagship frontline phase III trials are CML, MPN and MDS. A considerable amount of thought and endeavour has been - and continues to be - put into plugging these gaps.
- Development of new studies in Supportive Care, Transfusion & Late Effects
  Having established the new NCRI Working Party, it is crucial that the newly formed group makes tangible progress in developing new studies in this important and fertile area for research. As outlined in Section 4, five areas for development have been identified and it will be important to ensure that ideas are translated into fully worked up funding applications within the next 12 months.

- Developing a CSG strategy for stem-cell transplantation and cellular therapies
  Historically, transplant studies have mostly been developed in an ad-hoc manner by single centres, with little or no consideration given to strategic planning, the size of the study population or overlap with disease-specific studies. Consequently, although there have been notable exceptions, these studies have become notorious for failing to recruit to time and target. One of the CSG's main challenges is to turn this situation around. To this end, the previous clinical lead for transplantation (Professor Karl Peggs) has worked closely with the BSBMT and wider the transplant community to establish a more co-ordinated and realistic approach to these studies. His successor on the group (Dr Andy Peniket) is well positioned to take this work forward through his involvement with the BSBMT.

Challenges:

- Securing funding for CSG studies
  - Obtaining funding for trials is becoming an increasing challenge. This is illustrated by RAPRIMA, which was to be the first ever UK multicentre randomised phase III trial in MDS. The study aimed to randomise ~400 patients with high risk MDS or low blast count AML who were unsuitable for intensive chemotherapy to antibiotic or antifungal prophylaxis, both or neither, in a 2x2 placebo-controlled factorial design. Sixty UK haematology centres would take part. In addition to its intrinsic value, it was anticipated that RAPRIMA would have wider benefits by engendering a culture of clinical research in this important but overlooked area. Given the pragmatic nature of the study coupled with the CSG's understanding that supportive care studies are not a high priority for Cancer Research UK, a funding application was initially submitted to the NIHR HTA in mid-2014. However, the application was rejected on the grounds of strategic fit. The proposal was subsequently submitted to LLR/Bloodwise in June 2015 following encouragement from the Director of Research (Professor Chris Bunce). Feedback from the committee was positive, and a resubmission was invited addressing issues around placebo costs and the linkage of funding to specific milestones. The revised proposal was considered at the February 2016 meeting but was not approved owing to a general shortage of funds.
  - RAPRIMA has been the main focus of the MDS Subgroup for two years as an attempt to engage the UK community in an MDS phase III trial, which has never happened before. The lack of effective drugs, the age and frailty of the patient group and the high dependence on supportive care in this patient population made this trial attractive. This saga begs the question of whether it is worthwhile developing new trials in areas such as this if it is not possible to obtain funding for trial delivery. Another example of a major funding problem relates to the SPIRIT3 trial in CML. The company that had agreed to fund the study (Ariad) has recently been taken over by another company (Incyte). The implications for study delivery are not yet clear.
- Alignment of academic and industry studies
  The CSG has excellent links with industry which have underpinned a succession of innovative and successful investigator-led and industry-led studies. Many companies now recognise the benefit of working with the CSG and its Subgroups to ensure that new studies are compatible with the existing portfolio and to proactively manage situations where studies compete for the same patient groups. It is therefore disappointing and

frustrating in equal measure when industry studies that directly compete with existing NIHR studies are added to the CSG portfolio without prior CSG consultation or approval. This is especially true of niche areas that require full national participation for successful trial delivery. Similar considerations apply to the implementation of the TSB Cell Therapy Catapult.

- Developing a coherent CSG strategy for TYA patients
  A significant proportion of haematological cancers affect the TYA age group, most notably ALL where there is compelling evidence that such patients fare much better with more intensive paediatric protocols. Based on this evidence, it has been agreed that TYA patients with Philadelphia negative ALL should be offered entry into the paediatric UKALL2011 trial rather than the adult UKALL14 study. In AML, the paediatric MyeChild study has recently opened for children up to 18 years. It is crucial that there is a consistent and joined up approach to AML patients aged 16-24 that is based solely on clinical considerations. To this end, a clinical lead has been appointed within the CSG (Dr Clare Rowntree) to work with the CCL CSG and delivery networks develop and implement an agreed strategy for these patients.

13. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – MDS Subgroup Strategy
- C – CML Subgroup Strategy
- D – AML Subgroup Strategy
- E – MPD/N Subgroup Strategy
- F – CLL Subgroup Strategy
- G – ALL Subgroup Strategy
- H – Myeloma Subgroup Strategy
- I – Supportive Care, Transfusion & Late Effects Working Party Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Appendix 6 – Strengths & Weaknesses from the Haematological Oncology CSG 2015 Progress Review

Professor Andrew Pettitt (Haematological Oncology CSG Chair)

Appendix 1

Membership of the Haematological Oncology CSG

Name	Specialism	Location
Professor Kwee Yong	Consultant Haematologist	London
Dr Robert Lown*	Consultant Haemato-Oncologist	Southampton
Dr Gillian Murphy	Consumer	Surrey
Mrs Lesley Roberts	Consumer	Leek
Professor Gordon Cook	Haematologist	Leeds
Professor Mhairi Copland	Haematologist	Glasgow
Dr Dominic Culligan	Haematologist	Aberdeen
Dr Adele Fielding	Haematologist	London
Dr Francesco Forconi	Haematologist	Southampton
Dr Paolo Gallipoli*	Haematologist	Cambridge
Professor Claire Harrison	Haematologist	London
Professor Peter Hillmen	Haematologist	Leeds
Dr Richard Kaczmarski	Haematologist	London
Professor Paul Moss	Haematologist	Birmingham
Professor Stephen O'Brien	Haematologist	Newcastle
Professor Andrew Pettitt (Chair)	Haematologist	Liverpool
Professor Ciro Rinaldi	Haematologist	Lincolnshire
Professor Nigel Russell	Haematologist	Nottingham
Dr Clare Rowntree	Haematologist	Cardiff
Professor John Snowden	Haematologist	Sheffield
Dr Alasdair Rankin	Research Director, Bloodwise	London
Ms Shamyla Siddique	Senior Trials Coordinator	Birmingham
Professor Walter Gregory	Statistician	Leeds
Dr Robert Hills	Statistician	Cardiff

