Front-Line therapy in CLL: Assessment of Ibrutinib-containing Regimes

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An NIHR Portfolio Study developed in association with the NCRI CLL Subgroup

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Trial Registration and Randomisation

Only authorised members of staff from hospital sites with appropriate trial approvals have permission to register and randomise participants into the trial.

24 hour Registration and Randomisation System

- Tel.: 0113 343 2290 or https://lictr.leeds.ac.uk/webrand/

Reporting Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

Complete the relevant SAE or SUSAR CRF for all SAEs and SUSARs occurring in the trial and email or fax to the CTRU within 24 hours of becoming aware of the event:

Fax: 0113 343 1487

A receipt will be sent for all received SAEs. ***If a receipt is not received within two working days contact the Data Management Team.***

Reporting Pregnancies

Report all pregnancies to the CTRU within 24 hours of becoming aware of the event using the Pregnancy Reporting Form.

Reporting Protocol Violations

Complete the Protocol Violations CRF for all drug administration errors and eligibility violations and email or fax immediately to the CTRU.

Fax: 0113 343 1487

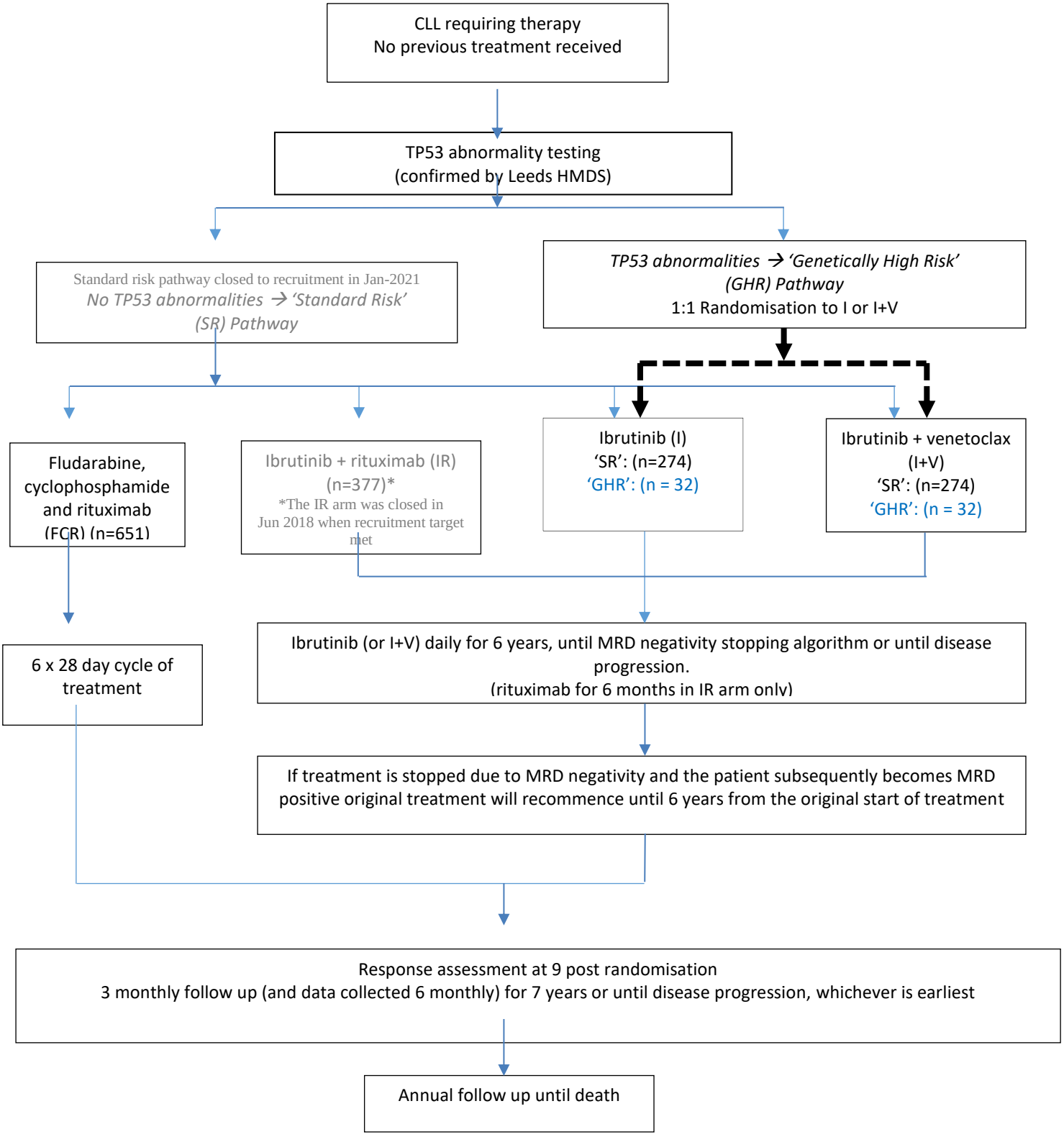
If the error is associated with an event which meets the criteria of an SAE or SUSAR, this must also be reported using the trial SAE or SUSAR form.

