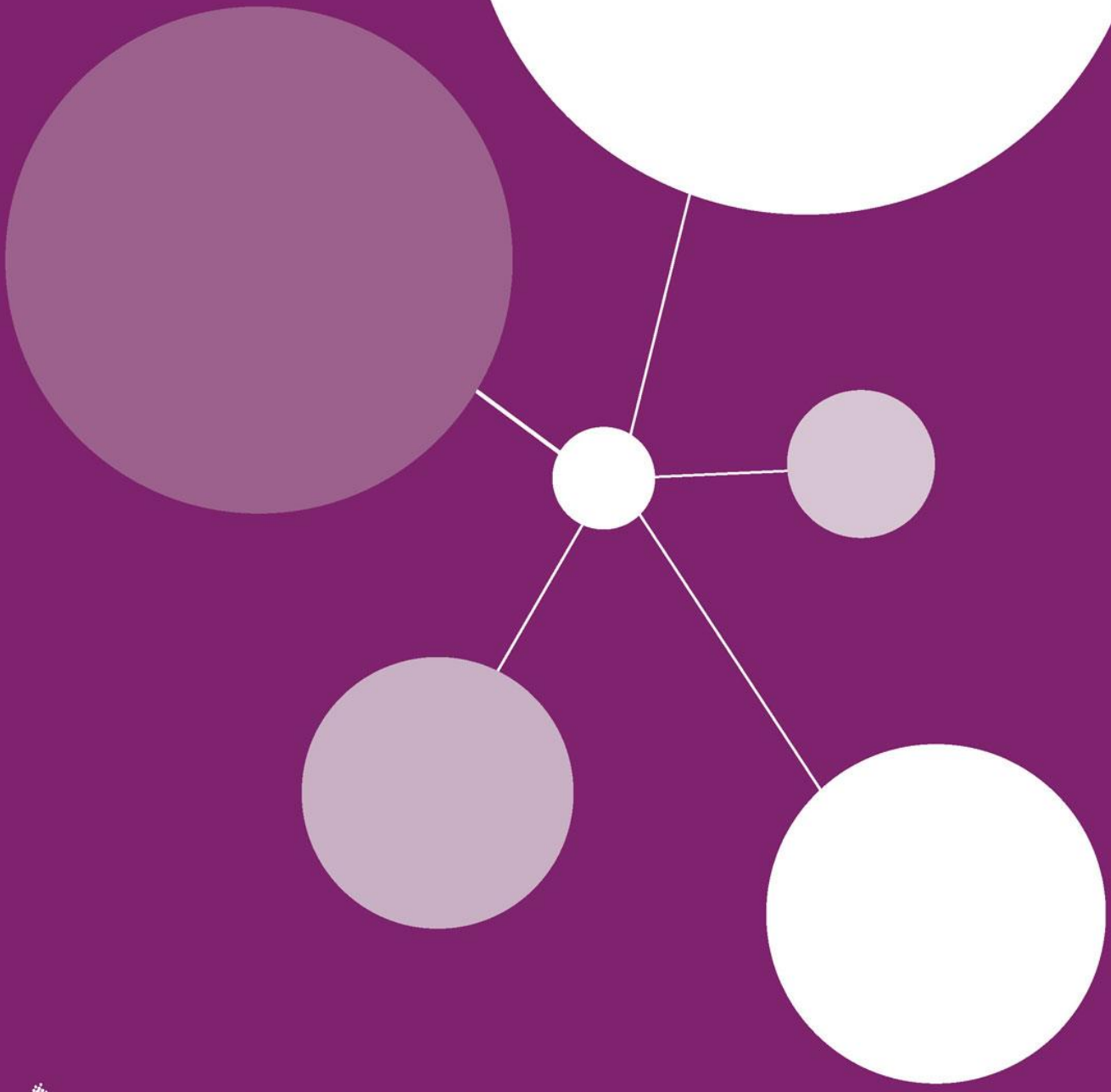
NCRI
National
Cancer
Research
Institute

NCRI Haematological Oncology Group

Annual Report 2018-19



Partners in cancer research

NCRI Haematological Oncology Group Annual Report 2018-19

1. Top 3 achievements in the reporting year

Achievement 1

Continued recruitment into and development of Phase III Trials

The Haematological Oncology CSG continues to recruit effectively into a wide portfolio of clinical trials. In the last 12 months we have completed recruitment in two Phase III trials – the original FLAIR trial including 772 patients with chronic lymphocytic leukaemia who are suitable for fludarabine-based chemotherapy. The results are expected in 2020.

In addition, we have modified the FLAIR trial to include the combination of two targeted therapies (ibrutinib plus venetoclax) to ask further questions after the original FLAIR reports. We have completed the recruitment into both the B cell and T cell arms of UKALL 14. This trial will report initial findings in late 2019. The overall trial portfolio for the CSG consists of over 100 studies. In addition, Aplastic Anaemia Working Party has successfully recruited the RACE Trial.

Achievement 2

Strengthening the Phase I/II infrastructure in the UK

This year the myeloma early phase accelerated trials programme under a core grant from Myeloma UK was launched. The CARP (Concept and Access Research Programme) is seeking to launch its first two trials in 2019.

The continued success of the Bloodwise Trials Accelerations Programme (TAP). To date, TAP has run 19 trials through TAP that cover all types of haematological malignancy. The IMPACT stem cell transplant network was launched in November 2018 in order to improve the delivery of clinical trials across the UK. IMPACT is jointly funded by Anthony Nolan, Leuka and NHS Blood and Transplant. The first transplant clinical trial has already been opened.

Achievement 3

Strategic restructuring of the disease specific subgroups

In October 2018 we held a CSG Strategy Day and defined a new strategy which we have implemented into a number of subgroups. The strategy includes the appointment of executive boards within each subgroup with rotational lead roles (vice-chair, biobank/governance, translational science, early phase/industry trials, communications), the appointment of trainee

representatives to each subgroup through the NCRI trainee scheme and a strategy to include biobanking and translational research programme in all of our disease groupings.

2. Structure of the Group

The CSG has seven subgroups focussing on specific disease areas (AML, ALL, CML, CLL, Myeloma, MPN, MDS), in addition to the Aplastic Anaemia Working Party (2017-2019). CSG members include 18 clinicians, two statisticians, a senior trial co-ordinator, two consumers, two NCRI trainees and observers from Cancer Research UK (CRUK) and Bloodwise. The CSG currently has representation from most regions in the UK including two from devolved nations.
Richard Kaczmarksi and Ciro Rinaldi rotated off the Group in summer 2018. Dragana Milojkovic, Kikkeri Naresh and Simon Watt were appointed. In October 2018 we welcomed two new trainee members (Thomas Fox and Gillian Horne) who have performed an analysis of the financial benefits of haematological oncology trials to the UK which they presented at the Annual Scientific Meeting of the British Society of Haematology in April 2019 in Glasgow as well as the acceptance of a letter to The Lancet due to be published shortly.

3. Group & Subgroup strategies

Haematological Oncology Group

Maintain a balanced and continuously replenishing portfolio of academic and industry studies in all major disease areas Over the last 12 months the CSG has maintained a balanced portfolio with Phase III trials for all of the main disease entities. In addition, there has been an increase in the utilisation of the Bloodwise TAP programme as well as the early myeloma trials unit and IMPACT network for stem cell transplantation for Phase I/II trials.
Biobanking and translation research development The CSG utilise biobanks samples from the various Phase III trials and increasingly these biobanked samples are being used for translational research. For example, the UK CLL Biobank based in Liverpool and biobanking samples from all of our Phase II and Phase III trials have now provided samples for over 35 translational projects.
Increase engagement with industry There are close links between the CSG and the pharmaceutical industry particularly in a number of disease areas such as acute myeloid leukaemia, myeloma and chronic lymphocytic leukaemia. This continues to grow as evidenced by a piece of work performed by our Trainee representatives that demonstrates in excess of £200million saving from three of our Phase III trials and this has been accepted by The Lancet as a letter.
Engage with charity-funded research infrastructure initiatives Several of our Phase III trials are funded by CRUK. There has been a close association with the Bloodwise TAP programme which has now delivered over 20 Phase I or II trials most of which are in the Haematological Oncology CSG disease areas including MDS, MPN, AML and CLL. In addition, the IMPACT network for stem cell transplant trials has been initiated and several trials are either open or will open shortly.
Engage with Genomic England Ltd (GEL) The haematological Genomics England Clinical Interpretation Partnership (GeCIP) has met and involves many members of the NCRI CSG and Subgroups. The CLL pilot scheme of GEL involves sequencing over 400 patient samples from patients entered into a number of CLL trials. The first abstracts and manuscript have now been submitted from the CLL Pilot and these report the whole genome sequencing of patients with CLL across a number of our CLL trials.
Increase consumer engagement Consumer representation is present on the CSG and each subgroup as well as many of our Trial Management Groups and Trial Steering Committees. We have also engaged with the patient disease specific groups to assist in the design and oversight of our portfolio of clinical trials. We have allocated one of our new members to work with the consumers to ensure that the questions raised in the patient survey are addressed from our trials where possible.

Acute Lymphoblastic Leukaemia (ALL) Subgroup (Chair, Dr Clare Rowntree)

Maintain a comprehensive programme of clinical research and correlative science accessible to all patients with ALL

Achievements of the Group include the completion of recruitment to both the B cell and T cell arms of UKALL 14. This trial will report initial findings in late 2019. The trial for elderly patients with ALL, UKALL 60+, also completed recruitment and closed in December 2018. The adult ALL subgroup continues to collaborate closely with the NCRI Children's Cancer & Leukaemia Subgroup in design of trials for teenagers and young adults. ALLTogether (the next paediatric and young adult ALL trial) has been funded by CRUK and is expected to open late 2019 / early 2020.

We actively collaborate with colleagues in Europe through the European Working Group for ALL (EWALL). A joint EWALL trial for elderly patients with Ph+ ALL is due to open 2019 and will be sponsored by Cardiff University with Professor Ottman from the ALL Subgroup leading the study as chief investigator.

The primary focus of the ALL Subgroup is to complete the design of the next frontline study for adults in the UK with ALL – UKALL15. This trial will encompass adults of all ages from 25 years upwards and will cater for patients fit for intensive treatment (previously treated on UKALL 14) and those less fit (previously treated on UKALL60+). The challenge is encompassing the rapidly changing landscape of novel drug availability that is currently being evaluated by NICE but the aim is to submit plans for UKALL 15 to CRUK in summer 2019.

In addition to providing good clinical trials for patients with ALL in the UK, the group is also focusing on developing a large and productive programme of correlative science. A CRUK program grant was awarded to enable work on samples from our upfront studies UKALL 14 and UKALL 60+ to determine genetic factors that may influence patient outcome related to treatments given.

Provide research training opportunities to generate a pipeline of future Chief Investigators

UKALL 15 will effectively be several trials within one large study. A trial working group has been set up with leads for each area of the study that will allow new leaders in ALL clinical trials to learn the processes under the leadership of Professor Fielding (chief investigator). Dr Clare Rowntree will lead on the T cell arm of the study (including lymphoblastic lymphoma), Dr Tobias Menne will lead on novel drug treatments for high risk patients. Dr Nick Morley will lead on the strategy for less fit elderly patients, Professor David Marks will be the transplant lead for the trial and Professor Oliver Ottman will lead on the Philadelphia positive ALL arm of the study.

As part of our long-term strategy to maintain a pipeline for new chief investigators for future trials, we have recruited a trainee representative to our group in 2018 (Dr Fox) who will be encouraged to join UKALL 15 planning discussions.

Acute Myeloid Leukaemia (AML) Subgroup (Chair, Professor Charles Craddock)

Run large multicentre clinical trials across the UK and with international collaborators

The AML Subgroup runs three clinical trials for adult patients with AML encompassing AML19 for patients aged 18-60 years; AML18 for patients >60 years fit for intensive therapy and the LI1 trial for elderly AML patients considered not fit for intensive therapy. These trials between them recruit approximately 100 patients per month and AML18 and 19 between then have randomised over 2000 patients.