*denotes trainee member

Membership of the Subgroups

ALL Subgroup		
Name	**Specialism**	**Location**
Professor Oliver Ottmann	Clinical Professor	Cardiff
Dr Anna Castleton	Consultant Haematologist	London
Professor Anthony Moorman	Epidemiologist	Newcastle
Dr Adele Fielding (Chair)	Haematologist	London
Dr Rachael Hough**	Haematologist	London
Professor David Marks	Haematologist	Bristol
Dr Andrew McMillan	Haematologist	Nottingham
Dr Tobias Menne	Haematologist	Newcastle
Dr Nick Morley	Haematologist	Sheffield
Dr Clare Rowntree	Haematologist	Cardiff
Ms Amy Kirkwood**	Statistician	London
Dr Bella Patel**		London

CLL Subgroup		
Name	**Specialism**	**Location**
Dr Anna Schuh	Consultant Haematologist	Oxford
Dr David Allsup	Haematologist	Hull
Dr Adrian Bloor	Haematologist	Manchester
Dr Chris Fegan	Haematologist	Cardiff
Dr George Follows	Haematologist	Cambridge
Dr Chris Fox	Haematologist	Nottingam
Professor Peter Hillmen (Chair)	Haematologist	Leeds
Dr Chris Pepper	Haematologist	Cardiff
Professor Andrew Pettitt	Haematologist	Liverpool
Ms Dena Cohen	Statistician	Leeds

CML Subgroup		
Name	**Specialism**	**Location**
Ms Sandy Crain	Consumer	London
Dr Nauman Butt	Haematologist	Liverpool
Dr Jenny Byrne	Haematologist	Nottingham
Professor Richard Clark	Haematologist	Liverpool
Professor Mhairi Copland (Chair)	Haematologist	Glasgow
Dr Paolo Gallipoli*	Haematologist	Cambridge
Dr Andrew Goringe	Haematologist	Cardiff
Professor Tessa Holyoake	Haematologist	Glasgow
Dr Brian Huntly	Haematologist	Cambridge
Dr Adam Mead	Haematologist	Oxford
Professor Steve O'Brien	Haematologist	Newcastle
Dr Graeme Smith	Haematologist	Leeds

AML Subgroup		
Name	**Specialism**	**Location**
Dr Robert Lown*	Haemato-Oncologist	Southampton
Professor David Bowen	Haematologist	Leeds
Professor Charles Craddock	Haematologist	Birmingham
Dr Dominic Culligan	Haematologist	Aberdeen
Dr Mike Dennis	Haematologist	Manchester
Dr Sylvie Freeman	Haematologist	Birmingham
Dr Gail Jones	Haematologist	Newcastle
Dr Steven Knapper	Haematologist	Cardiff
Professor Mary Frances McMullin	Haematologist	Belfast
Professor Nigel Russell (Chair)	Haematologist	Nottingham
Professor Keith Wheatley	Statistician	Birmingham

MDS Subgroup		
Name	**Specialism**	**Location**
Professor David Bowen	Haematologist	Leeds
Dr Jamie Cavenagh	Haematologist	London
Dr Dominic Culligan (Chair)	Haematologist	Aberdeen
Dr Mike Dennis	Haematologist	Manchester
Dr Mark Drummond	Haematologist	Glasgow
Emma Das Gupta	Haematologist	Nottingham
Dr Sally Killick	Haematologist	Bournemouth
Dr Juliet Mills	Haematologist	Worcester
Professor Ghulam Mufti	Haematologist	London
Dr Manoj Raghavan	Haematologist	Birmingham
Dr Paresh Vyas	Haematologist	Oxford

MPD/N Subgroup		
Name	**Specialism**	**Location**
Dr Sahra Ali	Haematologist	Hull
Dr Nauman Butt	Haematologist	Wirral
Dr Mark Drummond	Haematologist	Glasgow
Dr Andrew Duncombe	Haematologist	Southampton
Dr Joanne Ewing	Haematologist	Birmingham
Professor Tony Green	Haematologist	Cambridge
Dr Claire Harrison (Chair)	Haematologist	London
Dr Steven Knapper	Haematologist	Cardiff
Dr Adam Mead	Haematologist	Oxford
Professor Mary Frances McMullin	Haematologist	Belfast
Dr Frances Wadelin	Haematologist	Nottingham

Myeloma Subgroup		
Name	**Specialism**	**Location**
Mrs Lesley Roberts	Consumer	Leek
Dr Jenny Bird	Haematologist	Bristol
Dr Andy Chantry	Haematologist	Sheffield
Professor Gordon Cook (Chair)	Haematologist	Leeds
Dr Mark Cook	Haematologist	Bristol
Dr Matthew Jenner	Haematologist	Southampton
Dr Guy Pratt	Haematologist	Birmingham
Dr Karthik Ramasamy	Haematologist	Oxford
Professor Mark Drayson	Immunologist	Birmingham
Professor Walter Gregory	Statistician	Leeds