2. CONTENTS

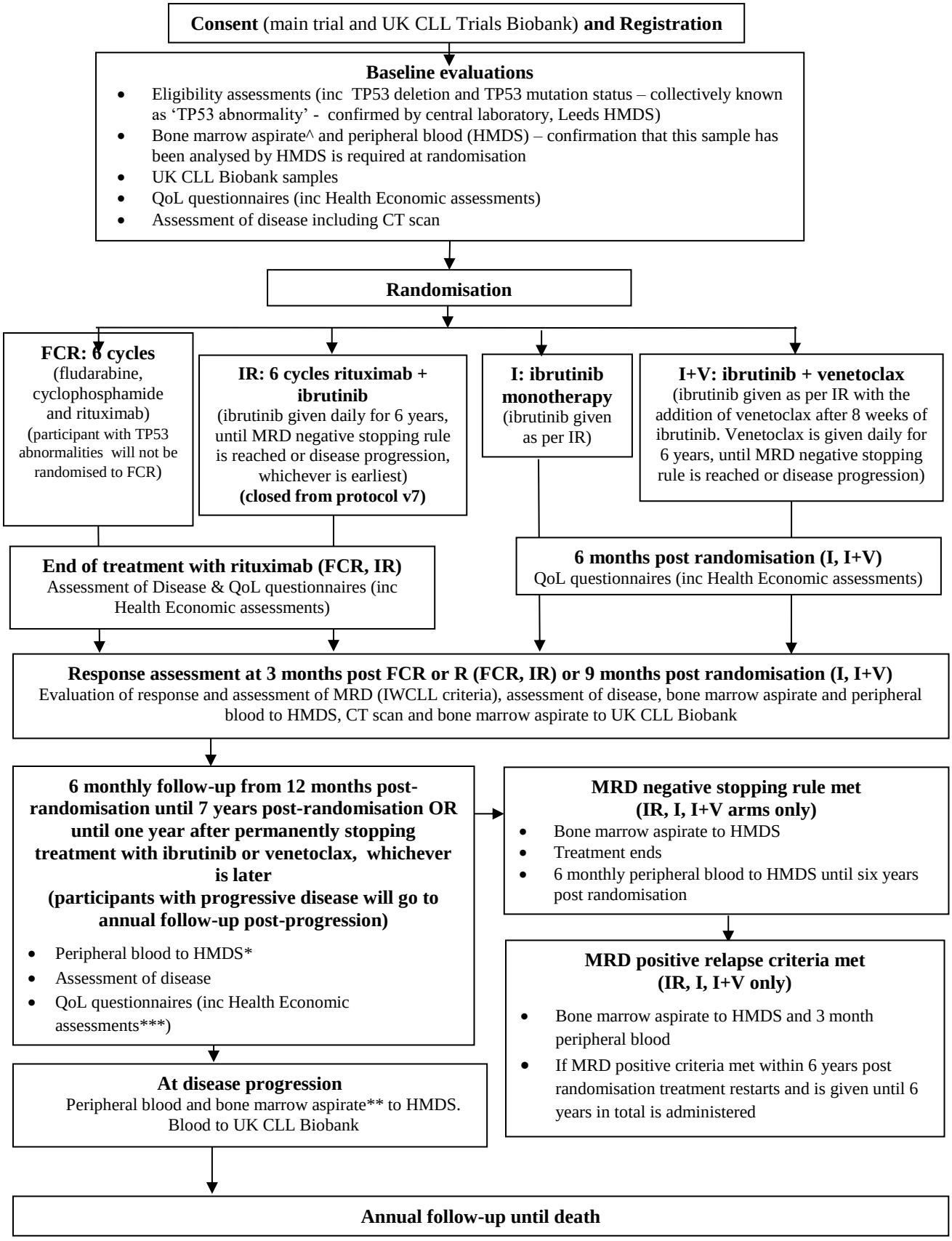
3. TRIAL FLOW DIAGRAMS

3.1 Summary of 'Genetically High Risk' and 'Standard Risk' Trial Participant Pathways

The only pathway open to recruitment is the genetically high risk pathway. The standard risk pathway is now closed to recruitment