The AML19 trial is currently undergoing amendment to reflect the NICE approval of both the Flt3 inhibitor and Mylotarg. The follow-on trial from LI1, EVOLVE, to be led by Professor Paresh Vyas and Dr Mike Dennis, is under development and is planned to include randomisation according to diagnostic mutational status in patients treated with a venetoclax backbone. An international collaboration which will include representation from French, Italian and German co-operative groups has been established to deliver, to registration standard, the first component of the EVOLVE trial in Flt3 ITD mutated patients.

Analyse treatment response in relationship to mutational profile in collaboration with the Sanger Institute

A master data set has been established for the Sanger analysis comprising and combining the genetic data with trial outcome data and patient demographics from over 3000 patients entered into AML trials. Genomic analysis of patients treated on AML18 will integrate, for the first time, genomics with MRD analysis, as a prognostic factor of outcome.

Design a follow-up trial for patients not fit for intensive therapy to replace the LI1 trials

Working with the UK IMPACT transplant trials cooperative, one of only two transplant networks in the world, the AML Working Party has made substantial practice in delivering two globally significant transplant trials.

Pro-DLI, the first randomised study examining the ability of donor lymphocyte infusions (DLI) to improve outcome in patients allografted for AML is recruiting well and is anticipated to close in September 2019.

AMADEUS, a randomised study examining the ability of maintenance post-transplant therapy using oral azacitidine (CC486) to improve outcome in patients transplanted for AML opened in June 2019 and is now recruiting. AMADEUS is being funded by Celgene so that it can deliver trial data with enhanced pharmacovigilance to registration standard. AMADEUS has the potential to demonstrate to the global pharmaceutical sector that the UK has the capacity, thanks to the strength of NCRI working parties, to accelerate delivery of high quality clinical trials to registration standard.

Chronic Lymphocytic Leukaemia (CLL) Subgroup (Chair, Professor Anna Schuh)

Complete recruitment in the RIAltO trial for patients unfit for fludarabine-based therapy

The Phase 3 RIAltO trial opened in December 2011 to compare ofatumumab plus chlorambucil (O+C) with ofatumumab plus bendamustine (O+B) in patients with previously untreated CLL considered unfit for FCR. The protocol was amended in September 2014 to investigate the addition of idelalisib (first-in-class inhibitor of the p110δ isoform of phosphoinositol-3 kinase) or placebo. However, all idelalisib/placebo treatment was withdrawn from the trial in March 2016 following safety analysis of idelalisib registration studies and recommendations from Gilead Sciences Ltd and regulatory authorities.

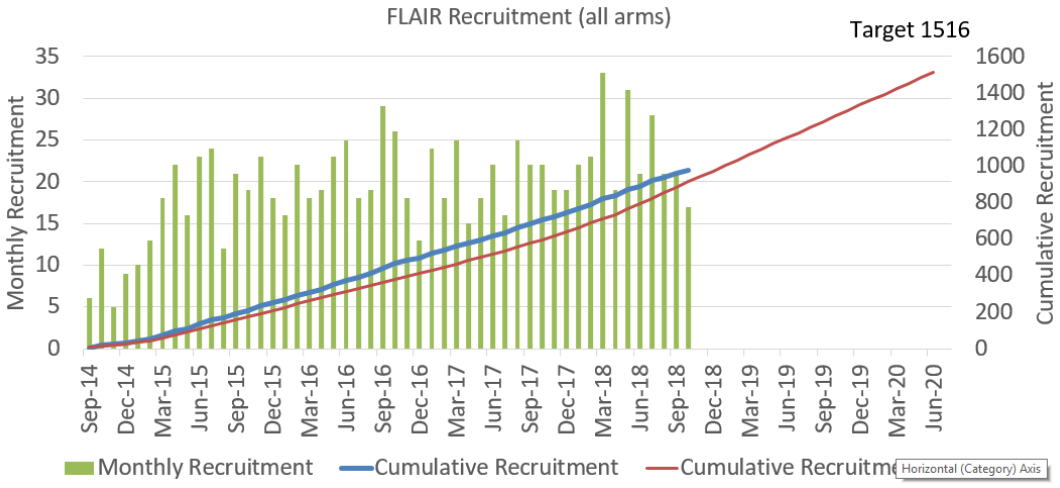
145 patients received idelalisib (73) or placebo (72). The median idelalisib exposure time was 3.3 months (IQR 1.2-7.3 months). As of January 2019, SAEs were reported in 79% of idelalisib-treated patients (87 grade 3-4 and 9 grade 5) compared to 50% of the placebo arm (38 grade 3-4 and 6 grade 5). The frequency of SAEs in the idelalisib arm was similar in both chemotherapy groups. After a median follow-up of 41.7 months (IQR 36.2-45.4 months), 28 PFS events have been reported in the idelalisib arm compared with 39 in the placebo arm (P = 0.070, log-rank test), while 10 and 16 deaths have been observed in the idelalisib and placebo arms, respectively (P = 0.218, log-rank test). Although 6-month mortality in the idelalisib arm was twice that of the placebo arm, only 2 deaths have been reported beyond 6 months in the idelalisib arm compared with 12 in the placebo arm. The early toxicity associated with the addition of idelalisib to frontline chemoimmunotherapy in CLL appears to be offset by improved long-term efficacy.

Consider a replacement for the RIAltO trial for patients unfit for fludarabine-based therapy

This remains under consideration by the Group.

Complete recruitment into the original FLAIR Trial: Done

A total of 772 patients were randimised in the first part of the FLAIR trial.



Roll out the amendment of the FLAIR Trial that adds two additional arms to the trial and increases the total number of patients in FLAIR to approximately 1,576 patients

This has been achieved.

Continue the rapid development of the Bloodwise TAP Trials

The Bloodwise TAP portfolio has continued with further reports from IcICLLe and CLARITY including a manuscript. A further year of treatment has successfully been added to CLARITY. Further plans to open a Richter's trial (STELLAR) which should open to recruitment in 2019.

Analyse whole genome sequencing for over 400 paired germ-line tumour samples from the ADMIRE, ARCTIC and RIAltO Trials

Samples of 385 patients have been sequenced and passed all quality checks. One sample batch containing 60 relapse samples is still in sequencing.

Baseline and most outcome clinical data (when available) is in the data centre. However, updated ARCTIC/ADMIRE data is still lacking.

The sequencing data is fully annotated and SNVs, indels, CNVs and SV have been called. Non-coding variants have been linked to BluePrint data and ATACseq and CHIP-seq and HiC from primary CLL (Campo, Mansson). We have also performed mutation signature, kataegis analysis and analysis of number and types of drivers. Telomere analysis (R Houlston) and analysis of genomic complexity (J Strefford) are being performed but have been delayed due to the ongoing access issue with the data centre.

A pipeline to feed this information into statistical analyses, in particular, non-negative matrix factorization-based clustering has been set-up in the data centre. We are now waiting to receive the updated clinical data from Leeds to link these different genomic measures to PFS. A manuscript is in preparation.

Apply for funding of the UK CLL Biobank

Unfortunately, funding applications to the MRC and CRUK have been unsuccessful. This continues to be an area of high priority for our group. An application has been submitted to Bloodwise.

Complete recruitment into the original FLAIR Trial

This was completed in the Summer of 2018 and the ibrutinib plus rituximab arm was dropped.

Chronic Myeloid Leukaemia (CML) Subgroup (Chair, Professor Mhairi Copland)

Improve treatment outcomes and patient experience for all CML patients

The NCRI CML Subgroup aims to contribute to the development of best practice in the management of CML. We have recruited new members with expertise that will add value and reinvigorate the subgroup. We are developing CML management guidelines for the UK and continue to deliver high quality clinical trials.

A BCSH CML guideline, developed and written by the CML Subgroup, is under final revision following review by patient groups and the BSH Soundings Board; this should be published later this year. In addition, members of the Subgroup contributed to a published consensus document on quantitative PCR testing for BCR-ABL (Cross et al, BJH 2018;182:777-788). Subgroup members also contribute to the European LeukemiaNet and the European Investigators for CML (EICML).

Final results of the SPIRIT2, CHOICES and DESTINY clinical trials were presented at EHA (CHOICES and DESTINY) and ASH (SPIRIT2) in 2018, and final manuscripts have been submitted for CHOICES (JCO), is under revision for DESTINY (Lancet Haematology), and in preparation for SPIRIT2 (possibly NEJM). DESTINY, in particular, has advanced patient care, demonstrating that it is safe for patients with a sustained deep molecular response (DMR; at least MR4) to half their TKI dose. This strategy is being adopted more widely, particularly for patients experiencing side effects.

Develop a clinical trials portfolio

We continue to develop our clinical trials portfolio. The MATCHPOINT trial in blast-phase CML reached its recruitment target in April 2018 and one-year data on all patients will be available shortly. MATCHPOINT is evaluating the safety and efficacy of FLAG-IDA chemotherapy in combination with ponatinb. A follow-up to MATCHPOINT is being discussed.

There are currently 3 clinical trials open for patients with TKI failure: (1) CALLS – a cohort study to evaluate next generation sequencing for identification of BCR-ABL kinase domain mutations in all phases of CML; (2) OPTIC – a randomised, phase 2 study to evaluate different doses of ponatinib in TKI-resistant chronic-phase CML; and (3) CABL001A2301 – a randomised phase 3 study of asciminib versus bosutinib in chronic-phase CML patients previously failing at least 2 TKIs.

The TASTER (Targeting STEm cell Resistance) trial, which will add a novel small molecule (currently idasanutlin or tazemetostat) into standard TKI therapy for patients with chronic and accelerated phases of CML with resistance to multiple TKIs is in set-up; we have experienced delays, particularly with the companies involved and are now aiming for FPFV q3.2019.

Another study of early switch to ponatinib for patients who develop a kinase domain mutation is currently under development. No front-line study in chronic-phase CML is proposed at present. We are exploring options to develop a follow-up trial to DESTINY.

Deliver high quality, internationally recognised translational research in CML

UK CML Investigators remain at the forefront of translational research in CML. The main translational research strengths in the group are in leukaemia stem cell biology (Copland/Huntly/Mead), leukaemia immunobiology (Clark, de Lavallade) and developing state-of-the-art PCR and sequencing techniques (Cross, Foroni, Khorashad, de Lavallade, Mead, Huntly) The SPIRIT2 Biobank is a rich source of translational research articles and presentations. Samples from both MATCHPOINT and DESTINY have been biobanked and will be an important resource for future translational studies. A project grant has been submitted to ESH to investigate leukaemia stem cells persisting in patients in deep molecular remission in the DESTINY clinical trial (outcome q3.2019).

In the last 12 months, 4 original articles have been accepted for publication/published using biobanked samples – 3 from SPIRIT2 (Zhang et al, Nat Med 2018;24:450-62, Toofan et al, Cell Death Dis 2018;9:927 and Nteliopoulos et al, Haematologica 2019; in press) and one from DESTINY (Austin et al, BJH 2018;doi:10.1111/bjh.15629). The TASTER clinical trial will deliver 3 translational work packages in addition to the clinical trial to better understand the biology of leukaemia stem cells and identifying and validate novel CML stem cell targets.

Increase patient partnership through patient and carer education days

The 2018 patient and carer education day was held on Saturday 22nd September (International CML Day) at the Priory Rooms in Birmingham. The event was very successful with ~100 CML patients and carers in attendance. The event was webcast and presentations made available via the CML Support website. The 2019 patient and carer education day will be held on 21st September 2019 at the Transport Museum, Leeds. The agenda for the day is being developed, and CML Support has been invited to provide their input regarding topics to be covered. Pharmaceutical companies with an approved product for the treatment of CML will be approached to sponsor the meeting. Again, we will webcast the meeting live to any patients and carers unable to attend on the day and make the presentations available via the CML Support website after the meeting.

Myelodysplastic Syndromes (MDS) Subgroup (Chair, Dr Sally Killick)

Develop a portfolio of Phase I, II and III studies which cover low and high risk MDS

The main priority for the MDS Subgroup is to improve the outcome of treatment for patients with MDS and allied conditions. The strategy of the MDS Subgroup is to develop a portfolio of Phase I, II and III studies which covers MDS and the allied conditions.