*denotes trainee member

**denotes non-core member

Supportive Care, Transfusion & Late Effects Working Party		
Name	**Specialism**	**Location**
Dr Eila Watson	Chair in Supportive Cancer Care	Oxford
Dr Stella Bowcock	Consultant Haematologist	London
Dr Harpreet Kaur	Consultant Haematologist	Sheffield
Dr Panos Kottaridis	Consultant Haematologist	London
Dr Donal McLornan	Consultant Haematologist	London
Dr Andy Peniket	Consultant Haematologist	Oxford
Dr Mallika Sekhar	Consultant Haematologist	London
Dr Simon Stanworth	Consultant Haematologist	Oxford
Dr Gillian Murphy	Consumer	Surrey
Professor John Snowden	Haematologist	Sheffield
Dr Sara Ali	Haematologist	Hull
Professor Jenny Byrne	Haematologist	Nottingham
Dr Nick Morely	Haematologist	Sheffield
Professor Andy Pettitt	Haematologist	Liverpool
Dr Clare Rowntree	Haematologist	Cardiff
Ms Laura Meehan	Haemato-oncology Lead Nurse	Glasgow
Professor Sam Ahmedzai	Palliative Medicine	Sheffield
Dr Feng Li	NCRI Survivorship Lead	London
Professor Annie Young	Nurse	Warwick
Dr Jo Armes	Research Fellow	London
Ms Jane Nunnick	Senior Haematology Research Nurse	Birmingham
Dr Rachel Taylor	Senior Research Manager	London

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

The CSG's scientific strategy is to improve the objective and patient-reported outcome of haematological cancers through the development and evaluation of stratified and/or response-adapted approaches to therapy based on predictive biomarkers and sensitive assessment of residual tumour burden, coupled with the optimisation of supportive care and recognition and management of late effects. At the core of this strategy is the need for innovative trial design, coupled with high-quality biobanking as a platform for cutting edge biomarker discovery/development projects. Engagement with Genomics England Ltd and co-ordination of research endeavours through the Haematological Oncology GeCIP will be a crucial part of this initiative.

Operationally, the CSG aims to maintain a balanced and continuously replenishing portfolio of academic and industry studies in all major disease areas, using data from the CSG's early-phase trial programmes (including those funded by LLR and Myeloma UK) to inform on the next generation of phase III studies. In addition, the CSG aims to expand research in supportive care, transfusion and late effects as important cross-cutting themes. This will be achieved through the recently established Working Party.

The CSG also aims to apply a more co-ordinated approach to transplant studies by working more closely with the BSBMT.

Finally, the CSG aims to establish closer collaborative links with the CCL and TYA CSGs to ensure an optimally co-ordinated approach for all TYA patients with leukaemia.

B – MDS Subgroup Strategy

The strategy of the MDS Subgroup is to develop a portfolio of Phase I, II and III studies which cover, as much as possible, low risk and high risk MDS and supportive care questions across all groups. There are a number of challenges in developing trials for MDS patients, which are more acute than for other malignant blood diseases. Firstly, patients are very elderly with a median age of about 73 years. The majority of these patients are managed in District General Hospitals and two thirds are managed with supportive care only, with no active MDS therapy being delivered. Secondly and linked to this, there are very few drugs that currently work in MDS. Presently, only two drugs have a license in MDS: azacitidine for high-risk patients and lenalidomide for a small group of low risk patients with del5q. Furthermore, a very small number of drug Companies have a relative monopoly of drugs for MDS and consequently trial development in this environment is frequently strategic. This is perceived so as not to develop internal competition between drugs and as such puts some restrictions on trial design and innovation by the subgroup. Finally, most drugs in development in haematological cancer are anti-proliferative in their activity. Whilst such therapies have a roll in high risk MDS, they have little or no roll in low risk MDS. Low risk MDS represents two thirds of the patients and treatments to improve bone marrow failure, particularly anaemia, improve supportive care strategies and delay progression of bone marrow failure are needed. Recently, Luspatercept, (ACE-536), has been developed to stimulate erythropoiesis independently of EPO, The group has adopted an exciting Phase II Commercial study in sideroblastic anaemia and this is exactly the type of approach needed in low risk MDS.

The MDS Subgroup strategy includes collaboration with the AML Working Group and UK transplant groups in high risk MDS where there is large overlap in treatment approaches, whilst developing standalone strategies at Phase II and III in supportive care, low risk MDS and novel combination therapies in high risk disease.

During the last 12 months, the MDS Subgroup has continued to recruit to the Phase II ELASTIC study of azacitidine and eltrombopag in high risk MDS and completed recruitment to the first two cohorts of patients. Despite recent closure of a global trial of the combination, SUPPORT, because of futility and a concern about possible progression on the combination, the IDMC has found no such concerns with ELASTIC so far and agreed to open Cohort 3. A joint study with the National Blood authority has recruited well from a difficult group of patients. REDDS. This is a pilot to see if a strategy of randomising MDS patients on supportive care between a permissive and a restrictive blood transfusion regimen is possible. Quality of life is the primary endpoint. The trial has recently opened in New Zealand and an identical pilot in Canada is running in parallel. If successful then the plan is to extend this into an International, multicentre, phase III trial. The Subgroup has received funding from Bloodwise for a phase II study in CMML to follow on from the successful CMML201 trial that was published in Leukaemia in 2014. This study will look at the safety and clinical effectiveness of the monocyte targeted HDAC inhibitor, Terfinostat. If there is acceptable toxicity profile and evidence of efficacy then the group strategy would be to take this forward in a randomisation against hydroxycarbamide or azacitidine. During the last year we have received ethics and MHRA approval and pending contract signatures the trial should open in the third quarter, 2016.

Recruitment to MDS trials remains a challenge internationally. The question of the role of iron chelation in elderly, low risk, MDS patients remains one of the most important. However all three trials run and supported by the subgroup have struggled. Our own De-Iron study looking at the role opened in some 20 UK sites with regular requests from new sites. However, despite several major amendments to ease entry criteria, recruitment remained slow and the DMEC decided to close the trial in November 2016. Thirteen patients were recruited and there is a plan to publish a short safety report once the final patient has completed the study.