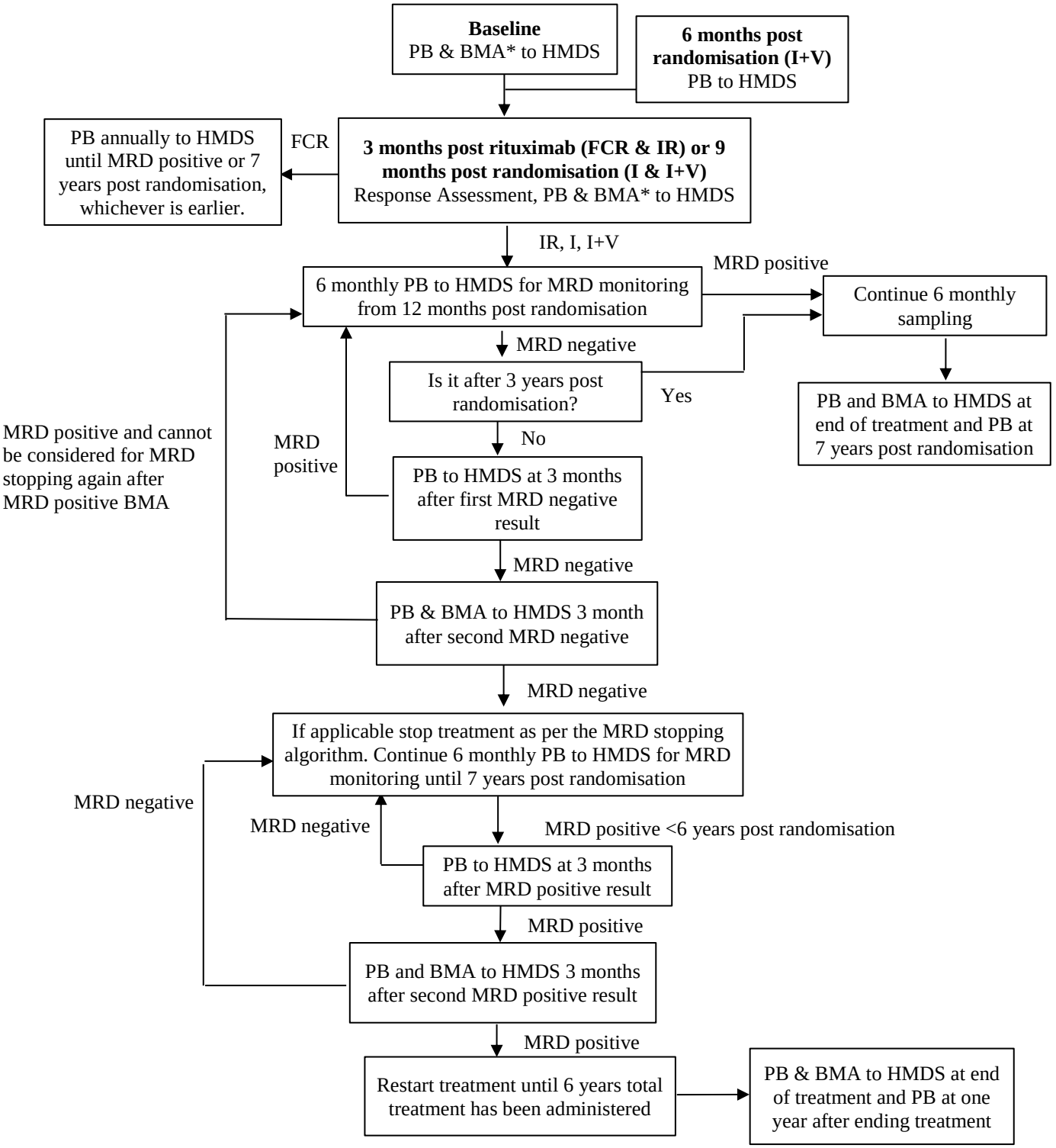


3.2 Detailed Trial Participant Pathways



^Only if lymphocyte count <$10x10^9$/L, * for FCR blood to HMDS annually until 1 MRD positive if 7 years post randomisation, **only performed if the only indication of progressive disease is cytopenia and/or lymphocytosis. ***After 2 years post-randomisation, Health Economics questionnaires completed annually; QoL completed 6-monthly

3.2 MRD Sampling



MRD minimal residual disease, PB peripheral blood, BMA bone marrow aspirate.
*BMA not sent if lymphocytes >$10x10^9$/L

4. BACKGROUND

4.1 Chronic Lymphocytic Leukaemia (CLL)

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia, affecting 6.9 per 100,000 population[1]. The incidence of CLL increases with age and twice as many men are affected as women. CLL results from the clonal proliferation of B-cells and is diagnosed by the pattern of expression of various cell surface antigens on the CLL cells. Patients most commonly present with lymphocytosis, lymphadenopathy, splenomegaly and systemic symptoms, such as fatigue, weight loss and malaise. The clinical course of CLL is highly variable with a median survival from diagnosis in the region of 7 years. Patients with more advanced disease (Binet stages B, C and progressive stage A) have a significantly worse survival.

4.2 Therapy for CLL

Over last few years there has been substantial improvement in the treatment of CLL. First line therapy has moved away from monotherapy using chlorambucil to combination immunochemotherapy like fludarabine, cyclophosphamide and rituximab (FCR) following evidence from large randomised trials[2]. FCR is the standard therapy resulting in improved survival, but only approximately 50% of patients are fit and/or young enough for FCR and even in those patients only 75% tolerate a full 6 cycles. In addition there is a small risk of developing late myelodysplasia and acute leukaemia thought to be due to the FC chemotherapy. The majority of patients relapse and require further therapy that is more difficult, associated with significant morbidity and potential mortality and eventually the majority of patients die from their CLL. Hence more effective, targeted therapies that improve remission rates and reduce relapses with fewer side effects are required.

4.3 Ibrutinib

The proliferation of CLL cells *in vivo* is dependent on signalling through the B-cell receptor (BCR) which is expressed at low levels on CLL cells. BCR activation leads to the transduction of signals through a series of intracellular molecules and leading to CLL cell proliferation. This provides a series of potential therapeutic targets on the BCR signalling pathway. Bruton's tyrosine kinase (Btk) is a key component of the BCR pathway to the extent that individuals born with mutated Btk produce no B-cells. Ibrutinib[3] is an orally administered small molecule selective irreversible inhibitor of Bruton's tyrosine kinase (Btk) currently under investigation in B-cell malignancies including chronic lymphocytic leukemia (CLL) and the related small lymphocytic lymphoma (SLL). *In vitro*, ibrutinib inhibited purified Btk and selected members of the kinase family with 10-fold specificity compared with off-target kinases. Ibrutinib has shown extremely promising results in relapsed, refractory CLL as well as in a small number of treatment naïve patients.

4.4 Rationale for the proposed study

Combination chemotherapy with FCR improves survival in CLL but is associated with significant short and long term toxicity with virtually all patients relapsing and eventually becoming refractory to therapy before dying either as a complication of the disease or it's therapy (usually due to infection). There is now clear evidence that CLL cell proliferation is dependent on stimulation through the B-cell receptor and since this pathway is specific for B-cells, including CLL cells, then this is a potential target in CLL. There are several molecules on the B-cell receptor pathway that have been targeted including Syk, PI3K delta and Bruton's Tyrosine Kinase (Btk), and all demonstrate activity. Of these agents it appears that ibrutinib is the most potent agent with relatively minor side effects in the early Phase II trials. In addition, these agents are not genotoxic and therefore would not be expected to lead to the late effects, such as MDS and AML, which are seen with FCR. One of the features of the BCR pathway antagonists is that they have a characteristic pattern of response with an

immediate improvement in symptoms and bulky lymphadenopathy but with a transient increase in circulating CLL cells which can take many months to resolve. The combination of ibrutinib and with chemotherapy and/or rituximab appears to prevent, or at least attenuate, this lymphocytosis. This should lead to a more rapid achievement of an objective response with the potential to stop ibrutinib earlier than with monotherapy. Further improvements in remission rates and duration of remission are unlikely to be fundamentally increased by simply escalating the dose of chemotherapy given, and if this strategy is employed the cost will be more immediate and late toxicity may be increased. Therefore the combination of ibrutinib and rituximab is a logical way to improve the therapy in CLL.

4.5 Protocol amendments

In order to keep the research question relevant it is necessary to adapt the trial to include new objectives, in addition to assessing the originally stated objectives.

4.5.1 Addition of ibrutinib + venetoclax (I+V)

Early data shows that venetoclax (V) (ABT-199) in combination with rituximab has impressive response rates in patients with relapsed/refractory CLL with an 86% overall response rate and 41% of patients achieving a CR or CRi[4]. The same study also showed that venetoclax leads to the eradication of detectable MRD in 53% of patients, which is not seen with any other targeted treatments. Based on pre-clinical data it is anticipated that the combination of V plus ibrutinib (I+V) will be highly synergistic given the complimentary modes of action of the two agents, as the ibrutinib arrests CLL cell proliferation and venetoclax is pro-apoptotic leading to their early cell death[5-6].