MDS remains a difficult disease with regards designing and delivering clinical trials, so the Group have spent the last 12 months considering a new approach. It is appreciated that the patients are often elderly, have multiple co-morbidities and may not wish to travel distances for treatment due to the impact on QoL. Trials therefore need to include those that can be delivered within district hospitals around the UK to maximise access and recruitment, alongside early phase trials run in tertiary centres.

Changes afoot:

- Introduction of a Terms of Reference document for the Senior Leadership Roles which has been ratified by the group
- Election of an Executive Board with rotational lead roles – vice-chair, biobank/governance, translational science, early phase/industry trials, communications
- Appointment of a trainee representative to the subgroup through the NCRI trainee scheme – currently underway
- Production of a Strategy Document that engages the whole group emphasising our strengths and direction of travel with emerging themes. A thematic approach would

allow us to concentrate on common areas across the disease as a whole (and allied conditions) rather than the current focus on disease subtypes

- Improvement in communication to haematologists and patients of available trials around the UK that are open and recruiting

The aim of the group is to design and develop clinical trials by bringing together pertinent and timely clinical questions with high quality scientific research. We continue to engage the wider non-clinical MDS scientific community to fully utilise the expertise available in the UK. Our portfolio includes investigator led studies, links to the NCRI AML subgroup to facilitate MDS trial entry and a strong commercial portfolio.
High-risk MDS is well represented in both the NCRI AML trials (AML18/19/LI-1) as there is considerable overlap in treatment approaches, and the commercial portfolio where many trials seek to improve survival over single agent azacitidine in high risk MDS with novel agents.
The challenge to the MDS subgroup has been to deliver clinical trials in patients with low risk disease where there is an unmet need. These patients account for approximately two thirds of MDS patients where the aims of treatment are to improve bone marrow failure, improve QOL & the consequences of supportive care and delay the progression to high risk MDS.

Priority areas for Clinical Research

1. Randomised Phase II/III trial of Danazol Vs VBaP Vs best supportive care. Dr's Drayson, Culligan, Raghaven, Killick, Mufti. This is a trial investigating danazol and the novel combination of valproate, bezafibrate and medoxyprogesterone for which there is scientific data supporting its use (Dr M Drayson's group). It is a trial aimed at low risk MDS, which fulfils the strategic aims of the group. The plan is for the trial to be phase II, then move to phase III with the best arm. This trial will have important clinical questions, tight diagnostic inclusion and strong translational research over a number of scientific groups. The trial will be open to all UK centres and the plan is to apply to CRUK for funding.
2. TEAMM 2 – collaboration. Dr's Drayson & Culligan. Following on from the disappointment of not having RAPRIMA funded, the group are collaborating with Dr Drayson regarding the inclusion of MDS patients into TEAMM 2 in a similar fashion to RAPRIMA, allowing resurrection of the hard work by our subgroup. This is a supportive care trial investigating antibiotic prophylaxis. Funding re-application to NIHR planned this summer.
3. REDDS2 – study design ongoing - Dr Stanworth (NHS Blood and Transplant) and David Bowen: transfusion support in patients with lower risk MDS. Funding bodies identified.
4. ASTX727 in CMML and MDS/MPN overlap. CI Dr D Wiseman. Unmet need for a UK trial for CMML following the closure of MONOCLE. ASTEX supportive. Discussed with the IWG and NCRI MPN groups. Funding TBC.
5. LI-2 – collaborative input to trial design for patients with high risk MDS with the AML subgroup.

Collaboration with research groups

The MDS subgroup continue to collaborate with the MPN & AML groups, NHS Blood and Transplant and the Aplastic Anaemia Working Party. The group feeds into the UK MDS Forum and presents at the Annual UK MDS Forum Education Day and Executive Board every autumn.

Myeloma Subgroup (Chair, Professor Gordon Cook)

Creation of a new brand for the clinical research cooperative which signifies the collaborative and unified approach within the UK

Now 4 years since the creation of the brand representing the UK research collaborative. There has been international adoption of this brand (as exemplified by election to the EMN Board, adoption by the International Myeloma Working Group) and number invitations to speak at international meetings on behalf of the UKMRA.

Foster engagement between practicing Haematologists in the UK, support their endeavours to participate in clinical research and involve them in the public advertisement of our results

We continue to advertise the efforts and successes of the group through the UKMF bi-annual meetings, through the UKMF symposium at the BSH and the now established UKMRA Trials day. We have broadened our social media footprint, though at present do not have a formal Communications strategy, rather we utilise the UKMF Communications strategy. The portfolio has an inclusivity approach to centres wishing to engage in our trials from early to late phase, though true phase I studies are based on capability not just capacity. This engenders ownership by the haematology community of the internationally impactful trials results.

Ensure the long-term strategy and continuity of clinical research activity

Through mentorship and encouragement in our inclusivity policy we aim to bring on new researchers (recently appointed consultants) and ensure that every TMG has at least one such colleague on the TMG, to engendered learning and encourage skill development to lead future trials. We now have a new trial proposal pathway policy, which again centres are mentorship and support of younger colleagues in developing research ideas to trial delivery and publication. We have also enrolled a trainee (Dr Charlotte Pawlyn) on the UKMRA, under my mentorship.

Myeloproliferative Neoplasms (MPN) Subgroup (Chair, Dr Adam Mead)

Ensure that basic science research in the UK remains cutting edge

The Subgroup is committed to supporting basic science in MPNs in the UK which continues to be world-leading. Highlights from 2018 include the development of an approach for "Personalized Prognostic Predictions for Patients with Myeloproliferative Neoplasms through Integration of Comprehensive Genomic and Clinical Information" from the research group of Professor Tony Green at the University of Cambridge that was published in the New England Journal of Medicine in 2018. This work shows how clinical and genomic information can be integrated to support personalised medicine. The Subgroup also has representation from a number of academic clinician scientists in training, ensuring that we meet our key strategic aim of supporting the training and career development of the next generation of MPN clinician scientists in the UK.

Ensure that MPN patients have the opportunity to participate in as diverse a portfolio of clinical trials as possible

The current MPN portfolio encompasses over 36 studies with a range of interventional and observational studies form both commercial and academic sponsors with an excellent track record of recruiting patients and with several members taking lead roles in these trials as global CIs. The Subgroup also prioritises studies investigating very rare subtypes of MPN such as systemic mastocytosis or 8p11 myeloproliferative neoplasms.

As detailed above, the primary results of the PV arm of the MAJIC study was presented in 2018. New studies which will open in 2019 include **MITHRIDATE**: a Multicenter International sTudy comparing ruxolitinib with either HydRoxycarbamIDe or interferon Alpha as first line ThErapy for high risk polycythemia vera (CI: Professor Claire Harrison). This is the first study of ruxolitinib as a first line treatment for PV and will recruit approximately 600 patients over five years. The **PROMise** study will open early in 2020 and will recruit patients with inadequate response to ruxolitinib – a group of patients with a major unmet clinical need.

Participate in and provide educational activities for clinicians and patients

The Subgroup supports regional and national meetings for MPN professionals and patients. In November 2017 we held the Myeloproliferative Neoplasms Advances Day for professionals with over 200 delegates and a range of international speakers. Overall feedback was excellent 8.8/10. The following day we held the MPN patient and carers' day, attended by approximately 250 patients from the UK. This meeting will be held again in November 2019. We regularly hold patient forums across the UK, most recently a forum in Oxford attended by over 80 patients and carers. In 2018 we established the MPN Leaders Programme, a professional development programme designed to support future haematology leaders (senior trainees and new consultants) specialising in the field of myeloproliferative neoplasms (MPN).

Ensure there are up to date comprehensive national guidelines for MPN via the BSH process

The MPN Subgroup supports guidelines for essential thrombcythaemia, polycythaemia vera (PV), myelofibrosis and eosinophilia. In 2018 we have updated PV guidelines (the new guideline is now published) and systemic mastocytosis guidelines are in development.

Support NICE appraisal of novel therapeutics in MPN

Members of the subgroup have supported NICE technology appraisals for ruxolitinib in myelofibrosis and polycythaemia vera.

4. Aplastic Anaemia Working parties (Chair, Professor Judith Marsh)

Remit of Aplastic Anaemia Working Party

The Aplastic Anaemia Working Party was established in order to bring together the community with an interest in AA in order to initiate and coordinate trials in AA. This has been achieved and the AA WP will re-amalgamate with the MDS CSG May 2019.

Progress to date

Current prospective studies

1. NHSBT HLA Epitope study: The manuscript is in an advanced stage and will be submitted to Blood.
2. EBMT RACE Phase 3 trial (ATG, ciclosporin with or without eltrombopag): As of 4/4/19, enrollment has stopped as the recruitment target (200) has been reached. UK is second largest recruiting country. Research samples continue to be sent to King's College London Haem-Onc Tissue Bank at a high rate for the ongoing translational research studies (funded by CRUK and Novartis Global). J. Marsh presented preliminary molecular data at EBMT2019 Annual Meeting in Frankfurt. Plan is to submit abstract to ASH 2019 to present the 3-month primary outcome data.

New trial proposal:

National prospective randomised trial of eltrombopag with ciclosporin versus eltrombopag with danazol in older patients with aplastic anaemia or hypoplastic myelodysplastic syndrome. Exploring funding sources.

New Phase I studies:

Production of expanded autologous regulatory T cells to treat patients with refractory aplastic anaemia in a phase I dose study (Funded by LifeArc and Aplastic Anaemia Trust, AAT, 15/3/19).

Phase 1 trial to evaluate the safety of CK0801 in refractory acquired idiopathic aplastic anaemia and hypoplastic myelodysplastic syndrome (Cellenkos/MD Anderson collaboration; funding being finalised)

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**	**Funding amount**
May 2018					
Not applicable					
November 2018					
PROMise: Investigation into the combination of a Plexxikon BETi with ruxolitinib in patients with high or intermediate-2 risk myelofibrosis not receiving an adequate response with ruxolitinib alone	Clinical Trial Award: CRUK Combinations Alliance	Dr Adam Mead	Successful	CSG/Subgroup developed	£532,057.85
CRUK/12/043: AML 18 - A trial for older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome		Professor Robert Hills	Conditionally supported	CSG/Subgroup developed	
ReFIL: Response of Flt3 Ligand to Induction chemotherapy in acute myeloid Leukaemia	Biomarker Project Award	Professor Matthew Collin	Not supported	CSG/Subgroup developed	
Other committees					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of CSG input**	**Funding amount**
A Randomised Phase III Trial Comparing Intermittent with Continuous Treatment Strategies in chronic lymphocytic leukaemia (CLL)	NIHR Health Technology Assessment Programme: Randomised Phase III Trial	Professor Peter Hillmen	Supported subject to Pharma contract	CSG/Subgroup developed	£2,964,249.07
Concept & Access Research Programme (CARP)	Early phase trial accelerated programme	Professor Gordon Cook	Supported – grant activated Jan2019	CSG/Subgroup developed	£846,682

6. Consumer involvement

Consumer Members, Mr Alan Chant and Dr Gillian Murphy, have continued their active participation within the CSG and also within their respective CSG Subgroups (Alan, Myeloma Subgroup; Gillian, ALL Subgroup). Alan and Gillian have attended CSG meetings and presented on key consumer issues, including regular updates on the progress of the NCRI Living With and Beyond Cancer JLA Priority Setting Partnership; informing members of results from relevant patient surveys [2018 Leukaemia Care Survey Report: Living with Leukaemia; Myeloma UK's Report - Patient Reported Outcome Measures (PROMs) in myeloma: are they fit for the future?]; and ensuring members were aware of opportunities to engage with the wider Consumer Forum (via Dragons' Den opportunities). Alan and Gillian have also contributed consumer comments to all of the funding proposals which have been developed through the CSG Subgroups in the reporting year (ReFIL, AML 18 ext., PROMise, VICTOR).