The phase III strategy of the Subgroup is to continue to support the large and successful AML trials delivered through the AML Working Group by including appropriate high-risk MDS patients and this currently includes AML 18, LI-1 and AML 19. However, the Subgroup continues to work towards a stand-alone Phase III trial. In terms of therapy the aim is to identify potential combinations with azacitidine that can then be randomised against azacitidine alone. However, this strategy worldwide has yet to identify a successful combination and RAvVA, which fully recruited and closed in late 2015, will add to this knowledge base and ELASTIC may identify an appropriate combination to test further.

Our lead approach for the last two or more years has been to develop a randomised, Phase III, placebo controlled trial of supportive care. This would randomise a wide range of high-risk MDS patients receiving azacitidine or low intensity therapy within the LI-1 trial to prophylaxis with an oral antibiotic or oral anti-fungal drug, both or neither. The primary endpoint would be time to first infection. However, a range of secondary endpoints would look at key health economic issues in these elderly patients, including time in hospital, use of IV antibiotics, antibiotic resistance, and hospital acquired infections and survival. The trial, RAPRIMA, was declined for funding by HTA as it did not fit into their current portfolio. However, a submission for funding was made to Bloodwise in July 2015 and following an invited re-submission in February 2016, with

appropriate modifications and clarifications, the Bloodwise Clinical Trials Committee recommended that the trial be funded. However, the Trustees of Bloodwise declined this recommendation because of financial difficulties at the Charity. This has been more than two years of work for the sub group and is incredibly disappointing. We have recently started work on a potential randomised phase II study of the novel regimen VBaP for anaemic low risk MDS patients and this will be a focus of the group going forward over the next year.

The Subgroup has developed a sizeable Company run portfolio of Phase II and III studies in high and low risk MDS. The group is running throughout the UK the pivotal, worldwide, randomised trial of oral azacitidine vs. placebo for low risk MDS patients (Celgene 003). However, the entry criteria are so precise, perhaps for Company strategic reasons, that recruitment has proved incredibly difficult. This year we are in the process of adding interesting drug trials including a large randomised phase III trial of Rigosertib vs. clinician choice for patients who have failed azacitidine (Open) and most interestingly a phase II trial of the drug Luspatercept, (ACE-536) that promotes erythropoiesis for sideroblastic anaemia.

The Subgroup has engaged with a number of Companies with the aim of developing a portfolio of Phase I studies. This is important given how few therapies are currently available for MDS patients. In particular high-risk patients who fail the only licensed treatment, azacitidine, have a dismal prognosis and this is a major area of unmet need. To this end we have continued to run a Phase I study of antI-IL3 antibody therapy in six sites in the UK which recruits very well and with the UK Government organisation; CATAPULT, opened a Phase I trial of anti-WT1 cytotoxic T-cell therapy in patients who have failed azacitidine.

Finally, the MDS-Bio tissue bank is one of the most successful ventures of this type. With over 5,000 samples and improving linked clinical data, this biomedical resource has already contributed to major breakthroughs in understanding the molecular basis of MDS and the basis of response to some treatments, such as lenalidomide. A significant number of publications in the very top impact factor journals have resulted and the subgroup is linking all future trial development with this platform. The first successful application of this linked approach is ELASTIC.

C – CML Subgroup Strategy

The aim of the CML Subgroup is to improve treatment outcomes and patient experience for all CML patients. In order to achieve this, our strategy is to develop a clinical trials portfolio, including both academic and commercial studies, which will enable us to offer a clinical trial to the majority of CML patients at all stages of their treatment journey. A second aim is to deliver high quality, internationally recognised translational research in CML through the continued support and management of the SPIRIT2 (and SPIRIT3) CML Biobanks.

Key achievements in the last year have been the completion of recruitment to DESTINY, offering optimally patients the opportunity to reduce and stop therapy and the opening of MATCHPOINT for patients with blast phase CML. The CHOICES trial has also completed recruitment and is in follow-up. In addition, there have been high profile presentations of the one year and two year SPIRIT2 data at ASH 2014 and BSH 2015, respectively. The SPIRIT2 Biobank has been very successful in enabling translational research, resulting in a number of publications in high impact journals. The subgroup is committed to physician training and patient education; it has recently welcomed a trainee member and continues to organise an annual Patient Meeting which is increasingly utilising social media and internet streaming to widen our audience and increase

participation. The Subgroup's main challenges are opening SPIRIT3 and developing an effective CML GeCIP sub-domain within the Haemato-oncology domain.

D – AML Subgroup Strategy

The aim of the AML Subgroup is to run large multicentre clinical trials across the UK and with international collaborators. Our objectives to improve outcome by introducing selective, novel and molecularly targeted therapies into the existing backbone of chemotherapy combinations developed in previous trials. Furthermore, we aim to identify molecular signatures of treatment response that will allow appropriate stratification of therapy.

The AML17 trial closed in Dec 2014 after recruiting over 3,500 patients in over 100 centres and will be replaced by AML19, which opens in Q2 2015. AML18 for older fit patients opened in November 2014 and is recruiting well. This is the first study to use MRD assessment to direct therapy in older patients with AML. The Subgroup continues to publish results in high-impact journals, with outcomes from the daunorubicin dose question being published in Blood. Furthermore, our experience of arsenic trioxide in APL is being used by TEVA for license extension for frontline therapy. We are at the forefront of the application of sensitive standardised PCR assays to predict outcome and guide molecularly targeted therapy as part of the molecular monitoring in AML17, and this will continue into AML19.