It is hypothesised that the addition of venetoclax to ibrutinib will reduce MRD levels faster and more effectively than I alone or IR, and therefore improving the outcomes, allowing the duration of therapy to be reduced, leading to a reduction in long-term toxicities and an overall cost saving. In order to evaluate the efficacy and safety quickly and efficiently, an I+V treatment arm has been added to the trial.

4.5.2 Addition of ibrutinib monotherapy (I)

FCR is currently the standard of care in front line CLL, and so this is the required comparator for all experimental therapies. However, an ibrutinib containing therapy is likely to become the standard during the life of this trial. Ibrutinib monotherapy is already widely used following phase III trials in relapsed refractory disease, and has shown convincing superiority over chlorambucil in unfit or elderly patients with previously untreated CLL in the phase III Resonate-2 trial[7]. IR is hypothesised to reach deeper responses than I alone, and therefore may become the standard of care in young, fit patients in future because it could mean that treatment could be interrupted in patients with low levels of disease.

It is therefore proposed to include an I alone arm at the time of the amendment alongside adding I+V. By adding I alone, we protect the trial in case FCR is superseded as standard of care during the life of the trial. If the outcomes of this trial were to show that I+V was better than FCR, but FCR was no longer the standard of care the trial would be hugely devalued. With the current proposed design we future-proof the amended trial so that if FCR is no longer the standard when the trial reports then we are also comparing I+V with ibrutinib monotherapy[7].

4.5.3 Amendment to the MRD stopping algorithm

Patients who are receiving ibrutinib, IR or I+V who become MRD negative (determined using multi-parameter flow cytometry according to the ERIC consensus protocol with a limit of quantification of 10^{-4} / 0.01%) will stop therapy as determined by the time taken for them to become MRD negative. There is evidence that the levels of disease decrease at a log-linear rate, so that patients who take longer to become MRD negative will also take longer for disease levels to continue to reduce to the level where treatment may be successfully stopped. Therefore, to aim to reduce disease to very low

levels (approximately below 10^{-8}) in all patients, treatment will be given until MRD negativity is reached, and then continued for that same time-period again i.e.:

- If MRD negativity is reached after 1 year, a further 1 year of treatment is received. If the patient is still MRD negative at the end of that year, treatment is stopped. These patients would receive a total of 2 years treatment.
- If MRD negativity is reached after 2 years, a further 2 years of treatment is received. If the patient is still MRD negative at the end of the 4 years, treatment is stopped. These patients would receive a total of 4 years of treatment.

Those who achieve MRD negativity after three years of therapy, or not at all, will continue therapy until intolerable toxicity, withdrawal of consent, or a total of 6 years of therapy, whichever comes first.

This strategy will be applied to participants randomised to IR, I and I+V and will replace the previous protocol strategy of stopping ibrutinib at MRD negativity plus 6 months.

There are four pathways for patients to stop treatment due to MRD negativity and treatment will stop after either 2, 3, 4 or 5 years (Section 11.13).

4.5.4 Re-starting treatment at MRD relapse

The stopping algorithm described in Section 4.5.3 will be assessed by monitoring MRD levels 6 monthly until 6 years post randomisation.

If participants have stopped treatment due to MRD negativity and then relapse at the MRD level before six years post randomisation, treatment with the original therapy (I+V or I monotherapy for I/IR participants) will be restarted to assess whether MRD negativity is re-achieved and to protect the primary endpoint PFS. This will not be considered as a progression event. Recommenced treatment will continue until a total of six years therapy has been given.

4.5.5 Peripheral blood MRD sample at six months post randomisation (I+V only)

Participants in the I+V arm will have a peripheral blood sample assessed for MRD at six months post randomisation. This is to assess a standalone secondary objective of plotting levels of MRD against time in the I+V arm as external data have suggested that this earlier timepoint is of interest.

4.5.6 Closure of IR arm

Once 754 participants have been randomised to FCR and IR combined the IR arm will be closed to recruitment. This was a planned part of the trial design and was not the result of any concerns regarding safety or efficacy of IR. Participants randomised from protocol version 7.0 onwards will be randomised to FCR, I or I+V. Participants previously randomomised to IR will continue on treatment and follow-up as per their original randomisation.

4.5.7 Addition of genetically high-risk patients with TP53 abnormalities*

Patients with >20% of chromosome 17p deleted were initially excluded from the trial because FCR is not an appropriate therapy in this group[8]. Ibrutinib is licensed for use in this population and recommended by NICE as a front line treatment in the UK[9]. Venetoclax as a monotherapy has been shown to induce good responses and MRD negativity in patients with 17p deletion/TP53 deletion/ mutation[10-11], and is licensed in this population for patients who are unsuitable for, or have failed to respond to, a B-cell receptor pathway inhibitor. The protocol has been amended to allow genetically high-risk patients, defined by a detectable TP53 disruption (any 17p deletion and/or TP53 mutation), into a biomarker driven randomisation, so that they can receive ibrutinib (I) or ibrutinib+ venetoclax (I+V) and will not be allocated to FCR. The safety profile of the I+V combination in this patient

group has been acceptable in other studies and comparable to patients without 17p deletion/TP53 deletion/ mutation[11-12]. The addition of a pathway for these rare, genetically high-risk, poor prognosis patients will allow us to generate good quality clinical data on a relatively large number of patients compared to previous trials in this group. In addition, it will allow the treatment strategies, including the duration of therapy based on achievement of MRD negativity, to be investigated in genetically high-risk, poor prognosis participants. Participants with a TP53 abnormality (17p deletion/TP53 deletion/ mutation) recruited from protocol version 9.0. onwards will be randomised to either I or I+V.