Gillian presented a Consumer Update at the CSG's Annual Trials Meeting. As requested, this talk was based on the latest haematology results from the National Cancer Patient Experience Survey (NCPES) and focussed on the "research question" (whether patients reported having had a discussion about research). Gillian also produced an updated report for the CSG's October meeting which included the 2017-18 NCPES data for further discussion, and the methodology behind the production of CSG-specific NCPES reports will be shared at the next Consumer Forum meeting.
Through their involvement with external groups and committees, Alan and Gillian ensure that their wider knowledge and perspectives can benefit the CSG. Both Alan and Gillian are active members of Trial Management Groups/Trial Steering Groups - Gillian is the patient representative on the ToTem TMG and Alan is the patient representative on the Myeloma XIV FiTNEss TSG; Both Alan and Gillian are NIHR Patient Research Ambassadors for local Trusts and Alan is an elected lay Trustee with NCRI and works closely with Myeloma UK on specific research initiatives and regularly attends two local Myeloma Support Groups.

Gillian is a patient representative on the NCRAS Haematology Expert Advisory Group (HEAG, formerly the NCRN NCIN Site Specific Clinical Reference Group for Haematological Cancers), and provides a link to the CSG with updates on the group's activities. She is also a Patient and Public Voice member of the NHS England National CAR T Clinical Panel (NCCP) for Acute Lymphoblastic Leukaemia. As well as being an active member of the UCL Clinical Trials Centre's Haematology Consumer Representative Group and the Royal Marsden/ICR Cancer BRC Patient and Carer Research Review Panel, Gillian is also a member of several patient groups, and supports the work of blood cancer charities (e.g. as an Anthony Nolan Peer Support Volunteer). As a Bloodwise Ambassador, Gillian was an invited speaker at the patient and carer session of the charity's annual Grantholders' Day, and used the opportunity to highlight PPI opportunities in blood cancer research.

Alan is involved with Oxford Oncology Clinical Trials Office, Oxford Blood Group and many wider PPI, research and translational groups including CRUK Early Diagnosis Advisory Group, UK Clinical Research Collaboration Board, Wellcome Trust, NIHR funding bodies (HTA and SPCR), and Oxford Biomedical Research Centre. As a member of two research groups for the latter he was a co-author of three studies – "Impact of PPI on enrolment and retention in clinical trials –

systematic review and meta-analysis" (BMJ Nov 2018), "PPI in UK surgical trials" (BMC Trials 2019) and "Frameworks for supporting PPI in research" (Wiley Jan 2019). Importantly, the first of these publications demonstrated evidentially that PPI has a positive impact on recruitment to trials (it concluded that attempts to enrol 100 patients for a trial would, on average, attract an additional 14 patients being recruited) and, especially, that PPI representatives with lived experience of the health condition would also significantly improve recruitment (a sound endorsement for the PPI representatives of the CSGs!).

Most importantly, each of the CSG's 7 Subgroups benefit from the involvement of active, experienced and knowledgeable patient representatives, including: Mr Richard Castle and Ms Jane Leahy (AML Subgroup); Ms Sandy Crane (CML Subgroup); Mr Garry Bisshopp and Mr Nick York, CLL Subgroup); Ms Sophie Wintrich (MDS Subgroup), and Ms Alisia O'Sullivan (MPN Subgroup). All have close, and in some cases, professional working links with blood cancer charities and support groups (Bloodwise, CML Support, Leukaemia Care, CLL Support, MDS UK Patient Support Group, MPN Voice and Myeloma UK) which ensure that the views of the wider patient communities are represented in the development of clinical trials within each Subgroup. All have been actively involved in Subgroup trial development and Jane Leahy was a named collaborator on the most recent AML Subgroup proposal (VICTOR).

The extent of Consumer involvement within each Subgroup was comprehensively highlighted at the CSG's Strategy Day during presentations by the Subgroup Chairs. In addition, in a Consumer-led action, the Subgroup patient representatives presented their views and input into the strategic development of the CSG in a paper which was included in the discussions.

The Consumer involvement within the Haematological Oncology CSG is extensive, and a key challenge for the future is to build upon the initial networking between Subgroup patient representatives, and to extend these links to include Consumers within other closely-related CSGs.

7. Priorities and challenges for the forthcoming year

Priority 1 In the forthcoming year the subgroups will continue to implement the CSG Strategy which will lead to a diversification of leadership across the CSG. Continued involvement by trainees both within the CSG but also with representation on each of our disease subgroups.
Priority 2 Replacement of key Phase III trials. AML18 and AML19 have been modified but require replacement. A working group will be established to prepare for the next large Phase III AML trial, AML20.
Priority 3 Ensure the continued funding and success of the Trials Acceleration Programme Network. It is required to diversify funding from Bloodwise.
Challenge 1 To ensure continued interaction with Pharma and to make sure that Brexit doesn't have any deleterious effect on our clinical trials.
Challenge 2 Research funding: It is vitally important that the CSG continues to have Phase III trials open in all of our principle disease areas as the trials are usually considered the standard of care for most UK haematology centres in diseases such as acute myeloid leukaemia and acute lymphoblastic leukaemia.
Challenge 3 Maintaining the Phase I/II capacity for haematological oncology that is provided by the Bloodwise TAP Programme, IMPACT for stem cell transplant and cellular therapies, Myeloma UK Clinical trials network and the CRUK/NIHR ECMC Network. There is a particular problem in that Bloodwise will cease to fund the TAP hub and it is a challenge to replace this funding.

8. Collaborative partnership studies with industry

The Haematological Oncology Clinical Study Group has extensive interactions with the pharmaceutical industry across all sub-groups and from Phase I/II to Phase III. Part of our strategy is that each sub-group should have a representative responsible for interaction with the industry. This has been highlighted by the recent acceptance of a letter to the Lancet demonstrating in excess of £200million of savings as a direct result of Pharma support for our portfolio.

For example, the CLARITY trial in TAP has been supported by both Janssen and Abbvie with the provision of drug and research support. This trial has resulted in the modification of FLAIR with further support from Pharma and for Janssen developing licencing studies building on from the combination pioneered in CLARITY. There are many other examples of Pharma interaction and support throughout our sub-groups. The Myeloma Subgroup (UKMRA) is in the process of setting up collaborative partnerships with industry partners to identify elements of their pipeline CDP that the UKMRA can perform thus access newer drugs earlier. Also, such partnerships aim to improve the chances of HTA approval through clever earlier design of trials seeking to fill data gaps. Develop scope and horizon scanning for interface with in vitro diagnostics (IVD) industry. This is in part a partnership with NIHR but also industry-facing initiative, including through the supportive care research programme.

9. Appendices

Appendix 1 - Membership of Haematological Oncology Group and Subgroups

Appendix 2 – Haematological Oncology Group and Subgroup strategies

- A – Haematological Oncology Group Strategy
- B – Acute Lymphoblastic Leukaemia (ALL) Subgroup Strategy
- C – Acute Myeloid Leukaemia (AML) Subgroup Strategy
- D – Chronic Lymphoblastic Leukaemia (CLL) Subgroup Strategy
- E – Chronic Myeloid Leukaemia (CML) Subgroup Strategy
- F – Myelodysplastic Syndromes (MDS) Subgroup Strategy
- G – Myeloma Subgroup Strategy
- H – Myeloproliferative Neoplasms (MPN) 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

Professor Peter Hillmen (Haematological Oncology Group Chair)

Appendix 1

Membership of the Haematological Oncology Group

Name	Specialism	Location
Mr Alan Chant	Consumer	High Wycombe
Dr Gillian Murphy	Consumer	Surrey
Professor Gordon Cook	Haematologist	Leeds
Professor Mhari Copland	Haematologist	Glasgow
Professor Charles Craddock	Haematologist	Birmingham
Dr Thomas Fox*	Haematologist	London
Professor Peter Hillmen (Chair)	Haematologist	Leeds
Dr Gillian Horne*	Haematologist	Glasgow
Dr Sally Killick	Haematologist	Bournemouth
Professor Judith Marsh	Haematologist	London
Professor Adam Mead	Haematologist	Oxford
Dr Dragana Milojkovic	Haematologist	London
Professor Stephen O'Brien	Haematologist	Newcastle
Dr Andrew Peniket	Haematologist	Oxford
Dr Clare Rowntree	Haematologist	Cardiff
Dr Anna Schuh	Haematologist	Oxford
Dr Simon Stanworth	Haematologist	Oxford
Dr Simon Watt	Haematologist	Manchester
Professor Kwee Yong	Haematologist	London
Ms Lavinia Davey	Nurse	Canterbury
Professor Kikkeri Naresh	Pathologist	London
Dr Alasdair Rankin	Research Director, Bloodwise	London
Ms Shamyla Siddique	Senior Trials Coordinator	Birmingham
Ms Amy Kirwood	Statistician	London

* denotes trainee member

Membership of the Subgroups

Acute Lymphoblastic Leukaemia (ALL) Subgroup		
Name	**Specialism**	**Location**
Dr Rachael Hough	Clinical Oncologist	London
Professor Oliver Ottman**	Clinical Professor	Cardiff
Mr John Reeve	Consumer	Hampshire
Professor Anthony Moorman**	Epidemiologist	Newcastle
Dr Adele Fielding (Co-Chair)**	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 (Co-Chair) **	Haematologist	Cardiff
Dr Sridhar Chaganti**	Haematologist	Birmingham
Dr Anna Castleton**	Haematologist	Manchester
Dr Bella Wrench	Scientist	London
Dr Caroline Furness	Haematologist	Bristol
Dr Debbie Yallop	Haematologist	London
Ms Amy Kirkwood	Statistician	London
Ms Pip Patrick	Trials Coordinator	London
Ms Laura Clifton-Hadley	Trials Coordinator	London

Acute Myeloid Leukaemia Subgroup		
Name	**Specialism**	**Location**
Dr Harpreet Kaur**	Consultant Haematologist	Sheffield
Dr Panos Kottaridis**	Consultant Haematologist	London
Mr Richard Castle**	Consumer	
Dr Sahra Ali**	Haematologist	Hull
Professor David Bowen	Haematologist	Leeds
Dr Jamie Cavenagh**	Haematologist	London
Professor Richard Clark**	Haematologist	Liverpool
Professor Mhari Copland**	Haematologist	Glasgow
Dr Dominic Culligan	Haematologist	Aberdeen
Professor Charles Craddock (Co-Chair)	Haematologist	Birmingham
Dr Mike Dennis	Haematologist	Manchester
Dr Sylvie Freeman	Haematologist	Birmingham
Dr Ann Hunter**	Haematologist	Leicester
Dr Brian Huntly**	Haematologist	Cambridge
Dr Gail Jones	Haematologist	Newcastle
Professor Asim Khwaja**	Haematologist	London
Dr Steven Knapper	Haematologist	Cardiff
Professor Mary McMullin	Haematologist	Belfast

Dr Frank Mussai**	Haematologist	Birmingham
Professor Nigel Russell (Co-Chair)	Haematologist	Nottingham
Dr Paresh Vyas**	Haematologist	Oxford
Dr Robert Lown	Haemato-Oncologist	Southampton
Dr Priyanka Mehta**	Haemato-Oncologist	Bristol
Ms Shamyla Siddique**	Senior Trials Coordinator	Birmingham
Dr Robert Hills**	Statistician	Cardiff
Professor Keith Wheatley	Statistician	Birmingham

Chronic Lymphoblastic Leukaemia (CLL) Subgroup		
Name	**Specialism**	**Location**
Dr Satyen Gohil*	Clincial Research Associate	London
Mr Garry Bisshopp	Consumer	Sussex
Mr Nick York**	Consumer	
Dr David Allsup	Haematologist	Hull
Dr Adrian Bloor	Haematologist	Manchester
Professor Stephen Devereux	Haematologist	London
Dr Chris Fegan	Haematologist	Cardiff
Dr Francesco Forconi	Haematologist	Southampton
Dr Chris Fox	Haematologist	Nottingham
Professor Peter Hillmen	Haematologist	Leeds
Dr Scott Marshall	Haematologist	Sunderland
Dr Chris Pepper	Haematologist	Cardiff
Professor Andre Pettitt	Haematologist	Liverpool
Dr Christopher Pocock**	Haematologist	Canterbury
Dr Guy Pratt**	Haematologist	Birmingham
Dr Anna Schuh (Chair)	Haematologist	Oxford
Dr Ben Kennedy	Haemato-Oncologist	Leicester
Professor Martin Dyer	Haemato-Oncologist	London
Ms Dena Cohen	Statistician	Leeds