E – MPD/N Subgroup Strategy

The MPN Subgroup aims to deliver world-class clinical and translational research, implement positive findings and enhance patient knowledge. The Subgroup's portfolio is very broad and recruiting well. This, in turn, has attracted multiple pharma companies to include the UK in their studies of novel agents and, in some cases, to provide novel agents for investigator-led studies. The Subgroup's portfolio comprises a good balance of academic and commercial trials, with several members taking lead roles in these trials as global CIs.

In terms of delivery of academic studies, the MOSAICC pilot has finished recruiting, MAJIC completed recruitment for ET and is recruiting strongly for PV, MPD RC112 is starting to recruit well, and MPD RC114 and Phazar should be opening shortly. For commercial studies the UK has top recruiting sites for the pacritinib studies PERSIST-1 and PERSIST-2, where the global CIs are Subgroup members. The Subgroup continues to generate translational research of the highest calibre. In particular, the flagship "Causes of Clonal Haemopoiesis" project has led to the discovery of a prevalent mutation in the calreticulin gene (NEJM 2013) and more recently the clinical importance of the sequence in which multiple mutations are acquired in MPNs (NEJM 2015) and the identification of factors that predispose to MPNs.

The Subgroup's partnership with patient representation and charities is strong. For the second year running, two national education events for clinicians and patients, respectively, were held in November; these back-to-back meetings are now firmly established as an important annual event in the haemato-oncology calendar. In addition, the Subgroup has supported five regional patient advocacy meetings throughout the UK during the reporting period. The group is developing a phase 1b study with tamoxifen to submit to TAP and a transfusion pilot for next year.

In addition we have developed a strategy for strong translational science from the MAJIC study which will hopefully run into the Phazar trial. We are seeking funding to pursue the MOSAICC study following completion of the pilot. Challenges include completing negotiations with Novartis regarding a frontline PV study. These negotiations have been ongoing for three years; the most

recent development has been a request for another proposal revision. Other challenges include completing BCSH guidelines on eosinophilia and mastocytosis.

F – CLL Subgroup Strategy

The CLL Subgroup has reported on the two randomized Phase II trials for fit patients requiring therapy (ADMIRE and ARCTIC) and has had accepted the HTA monograph reporting the results of the ARCTIC Trial. We are now in the process of preparing several manuscripts from these studies. The next phase III trial for this group of patients, FLAIR, opened in September 2014 and is ahead of its recruitment target with more than 100 patients randomized and over 50 Centres open to recruitment. The most recent phase III trial for elderly patients, Complement 1, has been successful published in the Lancet in 2015. The follow-on trial, RIAltO, has been modified to include one of the novel small targeted therapies, idelalisib, and continues to recruit. In addition we have opened a third phase III trial, the GALACTIC Study, which looks at the consolidation of remissions in order to deepen remissions and improve time to progression. The CLL Subgroup has also successfully supported a series of early phase trials within the LLR Trials Acceleration Programme, namely IcICLLe, CALiBRe and CyCLLe, which are being used to understand the mechanisms of action of novel agents, to study combination of agents biologically and to inform the design of future phase III trials.

In addition, the UK CLL Biobank continues to successfully recruit patients and the stored material is being used for a large number of translational research studies including the whole genome sequencing of 1,000 CLL genomes from our trials. The strategy for the Subgroup is to streamline the phase II trials, translational research of the group and our phase III trials to move rapidly towards logical combinations of agents, to test them quickly, to progress to prolongation of remissions and as quickly as possible to cure.

G – ALL Subgroup Strategy

The ALL Subgroup aims to maintain a comprehensive programme of clinical research and correlative science accessible to all patients with ALL and in doing so provide research training opportunities to generate a pipeline of future Chief Investigators. Delivery of the Subgroup's strategy is based on proactive engagement with local PIs, industry and international collaborative groups. Achievements include excellent accrual into the main frontline trial (UKALL14), which is recruiting ahead of schedule, and excellent collaboration with industry. For example, a UK centre (Royal Free) was the highest recruiter to a recent Amgen study of blinatumomab (BITE). In addition, the Subgroup has maintained its succession of high-profile publications and international presentations.

Challenges include delivering to time and target the frontline trial for older patients (UKALL60+). This has been addressed through the provision of an additional trial coordinator by the UCL CTU. Other challenges include the establishment of referral pathways and logistical/administrative support required for the successful delivery of trials for important but niche populations. In addition, it has proved very difficult to work with international partners. Thus, the interpretation of EU regulations differs widely between countries, and generating a protocol which is acceptable to two different competent authorities with an academic sponsor is at the limit of what can be achieved with the limited funding we have available compared to commercial organisations.

H – Myeloma Subgroup Strategy

The Myeloma Subgroup continues to oversee a large and complex trial portfolio, ranging from phase II-III clinical intervention studies and incorporating governance of an accelerated therapy

Clinical Trials Network (Myeloma UK CTN) focusing on phase I-IIb trials. This comprehensive portfolio incorporates both academic and commercial studies, contributing significantly to the overall accrual and output of the Haemato-Oncology CSG. To date, the completion and publication of our outputs have significantly contributed to the clinical practice both in the UK and internationally. Following from the publication of the first manuscript from the successful phase III Myeloma X trial, the results have now been incorporated into the International Myeloma Working Group Guidelines on relapsed disease management. The current front-line phase III study, Myeloma XI/XI+ is nearing recruitment target, so planning is underway for a replacement frontline phase III strategy: Myeloma XIV and XV. The frontline supportive care study, TEAMM, continues to recruit ahead of schedule and our phase II allogeneic stem cell transplantation, the LenaRIC trial, has now successfully completed recruitment. The Myeloma UK CTN continues to expand its trial portfolio, with three studies completed, two studies actively recruiting and four in the planning stage. The portfolio continues to be attractive to commercial collaborators.