The randomisation for participants with a TP53 abnormalities* will be separate from the randomisation for standard risk participants, and will not contribute to that sample size or analysis population. In order to provide useful data, and recruit the sample sizes required to meet the TP53 abnormalities end-points, the plan is keep the randomisation open for genetically high risk patients with TP53 abnormalities after the randomisation for the standard risk arms are closed.

Important notes on terminology:

- The deletion of the TP53 gene occurs on chromosome 17 at location 17p13 therefore 'TP53 deletion' (of the gene) is sometimes referred to as '17p deletion' (of the chromosome).
- For a patient to be eligible for the 'genetically high risk' pathway, a patient needs to have either a TP53 deletion (which equates to '17p deletion') and/ or a TP53 mutation.
- The collective term 'TP53 abnormality' will be used on the Leeds HMDS reports, which means a TP53 deletion and / or TP53 mutation is present.
- TP53 can also be referred to as 'p53'.

4.5.8 Addition of cardiac monitoring measures

In a recently published paper[18] it is cited that 'ibrutinib is associated with dramatic efficacy against B-cell malignancies. Yet, ibrutinib has been linked with potentially-limiting cardiotoxicity, including emerging reports of profound hypertension'. The key points highlighted in this paper are as follows:

'1) Among lymphoid malignancy patients treated with ibrutinib, the subsequent incidence of new hypertension is nearly 72%.
2) Development of new or worsened hypertension following ibrutinib initiation associates with a more than two-fold increased risk of other cardiac events.'

Based on this and review of the FLAIR safety data and advice from the FLAIR Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC), the protocol has been amended to include cardiac monitoring measures for participants with a history of hypertension (defined as on medication for hypertension) and / or cardiac disease or who develop hypertension whilst on trial treatment. In order to ensure balanced reporting of adverse events related to hypertension and to monitor hypertension emergent on trial treatment, blood pressure monitoring and management is being introduced for all participants on trial treatment in all arms, including FCR, as well as all ibrutinib-containing arms. Therefore, cardiac monitoring is being implemented for the following groups of people:

Group of people	Section in protocol
New participants entering the trial from protocol version 9.0 onwards	Section 11.5.1
Participants on trial treatment at the time of implementing protocol version 9.0	Section 11.5.1
Participants who meet the MRD re-starting criteria	Section 11.5.1 and Section 11.14

4.5.9 Urgent Safety Measure: ACE inhibitors and ibrutinib

On 15-Jul-2021, an urgent safety measure was implemented regarding the potential interaction between ACE inhibitors (a type of antihypertensive) and ibrutinib.

This is because it was identified during an interim analysis of the FLAIR study that participants randomised to ibrutinib + rituximab had an elevated risk of sudden or cardiac death if they were on ACE inhibitor treatment at study entry versus participants not on ACE inhibitors at study entry. Although the number of sudden or cardiac deaths overall was very small, the FLAIR Data Monitoring and Ethics Committee and Trial Steering Committee reviewed the relevant safety data and advised that urgent action be taken to limit risk to trial participants on ibrutinib-containing regimes and ACE inhibitors.

The urgent safety measures taken were as follows:

1. Review all participants on FLAIR who are currently receiving ibrutinib and confirm if they are currently receiving an ACE inhibitor.
2. For any participants receiving both ibrutinib and an ACE inhibitor, either:
    a. Stop the ACE inhibitor and move participants to an alternative antihypertensive treatment, or
    b. Stop the ibrutinib. If it was decided to stop ibrutinib this was discussed with the Chief Investigator beforehand.
3. Specific concerns about changing a participant to an alternative antihypertensive treatment were discussed with a cardiologist to agree the best course of action for each individual.
4. For any participants being screened for trial entry or who had been randomised but not started treatment:
    a. ibrutinib therapy was only started after confirmation that the participants were not receiving an ACE inhibitor. If they were receiving an ACE inhibitor, this was changed to an alternative antihypertensive before commencing ibrutinib.

4.5.10 Addition of I vs. I+V MRD interim analysis

A formal interim analysis is added for the co-primary efficacy endpoint of the proportion of participants who are MRD negative at any time up to 2 years of post-randomisation in the comparison of I+V vs. I. The interim analysis will occur 2 years after the 274th participant was randomised and will include the first 274 randomised participants only.

Emerging data, such as the results of the CLARITY trial [20], indicated that the expected MRD negativity rate of the combination I+V is in fact greater than the original assumptions used in the design of the Amendment in Section 4.5.1 and Section 4.5.2. The assumptions of the I vs I+V MRD comparison is that there is 90% power to detect an improvement from 10% in I to 20% in I+V and there is 90% power to detect an improvement from 5% in I to 13% in I+V. However, CLARITY reported an MRD negativity rate of 36% in the bone marrow in 53 relapsed/refractory CLL patients after 12 months of I+V treatment [2]. In consultation with the FLAIR independent DMEC and TSC, it has been decided that if the true MRD negativity rate is likely higher than the original trial assumptions, it is important to release results early, if possible, to provide these results to the scientific community.

4.6 Pragmatic Changes Due to Covid-19

4.6.10 Summary of Changes

In light of the Covid-19 pandemic, the following pragmatic changes have been made based on a risk assessment by the FLAIR Trial Management Group (TMG). It is important to note that although there is some increased flexibility based on a clinical risk-benefit assessment by the Principal Investigator (or delegated Investigator) for participants who are already randomised, every effort should be made to follow the protocol, and it remains mandatory for eligibility assessments (including the screening ECHO when required) and venetoclax dose escalation safety tests (due to the risk of tumour lysis syndrome) to be done in accordance with the protocol.

Please also refer to the information in Appendix M, and the latest Covid-19 guidance and communications provided by the Leeds CTRU to the PIs/ sites.