Chronic Myeloid Leukaemia (CML) Subgroup		
Name	**Specialism**	**Location**
Ms Sandy Crane	Consumer	
Dr Nauman Butt**	Haematologist	Liverpool
Dr Jenny Bryne	Haematologist	Nottingham
Professor Richard Clark	Haematologist	Liverpool
Professor Mhairi Copland (Chair)	Haematologist	Glasgow
Dr Paolo Gallipoli	Haematologist	Cambridge
Dr Andrew Goringe	Haematologist	Cardiff
Dr Brian Huntly	Haematologist	Cambridge
Dr Adam Mead	Haematologist	Oxford
Professor Stephen O'Brien	Haematologist	Newcastle
Dr Graeme Smith	Pathologist	Leeds

Myelodysplastic Syndromes (MDS) Subgroup		
Name	**Specialism**	**Location**
Ms Sophie Wintrich**	Consumer	
Mr Dan Wiseman	CRUK Representative	Manchester
Professor David Bowen	Haematologist	Leeds
Dr Catherine Cargo**	Haematologist	Leeds
Professor Jamie Cavenagh	Haematologist	London
Dr Tim Chevassut**	Haematologist	Brighton
Dr Dominic Culligan	Haematologist	Aberdeen
Professor Ghulam Mufti	Haematologist	London
Dr Simone Green**	Haematologist	Hull
Dr Wendy Ingram**	Haematologist	Cardiff
Dr Harpreet Kaur**	Haematologist	Sheffield
Dr Sally Killick (Chair)	Haematologist	Bournemouth
Dr Austin Kulasekararaj**	Haematologist	London
Professor Judith Marsh**	Haematologist	London
Dr Juliet Mills	Haematologist	Worcester
Professor Ken Mills**	Haematologist	Belfast
Dr Jane Parker**	Haematologist	Northampton
Dr Lynn Quek	Haematologist	Oxford
Dr Manoj Raghavan	Haematologist	Birmingham
Dr Kavita Raj**	Haematologist	London
Dr Alexander Sternberg**	Haematologist	Swindon
Dr Christopher Dalley**	Haemato-Oncologist	Brighton
Dr Priyanka Mehta**	Haemato-Oncologist	Bristol
Ms Rebecca Bishop**	Senior Trial Coordinator	Birmingham
Dr Rachel Blundred**	Senior Trial Coordinator	Birmingham
Ms Aimie Houlton	Statistician	Birmingham

Myeloma Subgroup		
Name	**Specialism**	**Location**
Ms Clare Shaw**	Clinical Trials Network Manager	London
Mr Alan Chant	Consumer	Maidenhead
Dr John Ashcroft**	Haematologist	Yorkshire
Dr Holger Auner**	Haematologist	London
Dr Supratik Basu**	Haematologist	Wolverhampton
Dr Reuben Benjamin**	Haematologist	London
Dr Jenny Bird	Haematologist	Bristol
Dr Stella Bowcock**	Haematologist	London
Professor Jamie Cavenagh**	Haematologist	London
Dr Andy Chantry	Haematologist	Sheffield
Dr Mike Chapman**	Haematologist	Cambridge
Professor Gordon Cook (Chair)	Haematologist	Leeds
Dr Mark Cook	Haematologist	Bristol
Dr Shirley D'sa**	Haematologist	London
Dr Hannah Hunter**	Haematologist	Plymouth
Dr Matthew Jenner	Haematologist	Southampton
Dr Martin Kaiser**	Haematologist	London
Dr Kamaraj Karunanithi**	Haematologist	Stafford
Dr Bhuvan Kishore**	Haematologist	Birmingham
Dr Ceri Marrin**	Haematologist	Cardiff
Professor Atul Mehta**	Haematologist	London
Dr Kim Orchard**	Haematologist	Southampton
Dr Roger Owen **	Haematologist	Leeds
Dr Rakesh Popat**	Haematologist	London
Dr Guy Pratt	Haematologist	Birmingham
Dr Neil Rabin**	Haematologist	London
Dr Karthik Ramasamy	Haematologist	Oxford
Professor Steve Schey**	Haematologist	London
Professor John Snowden**	Haematologist	Sheffield
Dr Richard Soutar**	Haematologist	Glasgow
Dr Matthew Streetly**	Haematologist	London
Dr Jane Tighe**	Haematologist	Aberdeen
Dr Cathy Williams**	Haematologist	Nottingham
Professor Kwee Yong**	Haematologist	London
Dr Charlotte Pawlyn*	Haematology Registrar	London
Dr Charles Crawley**	Haemato-Oncologist	Cambridge
Professor Mark Drayson	Immunologist	Birmingham
Ms Monica Morris**	Myeloma UK Representative	London
Mr Eric Low**	Myeloma UK Representative	London
Dr Sarah Brown	Statistician	Leeds
Professor Walter Gregory**	Statistician	Leeds
Ms Wendy Notowicz**	UK Myeloma Forum Representative	

Myeloproliferative Neoplasms (MPN) Subgroup		
Name	**Specialism**	**Location**
Ms Alisia O'Sullivan**	Consumer	
Mr Tim Somervaille**	CRUK Representative	Manchester
Dr Sahra Ali	Haematologist	Hull
Dr Joanna Baxter**	Scientist	Cambridge
Dr Nauman Butt	Haematologist	Liverpool
Dr Catherine Cargo**	Haematologist	Leeds
Dr Peter Campbell**	Haematologist	Cambridge
Dr Frederick Chen**	Haematologist	Birmingham
Dr Eibjilin Conneally**	Haematologist	London
Professor Nick Cross**	Scientist	Southampton
Dr Mark Drummond	Haematologist	Glasgow
Dr Andrew Duncombe	Haematologist	Southampton
Dr Hesham Eldaly	Pathologist	Cambridge
Dr Joanne Ewing	Haematologist	Birmingham
Ms Sonia Fox**	Senior Trials Coordinator	Birmingham
Dr Sebastian Francis**	Haematologist	Sheffield
Dr Mamta Garg	Haematologist	Leicester
Dr Anna Godfrey**	Haematologist	Cambridge
Professor Tony Green	Haematologist	Cambridge
Professor Claire Harrison	Haematologist	London
Dr Clodagh Keohane**	Haematologist	Cork
Dr Stephen Knapper	Haematologist	Cardiff
Dr Jashmid Khorashad	Scientist	Imperial
Dr Jonathan Lambert**	Haematologist	London
Dr Donal McLornan**	Haematologist	London
Professor Mary McMullin	Haematologist	Belfast
Dr Adam Mead (Chair)	Haematologist	Oxford
Dr Dragana Milojkovic**	Haematologist	London
Dr Jyoti Nangalia**	Haematologist	Cambridge
Dr Beth Psaila**	Haematologist	Oxford
Dr Deepti Radia **	Haematologist	London
Dr Shekouhi Satareh**	Haematologist	London
Dr Mallika Sekhar**	Haematologist	London
Dr Frances Wadelin	Haematologist	Nottingham
Dr Jonathan Wallis**	Haematologist	Newcastle
Ms Louise Wallis**	Research Nurse	Bournemouth
Ms Claire Woodley**	Research Nurse	London
Mrs Sonia Fox**	TAP Trials Team Leader	Birmingham

* denotes trainee member
**denotes non-core member

Appendix 2

Haematological Oncology Group & Subgroup Strategies

A – Haematological Oncology Group Strategy

The Haematological Oncology CSG was originally established through the merging of several independent MRC Working Groups which became Subgroups under the new NCRI structure. Although the WGs were individually successful, the establishment of a parent CSG created an opportunity to consider research priorities in a more holistic way, identify common objectives and share best practice. This resulted in the development and delivery of a new generation of cutting-edge studies. Owing to the accessibility of fresh tumour material, haematological oncology has always led the way in molecular stratification, and the advent of new technologies, coupled with the development of highly targeted therapies, now presents an opportunity for haematological oncology be at the vanguard of the development of precision medicine in cancer.
Scientific strategy.

The CSG's overall 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 quantification of residual tumour burden, coupled with the optimisation of supportive care and of 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 biomarker discovery/development and the identification of new drug targets. It is crucial to ensure optimal connectivity between clinical research and basic/ translational science in order to produce the strongest possible funding applications. It is also important to ensure seamless connectivity between the Group's early-phase clinical research and late-phase trials to ensure that the early-phase trials have an explicit purpose within the portfolio and that preliminary observations of interest are subjected to definitive testing in the most efficient way possible.

Priority areas for clinical research

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 to inform on the next generation of phase III studies. In addition to the 7 disease specific sub-groups the CSG has established a Working Party to develop research proposals in Aplastic Anaemia. The Group aims to apply a more co-ordinated approach to transplant studies by working more closely with the BSBMT and establish closer collaborative links with the CCL and TYA CSGs to ensure an optimally co-ordinated approach for all TYA patients with leukaemia.
Biobanking and translational research
Precision medicine requires the identification of molecularly defined patient subgroups who are likely to benefit from specific, targeted therapies. This, in turn, requires the identification of new drug targets and the development of predictive biomarkers. Samples obtained from patients recruited into clinical trials provide an ideal – and in many cases unique - resource for such translational research, and one of the CSG's priorities is to ensure that all of its major studies are supported by high-quality biobanking coupled with a comprehensive and co-ordinated programme of correlative science employing cutting-edge technologies. It is equally important that information generated from laboratory research programmes is used to inform on the design of new clinical trials.

Engagement with industry

Industry engagement is of fundamental importance to the CSG owing to the need to investigate new drugs that are not available through the NHS. Pharma companies may also provide a potential source of funding for trial coordination, biobanking and correlative science. The Group's relationship with industry has evolved in an organic fashion through the endeavours of individuals to develop clinical trials and is, for the most part, excellent. It is, however, crucial that all proposals for new industry-sponsored studies are discussed with the CSG in order to plan the portfolio and minimise competition for niche study populations.

Engagement with charity-funded research infrastructure initiatives

The CSG is fortunate to have access to additional clinical research capacity via the TAP, IMPACT and Myeloma UK Clinical Trials Networks. To fully exploit the opportunities provided by these initiatives, it is crucial that there is full strategic alignment between all parties through cross-membership of the respective groups. The CSG also needs to links in with the CRUK/NIHR ECMC Network, especially given the proposal to form a Haemato-Oncology Group within the ECMC Network.

Engagement with Genomic England Ltd (GEL)

Haemato-oncology has been at the vanguard of the GEL 100,000 Genomes Project owing to the relative ease in obtaining fresh tumour material. Following closure of the programme in December 2018, there has been a switch to national commissioning of routine molecular diagnostics to centrally performed whole-genome sequencing (WGS), starting with AML/MDS. In order to facilitate close links with the NHSE WGS the Clinical Lead for the Haemato-Oncology GEL Clinical Interpretation Partnership (GeCIP) has been co-opted onto to the CSG.

Trial delivery

Delivering trials to time and target remains one of the key priorities of the CSG. It is therefore important that the CSG engages effectively with the delivery networks. This will be achieved by involving Subspecialty Leads (SSLs) in CSG meetings and by continuing to showcase the CSG portfolio at the annual trials review meeting. Consideration is being given to holding a national joint meeting with SSLs.

Consumer engagement

Consumer representation on the CSG is crucial, not only for writing and commenting on patient information sheets, but also for formulating new research questions, gauging patient acceptance of new studies, optimising trial design and publicising new studies within the patient community. It is also important that the CSG has broad geographical representation.

CSG membership

In order for the CSG to fulfil its function, it is crucial that CSG members cover a broad range of expertise including the seven main disease areas (AML, ALL, CML, CLL, MPN, MDS, myeloma). Given the importance of optimising trial design, the CSG also places much emphasis on statistician representation. The appointment of a senior trial coordinator to the Group provides expertise in trial delivery. The CSG feels that the balance in membership is about right but that it could benefit from the inclusion of a senior research nurse at the next rotation. The CSG has implemented the rotation of sub-group chairs according to the NCRI guidance with a rotation of the chairs of the ALL, AML and MDS in the last 12 months.