The Subgroup's priorities over the next year will be to strategize our future plans for trial development in all stages of disease whilst maintaining the current balance between commercial and academic studies, delivering studies to time and target and continue to develop translational aspects of the portfolio. We will endeavour to be utterly inclusive in our working as we aim to be internationally competitive in a very high standard academic space.

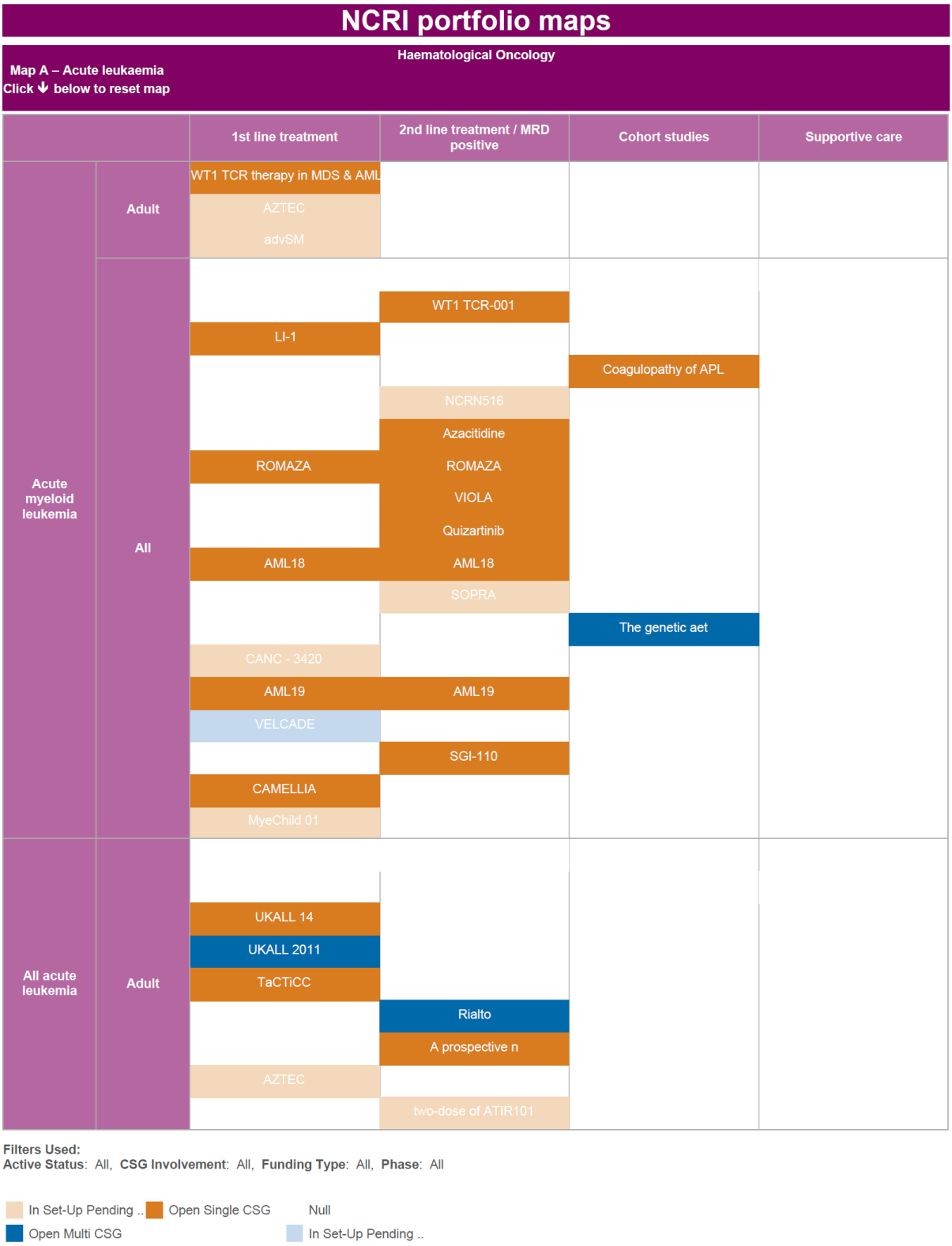
I – Supportive Care, Transfusion & Late Effects Working Party Strategy

A formal proposal for an NCRI Working Party (WP) to develop a portfolio of supportive care and late effects studies primarily related to haemato-oncology was approved by the NCRI Executive in March 2015 by the CSG's designated lead in this area (Professor Snowden). It is envisaged that the WP, chaired by Prof John Snowden, will be a collaboration with the Supportive & Palliative Care CSG. Over a two year period, the WP will aim to assess the feasibility of a Subgroup to cover studies of blood transfusion, late effects and survivorship, bone oncology, palliative care and psychosocial aspects.

The WP will facilitate the development of a structured trials portfolio, joint "ownership" of cross-cutting themes by the relevant subgroups, allocation of primary responsibility for shared studies within the CSGs, and the exploitation of synergies with other groups. The WP Chair has dual membership of the Haem Onc CSG and the Supportive and Palliative Care CSG and includes nominated representatives from the all disease-specific Subgroups within the Haem-Onc CSG, as well as from the Lymphoma CSG. Psychosocial Oncology and Survivorship CSG, TYA CSG and consumer representatives will also be invited. Given the importance of Transfusion Medicine in the supportive care of haematological cancers, two representatives from the NIHR Haematology CSG (transfusion interest – one NHSBT, one non-NHSBT) have been co-opted as members. Over the two year period, two face-to-face meetings and six teleconferences are expected.