Category	**Change(s)**	**Protocol section(s)**
Covid-19 clinical risk-benefit assessments	• Implementation of Covid-19 Clinical Risk-Benefit Assessments • Participant safety is paramount and the Principal Investigator (or delegated Investigator) is responsible for making clinical decisions for the participants in the trial and to determine the best course of clinical action based on a risk-benefit assessment for each individual participant. • The PI (or delegated Investigator) should continue to reassess the risk/benefit of randomising new participants and the continued study involvement for each participant.	Section 4.6.10
Venetoclax Dose Escalation	• Due to the risk of Tumour Lysis Syndrome (TLS), venetoclax dose escalation safety tests must to be done in accordance with the protocol. • If the Covid-19 risk is high, based on a clinical risk-benefit assessment, it is permissible for the investigator to make the clinical decision to temporarily defer the initiation of venetoclax and dose escalation and continue the patient on ibrutinib monotherapy until the Covid-19 risk is acceptable	Section 10.24 Section 10.3.3 Section 10.6
Visits	• Telephone/ video consultations in addition to face-to-face visits • Increased flexibility with method of completing Quality of Life questionnaires to participants (posting to participant possible rather than only being completed in clinic) •	Section 11.12 Section 11.12.1 Section 11.12.2 Section 11.18
Assessments	• Increased flexibility regarding where and when some assessments (e.g blood tests, blood pressure tests) are done	Section 11.5.1 Section 11.6 Section 11.7 Section 11.10 Section 11.11 Section 11.12.2

ECHO	• Screening ECHO remains mandatory (for those meeting the criteria of a screening ECHO) • Increased flexibility for timing of ECHO for participants who have already been randomised	Section 11.5 Section 11.5.1
Investigational Medicinal Product	• Increased flexibility in amount and frequency of dispensing and methods of delivering to participants. • Prescriptions can be brought forward and/or provided to cover an extended period of time. • If it is not possible for the participant to visit the hospital to collect their IMP in person, the treatment can be delivered to the participant by following the local NHS Trust policy	Section 9.1.1 Section 9.1.2
Re-Consent	• Increased flexibility regarding re-consent methods • Initial informed consent to enter the trial remains as in person during a hospital appointment with the clinician obtaining consent	Section 8.3 Section 8.3.1
Monitoring Visits	• The protocol already allowed for remote monitoring methods. • For clarity, one sentence has been added:*Remote monitoring methods (including virtual/telephone review of source data) may be used to verify source data and will approved by CTRU.*	Section 16.2
Confirmation of TP53 abnormality eligibility status	• Confirmation of TP53 abnormality eligibility status by Leeds HMDS remains mandatory and the preference is that this is done by Leeds HMDS analysing the samples • In certain cases where a different accredited laboratory has already issued a report about a potential participant's TP53 abnormality status, it may be possible for Leeds HMDS to provide confirmation of TP53 abnormality eligibility status based on the report from the different accredited laboratory. It is anticipated that this method may be used if a patient urgently requires treatment. • In all cases, Leeds HMDS retain responsibility for confirming TP53 abnormality eligibility status, whether that is via analysing the samples, or via reviewing a report from a different accredited lab, and a participant must not be randomised until the site receive a report from Leeds HMDS	Section 8.4
MRD stopping rules	• Missed assessments can be rescheduled for when Covid-19 risk is acceptable and added that treatment stop date will still be calculated from the first MRD Negative test. • Added in "approximately" in brackets when referring to the stopping treatment period. • Relaxing the rules by adding "or as soon as feasible after six months when Covid-19 risks are	Section 11.13 Section 11.15

	acceptable" in terms of when we expect the bone marrow sample to be taken	
Covid-19 Risk Mitigation Plan	• New Appendix	Appendix M

4.6.11 Closure of Standard Risk Pathway

Although the initial plan was to continue recruiting to meet the original recruitment target of the 'standard risk' pathway, in light of Covid-19 and the availability of new treatment options (some of which are oral regimes and can be given with fewer hospital visits compared to FCR), there was a significant reduction in recruitment rate and, as of Jan-2021, the FLAIR Data Monitoring and Ethics Committee and the Trial Steering Committee approved closure of recruitment to the standard risk pathway.

The trial statisticians estimated the power to answer the primary trial endpoints based on recruitment finishing early and confirmed that based on the number of participants randomised as of Jan-2021, each comparison will have an acceptable level of power, and as such finishing recruitment early will not comprise the integrity of the comparisons

- Progression-free survival in I+V vs. FCR: Final analysis is event-driven and the power is unchanged at 80%. We estimate that the timing of analysis may be delayed by a maximum of 6 months.
- Minimal residual disease negativity in I+V vs. I: Power of comparison will be 88% based on the original assumptions.

4.6.12 Covid-19 Vaccines

Based on a risk assessment by the Trial Management Group:

- Participants on the FLAIR trial and potential participants can receive non-live Covid-19 vaccines. in line with the national Covid-19 guidance and in line with guidance provided by AbbVie and Janssen. The use of live, attenuated ('weakened') vaccines in immune-compromised patients is prohibited. Vector-based (e.g. adenovirus) vaccines are not considered to be 'live' vaccines
- The timing of when the deployed Covid-19 vaccine is given is flexible
    - There is no minimum time period between any dose of trial IMP and dosing with a deployed vaccine
    - It is not a requirement for a potential FLAIR participant to have received the Covid-19 vaccine before starting CLL treatment on FLAIR.
- Details of the deployed vaccine (type of vaccine, dates given) should be documented in the medical notes and as a concomitant medication in the CRFs.

4.6.13 If a participant contracts Covid-19

If a participant contracts Covid-19:

- The local area Covid-19 treatment and quarantine guidance should be followed for participants diagnosed with, or suspected to have Covid-19
- Based on a clinical risk-benefit assessment, it is the site PI's responsibility, in conjunction with any other specialists providing care, to decide whether to temporarily halt the participant's CLL treatment. The Chief Investigator and/ or Co-Investigators (contact details

listed in the front of the protocol) can be contacted, copying the CTRU_Flair@leeds.ac.uk inbox, if additional guidance is required.

All adverse events (AEs) and serious adverse events (SAEs) must be reported in line with instructions for safety reporting documented in section 12.

For CLL patients who have had their CLL treatment paused due to symptomatic Covid-19, it is anticipated that a negative Covid-19 swab is required before re-starting CLL treatment as part of standard of care, and therefore sites are advised to also follow this principle for FLAIR trial treatment.