Training opportunities

The long-term sustainability of clinical research depends on there being a pipeline of future clinical researchers, and it is crucial that the clinical research community provides training opportunities for such individuals. The CSG is committed to contributing to this process by taking part in the CSG Trainee Scheme. In addition, the CSG is encouraging the membership and participation of trainee representatives on each disease sub-group.

B – Acute Lymphoblastic Leukaemia (ALL) Subgroup Strategy

Top achievements in the reporting year

Achievement 1

Fully recruited to both arms of UKALL 14 in 2018. The results of the randomised questions are expected late 2019.

Achievement 2

Completed UKALL 60+ December 2018. The results of this study will inform the design of the treatment arm for patients not fit for intensive chemotherapy in UKALL 15.

Priorities and challenges for the forthcoming year

Priority 1

The main priority of the ALL subgroup is to improve the outcomes of treatment for patients with ALL. This includes working in collaboration with paediatric colleagues to determine the optimal treatment for young adults resulting in improved survival whilst limiting long term toxicity effects such as infertility and secondary malignancies. It also includes determining a standard of care for patients unfit for intensive treatments including elderly patients and those with comorbidities. The aim is to have a front line trial for all patients with newly diagnosed ALL in the UK with the priority for 2019 being to complete the design of UKALL 15 and to submit to CRUK for funding in June 2019

Priority 2

Patients of all ages with relapsed / refractory ALL continue to have extremely poor outcomes and designing phase II trials for these patients in collaboration with partners from industry is an important part of our strategy within the ALL subgroup.
The aim is to offer a program of phase II studies offering novel therapies including CAR-T cell approaches to patients with high risk disease as well as those with relapsed / refractory disease

Priority 3

In addition to providing good clinical trials for patients with ALL in the UK, the group is also focusing on developing a large and productive programme of correlative science. A CRUK program grant was awarded to enable work on samples from our upfront studies UKALL 14 and UKALL 60+ to determine genetic factors that may influence patient outcome related to treatments given.

Challenge 1

Maintaining high quality upfront studies for all newly diagnosed patients with ALL in the UK.

Challenge 2

NICE are currently reviewing the use of blinatumomab for MRD positive patients post induction chemotherapy for B cell ALL. This technology appraisal has been delayed twice within the past year and the outcome is now awaited. If blinatumomab is recommended for patients in this category then this will change the standard of care for approximately 50% of adult patients and will require a complete rewrite of UKALL 15 control arm.

C – Acute Myeloid Leukaemia (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.

Priority

To analyse treatment response in relationship to mutational profile in a collaboration with the Sanger Institute based upon an analysis of samples from over 2,400 patients entered into our trials. This will help inform the design of the next generation of NCRI AML trials.

Challenge

Design a follow-up trial for patients not fit for intensive therapy to replace the LI1 trials

Working with the UK IMPACT transplant trials cooperative, one of only two transplant networks in the world, the AML Working Party has made substantial practice in delivering two globally significant transplant trails. Pro-DLI, the first randomised study examining the ability of donor lymphocyte infusions (DLI) to improve outcome in patients allografted for AML is recruiting well and is anticipated to close in September 2019. AMADEUS, a randomised study examining the ability of maintenance post-transplant therapy using oral azacitidine (CC486) to improve outcome in patients transplanted for AML opened in June 2019 and is now recruiting. AMADEUS is being funded by Celgene so that it can deliver trial data with enhanced pharmacovigilance to registration standard. AMADEUS has the potential to demonstrate to the global pharmaceutical sector that the UK has the capacity, thanks to the strength of NCRI working parties, to accelerate delivery of high quality clinical trials to registration standard.

D – Chronic Lymphoblastic Leukaemia (CLL) Subgroup Strategy

Summary of main achievements and challenges

Achievements

The CLL subgroup had a very successful year, the main highlight being the report of the initial results of the CLARITY Study (ASH in Dec 2017 and 2018; now under review with JCO). The An abstract summarising the initial data from the Rialto trial has been submitted to EHA.
Recruitment into our flagship Phase III trial FLAIR remains ahead of schedule and will end in Q1 2020.
The main translational programme, the CLL Genomics England Pilot, has finished recruitment and is now in its analysis phase. A first paper has been published (Klintman et al BJH; July 2018). 906 patients were retrospectively consented, with 400 tumour-normal pairs sequenced including sequential samples at relapse. Further analyses of samples from the same patients (methylome and proteomics) are ongoing.
Following on from Prof Peter Hillmen's appointment as the chair of the haem-onc group after 15 years of excellent subgroup leadership, Anna Schuh was appointed as his successor.

Challenges

The main challenge for the subgroup going forward is the lack of available funding for haematology research in the UK:
Attempts to attract funding from CRUK and MRC for the UK CLL biobank infrastructure have been unsuccessful so far. Efforts to transform access to samples and matched whole genome sequencing data (the Genomics England CLL Exemplar) into multi-omics research funding support from pharma or biotech companies have also not come to light. The future of TAP that has greatly facilitated the CLL early phase portfolio so effectively is less certain.

Strategy review for the group

Our overarching strategy consists of underpinning our excellent clinical research portfolio with an innovative and comprehensive experimental medicine programme.
Going forward, the group will address the following outstanding research questions with its strategy:

1. CLL remains largely incurable. Development of resistance to targeted therapies given as monotherapy invariably occurs at least in the relapsed-setting. Combination therapy given to treatment-naïve patients might change this pattern. However, the molecular mechanisms underlying therapy resistance are only incompletely understood.

The FLAIR study directly addresses this question with its I&V arm and FLAIR sample collection is ongoing. As a basis to future in-depth mechanistic studies, over 150 FLAIR patients have undergone whole genome sequencing.

2. Continuous targeted therapy is not what patients prefer, might be less effective than intermittent dose schedules and is definitely more expensive.

A new study (CI Peter Hillmen) has been approved for funding by the HTA. Indications for treatment holiday and continuation will be directed by MRD analyses.

3. Data on long-term side-effects of the new agents and their impact on quality of life in the real world remains largely unknown and is currently not systematically captured.

A long-term registry is being set-up via the Leeds CTRU (P Hillmen)
In parallel, we will try to evaluate live-feeds from NHS databases into the GEL data centre as a complementary way to accessing clinical outcome data (A Schuh)

4. As patients live longer, high-grade transformation is seen more frequently. It remains to be seen whether the incidence of this life-threatening complication will reduce as targeted agents move into frontline. In the meantime, there is a high unmet clinical need for this patient group.

STELLAR (CI: A Schuh), the new platform trial for patients with high-grade transformation, will open for recruitment in May. Results of the CHOP-OR genomics and transcriptomics study have been submitted.

5. Patients struggle with the concept of "watch and wait". A more precise definition of the disease risk at all its stages including the early diagnosis stage is required.

Oxplored is a prospective sample collection study that will start recruiting 1650 probands with a pre-malignant B-cell phenotype in May. The aim will be to perform comprehensive genomics and immuno-oncological studies.

Important infrastructure to deliver our strategy been set up (broad range of clinical and scientific expertise; central biobanking; access to GEL data centre), but a more coordinated translational research programme spanning across biological mechanisms, diagnostics, novel drug target discovery is required to build a truly "experimental medicine" programme.

We therefore propose to restructure the subgroup into a wider group of CIs, PIs and scientists and a core working group that will meet by TC on a bi-monthly basis. The core will include leads for:

1. (Epi)Genomics (Jon Strefford)
2. Molecular diagnostics (A Rawstron; A Schuh)
3. Biobanking (A Pettitt; M Oates)
4. Early & late Phase clinical trials (T Munir, P Hillmen)
5. Rare LPDs (S Iyengar)
6. Early interception (A Schuh)
7. Micro-environment/basic science (P Patten)
8. Novel immunotherapy (A Bloor)
9. High-grade transformation (A Schuh)
10. Long-term clinical trial registry
11. Real-life data collections (C Fox, A Hockaday)
12. Patient communication (B Kennedy)
13. Training (TBD)

In addition to working together to deliver on the strategic aims described above, the working group will develop:

- Sustainable solutions for delivery of a joint genotype-phenotype database that would be accessible to all subgroup members with data feeds from NHS digital; Genomics England, interactions with Horizon and other similar data sharing initiatives
- Opportunities for joint and/or coordinated grant applications
- Effective and co-ordinated interactions with pharma and biotech
- Opportunities for joint working and sharing of resources with other subgroups in the CSG and the lymphoma CSG
- Expansion of international collaborations: Joint trials in rare molecular subtypes and Global Haematology

Finally, the subgroup will host the IWCLL Workshop Edinburgh 2019: This is the biggest CLL specific conference world-wide. We have put the conference team in place and are currently working on the programme design.

E – Chronic Myeloid Leukaemia (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. Over the next 12 months, a key deliverable will be opening the TASTER clinical trial (CI: Professor Mhairi Copland). A second aim is to deliver high quality, internationally recognised translational research in CML through the continued support and management of the SPIRIT2, DESTINY and MATCHPOINT clinical trial CML Biobanks.

Moving forward, our strategy over the next 12 months is to develop in the following areas:

1. Clinical trials: our key strategic aims are to (1) open the TKI-resistance study TASTER – funded by CR-UK-EMERP by q3.2019; (2) to develop a de-escalation/discontinuation follow-up study to DESTINY; (3) to complete recruitment to the cohort study 'CALLS' (CI: Dr Hugues de Lavallade) open in sites across the UK, a commercial study in collaboration with Incyte to assess Next Generation Sequencing for the diagnosis of BCR-ABL kinase domain mutations; (4) continue to recruit to the commercial studies (a) OPTIC, which is a phase 2 dose finding study of different doses of ponatinib; and (b) CABL001A2301, a phase 3 study (2:1 randomisation) comparing asciminib with bosutinib. We will continue to engage with industrial partners, where appropriate to open additional commercial studies in the UK. Dr de Lavallade is also working with Incyte to develop a clinical trial with ponatinib for patients that develop a BCR-ABL mutations on TKI. In terms of a front-line study for patients with newly diagnosed chronic phase CML, we acknowledge that this is a challenging area for clinical trial development at present, but continue to horizon scan potential opportunities that may fit with UK practice and current approvals.
2. Presentations/Publications: Over the next 12 months, we will aim to have the final manuscripts for SPIRIT2, DESTINY and CHOICES clinical trials published. We also aim to present the first year of follow up for MATCHPOINT at ASH in December and submit an initial manuscript in tandem with this to JCO. In addition, we will publish the BCSH CML guideline in the next 12 months in the British Journal of Haematology. We plan to identify further sub-studies from SPIRIT2 for presentation/publicaiton
3. Correlative science: The clinical trial biobanks continue to be a rich source for research projects and publications. Over the next 12 months, the Subgroup aims to secure finding to further evaluate samples from the DESTINY clinical trial (project grant currently submitted by Copland). The correlative science work packages for TASTER are in progress (Copland, Vetrie) and will feedback to the subgroup initially. Results from GeCIP are beginning to come back, and we will consider how we progress with this and identify further potential subsets of patient samples for analysis.
4. CML Registry: The CML subgroup is committed to developing a Registry to collect data on CML patients, in particular in relation to treatment-free remission and paediatric CML. We aim to identify funding that will allow us develop a Registry in these areas.
5. Patient partnership: We have a consumer representative on our Subgroup who is a very active contributor to meetings and study design. We will be holding a patient and carer education day later in the year – Leeds on 21st September 2019. The meeting will also be webcast live and available for download thereafter to reach as many patients as possible.
6. Subgroup membership: Over the few months, Professor Copland will step down as subgroup chair, and a successor appointed. We aim to enrol a clinical nurse specialist to the CML subgroup.

F – Myelodysplastic Syndromes (MDS) Subgroup Strategy

The main priority for the MDS subgroup is to improve the outcome of treatment for patients with MDS and allied conditions. The strategy of the MDS Subgroup is to develop a portfolio of Phase I, II and III studies which covers MDS and the allied conditions.