Appendix 3

Portfolio maps



NCRI portfolio maps

Haematological Oncology

Map B – Chronic leukaemia
Click ↓ below to reset map

		1st line treatment	2nd line treatment / MRD positive	Cohort studies	Supportive care
Chronic lymphocytic leukaemia	Null	MONOCLE			
	All	CLARET			
				FCLL	
				Genetic Epidemi	
				Investigating D	
		RIAltO			
			COSMIC		
			A PHASE Ib MULT		
			PCI-32765 (Ibrutinib)		
			A Phase I trial -DI-B4		
			NCRN580		
				IciCLLe	
		FLAIR			
				Mathematical mo	
		SINE	SINE		
		OBINUTUZUMAB			
		CANC - 3721			
		GALACTIC			
				Leukapheresis	
				Calibre	
		AZTEC			
			OR00208 Combined with Idelalisi		
		advSM			
			DURVALUMAB		
		CLARITY			
Chronic myeloid leukaemia	All				
			WT1 TCR-001		
		SPIRIT 3 study			
			Matchpoint		
			Moxetumomab pasudotox		
				bosutinib CANC - 4834	
		AZTEC			
			Ponatinib Vs Nilotini		
			two-dose of ATIR101		

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG In Set-Up NHS Per.. Suspended Single ..
Open Multi CSG In Set-Up Pending ..

NCRI portfolio maps

Haematological Oncology
Map C – Myelodysplastic syndrome, myeloproliferative neoplasms, transplant trials
Click ↓ below to reset map

		1st line treatment	2nd line treatment / mrd positive	Cohort studies	Supportive care
Myelodysplastic syndrome	All	LI-1 AZACITIDINE + BSC KALLISTO ELASTIC CANC - 3420 advSM		MDSBio	REDDS
Myeloproliferative neoplasms	All	LDE225 and ruxolitinib Pegasys Momel. vs. Rux. RETHINK Givinostat in JAK2V617F positive CMNs	MAJIC POSTAGE	Clonal BC Disorders Molecular patho	
Transplant trials	All	ProT4 (Prophyla CMV TCR001 UK Haplo v1.0 FIGARO ICAT MPD-RC 114 study WT1 TCR therapy in MDS & AML	ProT4 (Prophyla FIGARO ICAT	Ocular and Oral	

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG Suspended Single ..
Open Multi CSG Null

NCRI portfolio maps

Haematological Oncology

Map D – Myeloma
Click ↓ below to reset map

		1st line treatment	2nd line treatment / mrd positive	Cohort studies	Supportive care
Myeloma	All	MYELOMA XI	MUK five	Analysis of Leu	TEAMM: Tackling
		ExAblate	ExAblate	Osteoclastogeni	
		OPTIMAL	POMALIDOMIDE	MMTA	Ixazomib Citrate
		CARDAMON	FACTOR	PREAMBLE	Multi myeloma
		Ixazomib	Bubblei	FAB-IE	ACUFOCIN
		Daratumumab	Carfilzomib	PF 04449913	
		TRALA	Pomalidomidein MM	DjiM	
		3x Daratumumab	MUK Eight	The MPN Experim	
		TiMM	3x Daratumumab	CANC - 3619	
			DTP3	iTIMM	
				WB-DW-MRI at 3T	

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG Suspended Multi C..
Open Multi CSG In Set-Up Pending ..

NCRI portfolio maps

Haematological Oncology

Map E – Other studies
Click ↓ below to reset map

		1st line treatment	Cohort studies	Relapsed	Supportive care
Adult	All	CENTAURUS IdelVChloramb iNNOVATE STUDY Imetelstat in MYF eSMART: Randomi Efficacy of fir	EBV assoc NK/T Molecular Inves Nm23-H1 Immunophenotypi V1: Dev't of PRO Measure BOOST - Biological Correlates of outcomes from Stem Cell Transplant	PARP inhib in B cell malig CREATE	Physical activ. TREATT
Child	All		Study of haemat Adverse drug re V1: Dev't of PRO Measure BOOST - Biological Correlates of outcomes from Stem Cell Transplant		Physical activ.

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. | Open Single CSG | In Set-Up Pending ..
Open Multi CSG | Suspended Single ..

Appendix 4

Publications in the reporting year

MDS-Bio

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Appendix 5

Major international presentations in the reporting year

MUK-six trial

Rakesh Popat, Sarah Brown, Louise Flannagan, Andrew Hall, Bhuvan Kishore, Matthew Streetly, Heather Oakervee, Simon Hallam, Matthew Smith, Kwee Yong, Gordon Cook & Jamie Cavenagh Bortezomib (Velcade), Thalidomide, Dexamethasone and Panobinostat (VTD-P) is a safe, well tolerated and efficacious Regimen for Patients with Relapsed Multiple Myeloma: preliminary results of the MUK-six trial. ASH 2015.

Myeloma X (Intensive) Trial

G Cook, C Williams, DA Cairns, A Hockaday, JD Cavenagh, JA Snowden, C Parrish, K Yong, J Cavet, H Hunter, JM Bird, G Pratt, S Chown, E Heartin, S O'Connor, J Ashcroft, JM Brown & TCM Morris on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. A Salvage Autologous Stem Cell Transplant (ASCT2) Induces Superior Overall Survival following Bortezomib-containing Re-induction Therapy for Relapsed Multiple Myeloma (MM): Results from the Myeloma X (Intensive) Trial. ASH 2015.