4.6.14 Co-Enrollment in Covid-19 Clinical Trials

Based on a risk assessment by the Trial Management Group, FLAIR participants can be co-enrolled in a Covid-19 clinical trial, however it is important to email the CTRU_Flair@leeds.ac.uk inbox with treatment details of the Covid-19 trial, so that the Chief Investigator/ Co-Investigators can confirm that there are no possible interactions between the Covid-19 treatment and the FLAIR IMPs

5. AIMS AND OBJECTIVES

The trial originally aimed to compare the effect on progression-free survival (PFS) of ibrutinib plus rituximab (IR) with that of fludarabine, cyclophosphamide and rituximab (FCR) in patients with previously untreated chronic lymphocytic leukaemia.

The amendment to include the additional trial arms (ibrutinib alone and ibrutinib plus venetoclax) will enable a comparison of PFS between ibrutinib plus venetoclax (I+V) and ibrutinib alone (I) with FCR, and a comparison of minimal residual disease (MRD) negativity rates in I+V with those in I.

The amendment to include an additional population of participants with TP53 abnormalities will allow a comparison of MRD negativity rates between I and I+V in patients with TP53 abnormalities.

Timelines for assessing all objectives are summarised in detail in section 15.2.

5.1 IR vs FCR objectives

5.1.1 Primary objective

- To assess whether IR is superior to FCR in terms of progression-free survival (PFS), as defined by IWCLL criteria (Appendix B)

5.1.2 Secondary objectives

To assess, and where appropriate compare for IR vs. FCR:

- Overall survival
- Proportion of participants obtaining undetectable minimal residual disease (MRD), as defined by IWCLL criteria
- Stopping I-containing therapy in MRD negative participants
- Restarting I-containing therapy on MRD relapse
- Response to therapy, as defined by IWCLL criteria
- Safety and toxicity
- Health-related quality of life
- Cost-effectiveness

5.2 I+V and I related objectives

5.2.1 Primary objectives

- To assess whether I+V is superior to FCR in terms of PFS
- To assess whether I+V is superior to I in terms of MRD negativity

5.2.2 Secondary objectives

To assess, and where appropriate compare for I+V vs. FCR and I:

- PFS of I+V in comparison with I
- PFS of I in comparison with FCR
- Overall survival
- Proportion of participants obtaining undetectable MRD, as defined by IWCLL criteria
- Stopping I-containing therapy in MRD negative patients
- Restarting I-containing therapy on MRD relapse
- Response to therapy, as defined by IWCLL criteria
- Safety and toxicity
- Health-related quality of life
- Cost-effectiveness

5.3 TP53 abnormality related objectives

5.3.1 Primary objective

- To assess whether I+V is superior to I in terms of MRD negativity

5.3.2 Secondary objectives

To assess, and where appropriate compare for I+V vs. I:

- PFS of I+V in comparison with I
- Overall survival
- Stopping I-containing therapy in MRD negative patients
- Restarting I-containing therapy on MRD relapse
- Response to therapy, as defined by IWCLL criteria
- Safety and toxicity
- Health-related quality of life
- Cost-effectiveness

6. DESIGN

FLAIR is a phase III, multicentre, randomised, controlled, open, parallel group trial in patients with previously untreated CLL. Participants were initially randomised on a 1:1 basis to receive FCR or IR in order to assess the original objectives. Following the addition of the I and I+V arms patients were randomised on a 1:1:1:1 basis to receive FCR, IR, I+V or I in order to assess the additional objectives. Once 754 participants had been randomised to FCR and IR, the IR arm was closed to recruitment and participants are randomised on a 1:1:1 basis to receive FCR, I or I+V. Participants with TP53 abnormalities will be randomised on a 1:1 basis to receive I or I+V. It is not appropriate for this group of participants to receive FCR.

Participants randomised to FCR will receive a maximum of 6 cycles with each cycle being repeated every 28 days. Participants randomised to receive IR will receive 6 cycles of rituximab with each cycle being repeated every 28 days. Ibrutinib will be taken daily for 6 years, until the MRD negative

stopping rules are reached or until disease progression. Participants randomised to I+V will receive ibrutinib for 8 weeks before venetoclax is added. Ibrutinib and venetoclax will be administered for 6 years, until the MRD negative stopping rules are reached or until disease progression. Participants randomised to I will receive ibrutinib daily for a total of 6 years, until the MRD negative stopping rules are reached or disease progression.

If participants randomised to IR, I or I+V stop treatment due to the MRD stopping rules and then go on to have MRD relapse (before 6 years post randomisation) their randomised treatment (at the point of stopping (with the exception of IR, where only I will be restarted)) will be recommenced until a total of 6 years of treatment has been administered.

The trial aims to provide evidence for the future first-line treatment of CLL patients by assessing whether:

- IR is superior to FCR in terms of PFS
- I+V is superior to FCR in terms of PFS,
- I+V is superior to I in terms of MRD negativity,
- and whether I, IR and I+V toxicity rates are favourable.

Other key endpoints to be assessed include: overall survival; attainment of undetectable MRD; response to therapy; health related quality of life and cost-effectiveness; as well as an evaluation of discontinuation and recontinuation of I-containing therapy if indicated.

Participants will be recruited by clinical teams from multiple ethically approved research centres around the United Kingdom based on their diagnosis of CLL and compliance with the eligibility criteria set out below.

7. ELIGIBILITY

Please note eligibility waivers to inclusion/exclusion criteria are not permitted.

7.1 Key points: ‘genetically high risk’ vs ‘standard risk' patient pathway

- Confirmation of the phenotype of disease and confirmation of the TP53 abnormality status (TP53 deletion and TP53 mutation) are required from the central laboratory, Leeds HMDS, **before** a patient is randomised to either the ‘genetically high risk’ or the ‘standard risk’ pathway.
- The collective term ‘TP53 abnormality’ will be used on the HMDS reports, which means a TP53 deletion and / or TP53 mutation is present
- The results of the TP53 abnormality (TP53 deletion and TP53 mutation) tests determine which pathway a patient is eligible for.
- Participants **with** TP53 abnormalities are eligible for the 2 arm ‘genetically high risk’ pathway (I+V or I).
- Participants **without** TP53 abnormalities are eligible for the 3 arm ‘standard risk’ pathway (FCR, I+V or I)

7.2 Actions to take based on Leeds HMDS reports determining eligibility

Important: the 'standard risk' pathway has now closed to recruitment.