MDS remains a difficult disease with regards designing and delivering clinical trials, so the group have spent the last 12 months considering a new approach. It is appreciated that the patients are often elderly, have multiple co-morbidities and may not wish to travel distances for treatment due to the impact on QoL. Trials therefore need to include those that can be delivered within district hospitals around the UK to maximise access and recruitment, alongside early phase trials run in tertiary centres.

Changes afoot:

- Introduction of a Terms of Reference document for the Senior Leadership Roles which has been ratified by the group
- Election of an Executive Board with rotational lead roles – vice-chair, biobank/governance, translational science, early phase/industry trials, communications
- Appointment of a trainee representative to the subgroup through the NCRI trainee scheme – currently underway
- Production of a Strategy Document that engages the whole group emphasising our strengths and direction of travel with emerging themes. A thematic approach would allow us to concentrate on common areas across the disease as a whole (and allied conditions) rather than the current focus on disease subtypes
- Improvement in communication to haematologists and patients of available trials around the UK that are open and recruiting

The aim of the group is to design and develop clinical trials by bringing together pertinent and timely clinical questions with high quality scientific research. We continue to engage the wider non-clinical MDS scientific community to fully utilise the expertise available in the UK. Our portfolio includes investigator led studies, links to the NCRI AML subgroup to facilitate MDS trial entry and a strong commercial portfolio.

High risk MDS is well represented in both the NCRI AML trials (AML18/19/LI-1) as there is considerable overlap in treatment approaches, and the commercial portfolio where many trials seek to improve survival over single agent azacitidine in high risk MDS with novel agents.

The challenge to the MDS subgroup has been to deliver clinical trials in patients with low risk disease where there is an unmet need. These patients account for approximately two thirds of MDS patients where the aims of treatment are to improve bone marrow failure, improve QOL & the consequences of supportive care and delay the progression to high risk MDS.

Successes from the group over the last year:

1. REDDS –Red blood cell transfusion thresholds and QOL in MDS: a pilot and feasibility study. Collaboration with NHS Blood and Transplant. Dr's Stanworth, Bowen & Killick. Recruited on time. Oral presentation at ASH 2018 – A feasibility randomised trial of red cell transfusion thresholds in MDS. Blood 2018 132:527

2. MONOCLE - Phase II study in CMML. CI Dr Steve Knapper. Safety and clinical effectiveness of the monocyte targeted HDAC inhibitor, Terfinostat. Following failure to achieve a pre-determined minimum number of clinical responses to terfinostat, patient recruitment was not continued to phase 2 of this phase 2 study. Drug tolerability was encouraging but renal effects are likely to preclude dose escalation. Trial was unable to demonstrate a clinically significant single agent disease modifying effect in CMML. Ongoing lab projects utilising the banked patient samples, including a grant application to study resistance mechanisms in CMML. Presentation at ASH 2018 Results of a phase 2 trial of the monocyte-targeted histone deacetylase inhibitor terfinostat in CMML – the UK Monocle Study. Blood 2018 132:1818

3. ELASTIC – Azacitidine and eltrombopag. CI Dr A Sternberg. Fully recruited, predicting last visit March 2019. Manuscript will follow.

Priority areas for Clinical Research

1. Randomised Phase II/III trial of Danazol Vs VBaP Vs best supportive care. Dr's Drayson, Culligan, Raghaven, Killick, Mufti. This is a trial investigating danazol and the novel combination of valproate, bezafibrate and medoxyprogesterone for which there is scientific data supporting its use (Dr M Drayson's group). It is a trial aimed at low risk MDS, which fulfils the strategic aims of the group. The plan is for the trial to be phase II, then move to phase III with the best arm. This trial will have important clinical questions, tight diagnostic inclusion and strong translational research over a number of scientific groups. The trial will be open to all UK centres and the plan is to apply to CRUK for funding.
2. TEAMM 2 – collaboration. Dr's Drayson & Culligan. Following on from the disappointment of not having RAPRIMA funded, the group are collaborating with Dr Drayson regarding the inclusion of MDS patients into TEAMM 2 in a similar fashion to RAPRIMA, allowing resurrection of the hard work by our subgroup. This is a supportive care trial investigating antibiotic prophylaxis. Funding re-application to NIHR planned this summer.
3. REDDS2 – study design ongoing - Dr Stanworth (NHS Blood and Transplant) and David Bowen: transfusion support in patients with lower risk MDS. Funding bodies identified.
4. ASTX727 in CMML and MDS/MPN overlap. CI Dr D Wiseman. Unmet need for a UK trial for CMML following the closure of MONOCLE. ASTEX supportive. Discussed with the IWG and NCRI MPN groups. Funding TBC.
5. LI-2 – collaborative input to trial design for patients with high risk MDS with the AML subgroup.

The MDS subgroup continue to collaborate with the MPN & AML groups, NHS Blood and Transplant and the Aplastic Anaemia Working Party. The group feeds into the UK MDS Forum and presents at the Annual UK MDS Forum Education Day and Executive Board every autumn.

G – Myeloma Subgroup Strategy

Strategic outline:

The UK Myeloma Research Alliance (UKMRA) was generated conceptually in 2014, as an initiative to bring comprehensive collaborative research under a single working group to delivery patient-impactful research into a collegiate work stream, with common goals and aligned strategy. The aim of the UKMRA is to be an internationally recognized cooperative with truly impacting clinical research that facilitates change in clinical practice within the UK and beyond whilst strategically providing the evidence-base for commissioning and regulatory authority decision-making. In order to drive this aim, we set up a senior leadership team to focus developing and delivering strategic goals in 4 aligned areas: Research Governance, Trial Design, Translational Research and Industry Liaison. This document sets out our aims in each of these areas, and how we aim to deliver these.

UKMRA Aims

Fundamental to the UKMRA strategy, our aims are:

- **Portfolio Development** - incorporating efficient trial design methodologies to ensure maximum impact with minimum time to delivery impact.
- **Innovation** – utilizing "umbrella" style trial designs to ensure a constant and seamless integration of new drugs into the portfolio.
- **Efficiency and Performance** – through the UKMRA governance structure we aim to make available *all* trials to *all* feasible sites.
- **Internal and External Communication** – through the leadership roles within the UKMRA, the relevance to both the myeloma community and pharmaceutical industry will be current and maintained via a comprehensive communications strategy.
- **Commercial Opportunities** – increase the scope of commercial partnerships and trial design to complement existing commercial clinical development programmes.
- **Health Technology Appraisals** – liaising with NICE, MHRA, NHSEngland (and devolved governments) where appropriate to support appropriate market access trials of key relevance to the NHS and UK patients
- **Future Growth and Development** –a continual monitoring of progress and especially external-facing partnerships will allow adaptability with regular review

To ensure the long-term strategy and continuity of clinical research activity, we aim to establish a robust plan centered on the development of succession planning through engagement of new personnel to work alongside established researchers. We aim to have correlative science at the centre of our studies, and thus there is a need to establish cellar and open biosampling governance. Taken together, we aim to publish our clinically impactful studies in high-ranking journals to change clinical practice.

Links to other CSGs, international groups and network subspecialty leads

The myeloma sub-group doesn't have any formal links with other CSG, though some peripheral involvement in our study discussion have been had with CTRad.

Until recently, the European Myeloma Network (EMN) has not included the UK trialists. Following a very constructive meeting in Paris in April 2018, there is now a move to become more collaborative as European myeloma clinical trialists, under the auspices of the EMN. This is to be ratified at the EMN board meeting in September 2018.

Funding applications in last year

Mostly CRUK. We confirmed the CRUK funding for two frontline phase III studies, Myeloma XIV and XV, due to open in the second half of 2018.However, some Bloodwise TAP funding has been successful, with NIHR funding a recently closed phase III (TEAMM study). We are in the process of devising a supportive care platform, ENCOMPASS which we intend to submit for funding consideration to NIHR

The funding for the early phase trials network, MUK CTN, has undergone a review, and a call for submissions to deliver a different funding model has been made in Q1 2018. The UKMRA has submitted a proposal for a core grant (Concept and Access Research Programme; CARP - CI G Cook) and is currently under consideration.

Collaboration partnership studies with industry

We have industry funding partnerships with our late phase trial programme. Myeloma XII ACCoRD study is supported by CRUK and Takeda, UKMRA Myeloma XIV is supported by CRUK and Takeda with some contribution from Celgene and UKMRA Myeloma XV is supported by CRUK and Amgen, Celgene and Sanofi.

In the early phase trials setting, we have industry partnership with Takeda (MUK8), Karyopharm (MUK12) and Takeda with some contribution from Celgene and Janssen and Amgen (MUK9).

Impact of CSG activities

The recently closed phase III studies have established the role of salvage ASCT (NCRI Myeloma X) and maintenance therapy in first line along with sequential biological agent-based induction (NCRI Myeloma XI/XI+). Myeloma X has informed both national and international guideline developments and an impact on real world clinical care has been demonstrated (BSBMT and EBMT registry activity highlighting the increase in the number of sASCT performed since the study reported.

Open meetings, trials days, strategy days

UKMRA Trials day June 2016, 2017 and the 2018 meeting is planned for 6th June 2018. We continue to have 3 additional business meetings per year, and quarterly senior leadership team meetings/telecons.

Priorities and challenges for the forthcoming year

The aim for the coming 12 months is to ensure the strategic integration of young investigators in the research programme of the sub-group continues, under the ethos of inclusivity and continuity planning. We need to secure core funding for our early phase portfolio and to engage with industry partners to secure new agents for phase I/II delivery in the face of strong international competition.

A leadership challenge is the impact of any NCRI representation restrictions placed on our collaborative. T currently works well, with the vice-chair elected to succeed the chair, who represents our group on the Haemato-oncology CSG. We have worked hard to form a cohesive and collaborative group, headed up by the senior leadership team. This has under-pinned our success to date and any disruption tom this could jeopardize further success.

H – Myeloproliferative Neoplasms (MPN) Subgroup Strategy

The overarching strategy of the MPN Subgroup is to build a strong diverse network of clinicians, nurses, scientists in partnership with patients. Our aims are to:

- Ensure that basic science research in the UK remains cutting edge.
- Develop new scientists and clinician scientists to carry forward today's legacy.
- Ensure that MPN patients (encompassing a broad range of different disease entities) have the opportunity to participate in as diverse a portfolio of clinical trials as possible.
- Support sample banks in MPN and deliver results from them.
- Participate in and provide educational activities for clinicians and patients this includes guidelines as well as face to face educational meetings.
- Ensure there are up to date comprehensive national guidelines for MPN via the BSH process.
- Support NICE appraisal of novel therapeutics in MPN.

Biobanking and translational research

The Subgroup supports cutting-edge translational research through large sample banks of MPN samples and promoting strong links between clinical and scientific research programmes. Over the last few years, members of the Subgroup, utilizing MPN sample banks, have made a number of major international contributions to the understanding of the genetics and biology of MPNs including the description of somatic mutations of JAK2, CALR and EZH2. Going forward, the Subgroup will continue to support patient biobanks, including sample collections linked to clinical trials.

There are extensive biobanking protocols built into academic studies run through the Subgroup, including PT1, MAJIC, PHAZAR, TAMARIN, and the forthcoming MITHRIDATE and PROMise studies and translational research studies utilizing these samples are underway. Through strong links with industry, members are also working with sample banks collected in industry studies, e.g. RESUME study of myelofibrosis (over 200 samples available). We have established a new study focused on familial MPNs (INForMeD study) that is recruiting well in Oxford and will be rolled out to a number of other sites over the next 12 months.