MOSAICC trial

Myeloproliferative Neoplasm Patient Symptom Burden and Quality of Life: Evidence of Significant Impairment Compared to Controls Using Multivariate Analysis, LA. Anderson, GJ Titmarsh, AC Dueck, A Duncombe, RA Mesa, RM Scherber, HE Kosiorek, F deVocht, M Clarke, MF McMullin, December 03, 2015; 126 (23)

Myeloproliferative Neoplasms: An in-Depth Case-Control (MOSAICC) Study, MF McMullin, A Duncombe, GJ Titmarsh, F de Vocht, L Fritschi, RA Mesa[7], M Clarke, LA. Anderson, December 03, 2015; 126

The RESPONSE Trial

Ruxolitinib in polycythemia vera: Follow-up from the RESPONSE trial.
Myeloproliferative Syndromes Leukemia, Myelodysplasia, and Transplantation Meeting: 2015 ASCO Annual Meeting

SPIRIT 2 (Clinical)

Osborne WL, O'Brien SG, Hedgley C, Foroni L, Apperley J, Terril P, Rowe P, McCullough J, Holyoake T, Pocock C, Byrne J, Bescoby R, Copland M, Clark R. SPIRIT2: An NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed chronic myeloid leukaemia – 2 year follow up. *British Society of Haematology, 55th Annual Scientific Meeting, EICC Edinburgh, 20th – 22nd April 2015.* Abstract 27.

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O'Brien SG. Assessment of Quality of Life in the NCRI Spirit 2 Study Comparing Imatinib with Dasatinib in Patients with Newly-Diagnosed Chronic Phase Chronic Myeloid Leukaemia, *The American Society of Hematology (ASH) 57th ASH Annual Meeting, Orlando, 5-8th Dec 2015; Blood 2015;*126: abstract 4024.

SPIRIT 2 (Biobank)

Baquero P, Karvela M, Mitchell R, Mukhopadhyay A, Pellicano F, Hopcroft L, Holyoake TL, Helgason GV. The autophagy related protein ATG7 regulates differentiation and energy metabolism of CML cells. *British Society of Haematology, 55th Annual Scientific Meeting, EICC Edinburgh, 20th – 22nd April 2015.* Abstract 9.

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AML17

A Comparison of 1 or 2 Courses of High Dose Cytarabine As Consolidation in Younger Patients with AML: First Results of the UK NCRI AML17 Trial Nigel H. Russell, Robert K Hills, Sylvie Freeman, Steven Knapper, Lars Kjeldsen, Ian Thomas, Jamie Cavenagh, Paul Cahalin, Mary Frances McMullin, MD, and Alan K. Burnett. American Society of Haematology (ASH) Annual General Meeting. Orlando 5th-5th Dec 2015.

Significance of Blast CD33 Expression for Effect of Gemtuzumab Ozogamicin at Different Doses in Adult Acute Myeloid Leukemia: Results from the UK NCRI AML16/17 Trials Khan Naeem, Robert K. Hills, Paul Virgo, Stephen Couzens Nithiya Clark Amanda Gilkes Angela Grech Peter Richardson, Steven Knapper, David Grimwade, Nigel H. Russell, Alan K. Burnett,Sylvie Freeman American Society of Haematology (ASH) Annual General Meeting. Orlando 5th-5th Dec 2015.

AML16

Outcomes of older patients experiencing reduced intensity conditioning allograft:results of the NCRI AML16 trial Nigel Russell , Robert Hills , Lars Kjeldsen , Mike Dennis , Charles Craddock , Richard Clark Alan Burnett. European Haematology Association (EHA) 20th Annual Meeting, Vienna 11th-14th June 2015

A comparison of limited consolidation chemotherapy therapy or not, and demethylation maintenance or not in older patients with AML and high risk MDS: long term results of the UK NCRI AML16 trial. Alan Burnett , Nigel Russell , Sylvie Freeman , Lars Kjeldsen , Donald Milligan , Christopher Pocock , Paul Cahalin , Jonathan Kell , Mike Dennis , Robert Hills. European Haematology Association (EHA) 20th Annual Meeting, Vienna 11th-14th June 2015

A comparison of daunorubicin/ara-c versus daunorubicin/clofarabine as induction treatment in older patients with AML and high risk MDS: long term results of the UK NCRI AML16 trial in 806 patients. Nigel Russell , Alan Burnett , Lars Kjeldsen , Donald Milligan , Paul Cahalin , Jonathan Kell , Mike Dennis , Robert Hills. European Haematology Association (EHA) 20th Annual Meeting, Vienna 11th-14th June 2015

AML15

A comparison of Daunorubicin/ Clofarabine and FLAG-IDA in high risk Acute Myeloid Leukaemia: results from the UK NCRI AML15 trial Alan Burnett, Nigel Russell, Lars Kjeldsen, Donald Milligan, Ann Hunter, Richard Clark, Mike Dennis, Robert Hills European Haematology Association (EHA) 20th Annual Meeting, Vienna 11th-14th June 2015

Appendix 6

Strengths & weaknesses from the Haematological Oncology 2015 Progress Review

Strengths

- The review panel considered the Group to be outstandingly high achievers.
- A successful and well organised Group, with strong leadership.
- Extended membership within subgroups is working well.
- A balanced portfolio containing an impressive number of studies, embracing novel trial designs, plus large scale phase III trials that scale the populations.
- Continue to develop studies that only the UK is able to undertake, e.g. de-escalation studies.
- Accrual exceeding that of the rest of Europe.
- A high success rates with funders.
- Strong consumer involvement.
- Consideration being given to quality of life studies.
- Collaborations with other groups.
- An open approach welcoming others to bring ideas to the Group and to join the Group.
- Strong biobank resources to allow translation of knowledge into future trial design.
- Translational studies are well organised - the next step would be to design specific studies on which the UK can take the lead.

Issues for the CSG to consider

- The review panel challenged the Group to become international leaders as well as national leaders.
- Further exploration of international collaborations for rare tumour types.
- The review panel await the outcome of the Supportive Care, Transfusion and Late Effects Working Party with interest.
- How to help other CSGs and to share their routes to success.
- The main CSG comprises mainly of Consultant Haematologists and it was suggested that this should be reviewed and revised.
- It was noted that succession planning has commenced and the review panel encouraged further thought to be given to this important topic.
- The CSG should lead on a workshop to explore cellular pathology.