Priority areas for clinical research

The Subgroup oversees clinical trials (phase I, II and III) across a broad range of different disease entities. Our overarching strategy is to ensure that clinical trial options are available for patients with each disease type (including rare diseases) both at first line and following failure of standard therapy. The key disease areas are:

- MPN epidemiology; we plan to open a large and innovative epidemiological study over the next 12 months (MOSAICC) aiming to better understand factors which predispose to MPN development.
- Polycythaemia vera; here we will be opening a large randomised trial of ruxolitinib versus best available therapy later this year (MITHRIDATE; CI: Claire Harrison).
- Essential thrombocythaemia; here a first line trial is currently lacking and is a priority for the Subgroup.
- Second line trial options are available for PV and ET patients including TAMARIN (actively recruiting) and MOMBAT (funding application to Wellcome Trust in progress) studies. These innovative studies have both resulted from translational research in the UK and are focused on repurposing of established treatments (tamoxifen in TAMARIN and methotrexate in MOMBAT) for therapy of MPN patients.

- Myelofibrosis; these patients with more advanced MPN have a major unmet need and we have a number of commercial trials in the portfolio as first and subsequent lines of therapy. New studies over the next 12 months will combination studies of ruxolitinib with venetoclax or bromodomain inhibition in myelofibrosis (PROMise study).
- Accelerated phase and blast crisis MPN – we anticipate that the PHAZAR study (combining azacitidine with ruxolitinib) will complete recruitment and be reported in 2019.

Engagement with Industry

The Subgroup works in close partnership with industry as exemplified by a number of studies with Subgroup members as global CI and a large number of industry studies, complementing academic studies, in the portfolio. Collaborations with industry have also been instrumental in supporting translational research in MPNs through funding of sample collections (MAJIC study). Collaboration with industry has also been essential to help underpin funding of major academic trial initiatives, e.g. MITHRIDATE is funded in part through Novartis.

Engagement with charity-funded research infrastructure initiatives

The Subgroup is closely linked with charity funded clinical research through the Bloodwise TAP network which has been instrumental in the delivery of a number of studies including MAJIC (first TAP study), PHAZAR, TAMARIN and MOMBAT.

Engagement with Genomic England Ltd (GEL)

MPNs are an excellent and tractable disease model to apply next generation sequencing technology and MPN subgroup members are fully engaged with the GEL initiative. Up to now, recruitment has been hampered by GEL requirements for germline control DNA which is not practical in most GMCs. In order to address this, we are working closely with GEL to establish new sample collection pipelines that will allow patients with unclassifiable MPNs to be recruited. Over 300 MPN patient samples have been (or will be) sequenced through GEL, including samples from MAJIC and PHAZAR clinical trials.

Trial delivery

The Subgroup has an excellent track record of successful delivery of trials and high recruitment into industry studies internationally.

Consumer engagement

The Subgroup has longstanding and ongoing consumer representation. The subgroup works closely with a national MPN charity (MPN voice) and oversees a number of patient/carer meeting nationally each year.

Appendix 3

Portfolio maps

NCRI Portfolio Maps

Haematological Oncology

Map B – Chronic leukaemia

ê below to reset map

		a) 1st line treatment	b) 2nd line treatment / MRD positive	c) Supportive care	d) Cohort studies/Translational
Chronic lymphocytic leukaemia	All	FLAIR A phase 1/2 study with Acalabrutinib and AZD6738 in high risk CLL Genentech GO29781 STELLAR	PCI/32765 (Ibrutinib) STELLAR		Investigating D Leukapheresis of white cells from patients with CLL for gene therapy ENABLE/ NGS Cell shape recognition technology TIDaL Efficacy and Safety of Acalabrutinib + Venetoclax +/- Obinutuzumab in Untreated CLL ZUMA-8
Chronic myeloid leukaemia	All	Ponatinib in Resistant Chronic Phase CML CLR_15_03 Activity of K0706 Leukaemia	ABL001 versus Bositunib in Chronic Myeloid Leukaemai Ask4More: Asciminib Add-on Phase II	Web-based video consultations in patients with CML	Analysis of Leu CALLS - CML and ALL Low Level Mutation Study Immune mechanisms in patients with CML Review of Sequencing 2nd gen TKIs with Chronic CML (Relapse)

Filters Used:
Active Status: All, **CSG Involvement**: Data collection in progress, **Funding Type**: All, **Phase**: All, **LCRN**: None

Open / multi resea..
In Setup / single re..
Open / single rese..

NCRI Portfolio Maps

Haematological Oncology

Map C – Myelodysplastic syndrome, myeloproliferative neoplasms, transplant trials

ê below to reset map

		a) 1st line treatment	b) 2nd line treatment / MRD positive	c) Supportive care	d) Cohort studies/Translational
Myelodysplastic syndrome	All	LI/1 AML18 AML19 advSM TAMARIN Atsral-3 Venetoclax in MDS FG-4592 in Anaemia with Lower Ris azacitidine for HR MDS/CMML/low /2 Multicentre open-label study of F	ntermediate-1 Risk Myelodysplastic CANC / 4888	The Commands Trial	MDSBio Analysis of Leu g agents +/- MBG453 in adult subje
Myeloproliferative neoplasms	All	inostat in JAK2V617F positive CM	Study of KRT-232 in Myelofibrosis 2a/b Study of KRT-232 in Polycythe		Clonal BC Disorders Molecular patho MONOCLE CE-536 in MPN-associated myelo oliferative Neoplasm Experimental CPI-0610 with or without ruxolitinib
Transplant trials	All	ICAT Safety of IV Brincidofovir for Adeno IN10120 t transplant for prevention of CMV	ICAT AZTEC	AMADEUS COSI	CARD s Host Disease in Patients Underg ALL-RIC itial Treatment for Chronic Graft-Ve

Filters Used:
Active Status: All, **CSG Involvement**: Data collection in progress, **Funding Type**: All, **Phase**: All, **LCRN**: None

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

NCRI Portfolio Maps

Haematological Oncology

Map D – Myeloma

ê below to reset map

		a) 1st line treatment	b) 2nd line treatment / MRD positive	c) Supportive care	d) Cohort studies/Translational
Myeloma	All	CARDAMON	DTP3	The Role of Frailty in Patients with Multiple Myeloma NSMM/5001, the INSIGHT/MM study	Osteoclastogeni
		TRALA	OP/103 Melflufen in Patients with Relapsed/Refractory		MMTA
		54767414SMM3001	Celgene Multiple Myeloma 0451/0204		PREAMBLE
		IDRIS	Phase I/II study evaluating AUTO2 in patients with multiple		DjiM
		REVAMP:Response evaluation in myeloma using 18F-FDG	Myeloma XII (ACCoRd trial) Version 1.0		MUK Nine a: Screening Study
		MUK Nine b: Optimum	NP39403-RO6870810 as monotherapy and in combination		Haemostatic function and cell signalling in multiple myeloma
		C16029: Phase 2/3 Randomized, Open-Label Study	CC-92480 with Dexamethasone in Relapsed & Refractory		MALIMAR
		CEPHEUS	MUK Twelve		Canova: Phase 3 t(11;14)-positive R/R Multiple
			bb2121_RR and HR Multiple Myeloma Study		Relapsed or Refractory Multiple Myeloma: Venetoclax and
					GSK 207497 DREAMM-6
					UVEA-Ixa
					BLOOM: Blood markers in multiple myeloma v1.0
				PERCEPT - myeloma transplant prehab study	

Filters Used:
Active Status: All, **CSG Involvement**: Data collection in progress, **Funding Type**: All, **Phase**: All, **LCRN**: None

In Setup / single re.. Suspended / singl..
Open / single rese..

NCRI Portfolio Maps

Haematological Oncology

Map E – Other studies

ê below to reset map

		a) 1st line treatment	b) 2nd line treatment / MRD positive	c) Supportive care	d) Cohort studies/Translational
Adult	All	UTX-TGR-204 ukemia AML 3674/0008-Forty Sev and pazopanib vs pazopanib in ad	Relapsed or Refractory Haemato RO7082859 & Atezolizumab in Non PembroWM ne high-risk pediatric & young adul	TREATT	EBV assoc NK/T Molecular Inves Complications of Haemopoietic Ste Immunophenotypi V1: Dev't of PRO Measure ematopoietic stem cell transplanta al Correlates of outcomes from Ste 15/007 nuclear cells in GvHD patients rec ch Blood Samples from Cancer Pa REACH 3 Effects of Medical Radiation Expos UK CLL LTFU Study Maribavir vs Valganciclovir in CMV CR-AIR-009 rm Follow Up Patients Treated wit Jazz JZP963-201 uate Efficacy and Safety of Avapriti CPI-0610 with or without ruxolitinib n of NiCord©, Expanded Cord Blo afety profile of radium-223 dichlorid HERACLES FREEDOM 2
Child	All	Study of Ibrutinib in Paediatric Patie	ne high-risk pediatric & young adul		V1: Dev't of PRO Measure al Correlates of outcomes from Ste LCH//IV Immune Response in Haematologi ch Blood Samples from Cancer Pa REACH 3

Filters Used:
Active Status: All, **CSG Involvement**: Data collection in progress, **Funding Type**: All, **Phase**: All, **LCRN**: None

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

Appendix 4

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. NCRI AML17 Measurable Residual Disease at Induction Redefines Partial Response in Acute Myeloid Leukemia and Stratifies Outcomes in Patients at Standard Risk Without NPM1 Mutations. Freeman *et al.* J Clin Oncol. 2018;36(15):1486-97.doi: 10.1200/JCO.2017.76.3425.	Demonstration that the assessment of minimal residual disease in AML by flow cytometry can improve outcome stratification by extending the definition of partial response after first induction and may help predict NPM1-wt standard-risk patients with poor outcome who benefit from transplant in the first CR.	Subgroup developed
2. PT1 intermediate arm Godfrey *et al.* Hydroxycarbamide Plus Aspirin Versus Aspirin Alone in Patients With Essential Thrombocythemia Age 40 to 59 Years Without High-Risk Features. J Clin Oncol. 2018 Aug 28:JCO2018788414. doi: 10.1200/JCO.2018.78.8414.	This study found that in patients with essential thrombocythaemia age 40 to 59 years and lacking high-risk factors for thrombosis or extreme thrombocytosis, pre-emptive addition of hydroxycarbamide to aspirin did not reduce vascular events, myelofibrotic transformation, or leukaemic transformation. Patients age 40 to 59 years without other clinical indications for treatment (such as previous thrombosis or haemorrhage) who have a platelet count < 1,500 × 10^9/L should not receive cytoreductive therapy.	This is a longstanding trial run over 20 years and led by core CSG members (Professor Claire Harrison, Professor Tony Green and Dr Anna Godfrey)
3. Myeloma XI Jackson *et al.* Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma(Myeloma XI): a multicentre, open-label, randomised, phase 3 trial.	Maintenance therapy with lenalidomide significantly improved progression-free survival in patients with newly diagnosed multiple myeloma compared with observation, but did not improve overall survival in the intention-to-treat analysis of the whole trial population. The manageable safety profile of this drug and the	Myeloma Subgroup developed

Lancet Oncol. 2019 Jan;20(1):57-73. doi: 10.1016/S1470-2045(18)30687-9.	encouraging results in subgroup analyses of patients across all cytogenetic risk groups support further investigation of maintenance lenalidomide in this setting.	
4. Myeloma IX Royle *et al.* Quality of life during and following sequential treatment of previously untreated patients with multiple myeloma: findings of the Medical Research Council Myeloma IX randomised study. Br J Haematol. 2018 Sep;182(6):816-829. doi: 10.1111/bjh.15459.	Demonstration that quality of life improves with therapy in myeloma	Myeloma Subgroup developed
5. Abbvie M13-982 Stilgenbauer S *et al.* Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol. 2018 Jul 1;36(19):1973-1980. doi: 10.1200/JCO.2017.76.6840. Epub 2018 May 1.	Redefinition of the standard of care for poor risk 17p deleted CLL.	CLL Subgroup supported

Appendix 5

Recruitment to the NIHR portfolio in the reporting year

In the Haematological Oncology Group portfolio, 42 trials closed to recruitment and 45 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
2014/2015	3132	3320	2972	3320	22.5	25.2
2015/2016	2370	2747	2370	2743	17.97	20.80
2016/2017	5534	2578	5522	2571	41.87	19.49
2017/2018	5309	2366	5277	2366	40.01	17.94
2018/2019	3451	2366	3393	2365	25.73	17.93