Randomisation of eligible participants will not take place until Leeds HMDS have confirmed that the participant has a suitable phenotype and confirmed TP53 abnormality status, as this will determine which pathway a patient is randomised to, the 'genetically high risk' pathway or to the 'standard risk' pathway.

The site (and Leeds CTRU) will receive one or more report(s) from Leeds HMDS which will confirm the following:

- That the patient has a suitable phenotype
- What the TP53 abnormality status of the patient is
- What level (high or low) of TP53 abnormality status a patient has (this is an important stratification factor)

To randomise the patients in the GEN24 randomisation system, please click on the 'genetically high risk' (TP53 abnormality) or the 'standard risk' (no TP53 abnormality) option based on the results/ wording on the Leeds HMDS report (highlighted in the table below).

Wording on Leeds HMDS report	**Action in randomisation system GEN24**
'The peripheral blood shows involvement with CLL. The CLL phenotype is typical and suitable for disease monitoring. There is evidence of a TP53 abnormality (**high level**, i.e. ≥20% TP53 deletion by FISH and/or TP53 mutation with ≥0.1 VAF by NGS). This patient is suitable for the '**genetically high risk'** pathway of the FLAIR trial with respect to the laboratory parameters.'	Randomise to the 'genetically high risk' pathway.
'The peripheral blood shows involvement with CLL. The CLL phenotype is typical and suitable for disease monitoring. There is evidence of a TP53 abnormality (**low level**, i.e. <20% TP53 deletion by FISH and/ or TP53 mutation with <0.1 VAF by NGS). This patient is suitable for the **'genetically high risk'** pathway of the FLAIR trial with respect to the laboratory parameters'	Randomise to the 'genetically high risk' pathway.
'The peripheral blood shows involvement with CLL. The CLL phenotype is typical and suitable for disease monitoring. There is no evidence of a TP53 abnormality by FISH and sequence analysis. This patient is not eligible for the genetically high risk pathway of the FLAIR trial with respect to the laboratory parameters.'	**No action**; patient cannot be randomised as standard risk pathway has closed

7.3 Inclusion criteria for the 'standard risk pathway'

Patients with the following characteristics are eligible for this study:

- At least 18 years old.
- Maximum age of 75 years old.
- A diagnosis of CLL or small lymphocytic lymphoma (by iwCLL criteria) with a phenotype that is acceptable for disease monitoring. The central laboratory, Leeds HMDS, will assess if the phenotype is acceptable and confirmation of this is required before randomisation.
- Binet's Stages C, B or Progressive Stage A
- Requiring therapy by the IWCLL criteria in that they must have at least one of the following:
  1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia.
  2. Massive (i.e. 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
  3. Massive nodes (i.e. 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
  4. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months as long as the lymphocyte count is over $30x10^9$/L
  5. A minimum of any one of the following disease-related symptoms must be present:

  (a) Unintentional weight loss more than or equal to 10% within the previous 6 months.
  (b) Significant fatigue (i.e. Eastern Cooperative Oncology Group PS 2 or worse; cannot work or unable to perform usual activities)
  (c) Fevers of greater than 38.0°C for 2 or more weeks without other evidence of infection.
  (d) Night sweats for more than 1 month without evidence of infection.
- Considered fit for treatment with FCR as determined by the treating clinician.
- World Health Organisation (WHO) performance status (PS) of 0, 1 or 2
- Able to provide written informed consent
- Biochemical values must be within the following limits within 14 days prior to randomisation and at baseline:
  - Alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN) OR Aspartate aminotransferase (AST) ≤3 x ULN.
  - Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

7.4 Exclusion criteria for the 'standard risk' pathway

Patients with the following characteristics are ineligible for this pathway

- Prior therapy for CLL
- History or current evidence of Richter's transformation
- Major surgery within 4 weeks prior to randomisation
- Active infection.
- TP53 abnormality
- Past history of anaphylaxis following exposure to rat or mouse derived CDR-grafted humanised monoclonal antibodies.*
- Concomitant warfarin (or equivalent vitamin K inhibitor) or other oral anticoagulant* treatment
- Concomitant ACE inhibitors
- Pregnancy, lactation or women of child-bearing potential unwilling to use medically approved contraception (defined in appendix J) whilst receiving treatment and for 12 months after treatment with rituximab has finished, or 30 days after treatment with ibrutinib or venetoclax has finished,

whichever is latest. Women must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction.

- Men whose partners are capable of having children but who are not willing to use appropriate medically approved contraception whilst receiving treatment and for 12 months after treatment with rituximab has finished, or 3 months after treatment with ibrutinib or venetoclax has finished, whichever is latest, unless they are surgically sterile. For male patients, the Investigator must discuss sperm banking prior to venetoclax treatment if they are considering preservation of fertility given the potential for decreased spermatogenesis.
- Central nervous system involvement with CLL.
- Symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)
- Respiratory impairment (e.g. bronchiectasis or moderate COPD)
- Other severe, concurrent diseases or mental disorders that could interfere with their ability to participate in the study.
- Inability to swallow oral medication
- Disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption (malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease etc)
- Known HIV positive
- Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded.**
- Positive serology for Hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a test for hepatitis C RNA (for example HCV RNA PCR). If positive the subject will be excluded
- History of prior malignancy, with the exception of the following:
  - Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician
  - Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
  - Adequately treated cervical carcinoma in situ without current evidence of disease.
- Persisting severe pancytopenia (neutrophils $<0.5 \times 10^9$/L or platelets $<50 \times 10^9$/L) unless due to direct marrow infiltration by CLL
- Current treatment with prednisolone of >10mg/day.
- Active haemolysis (patients with haemolysis controlled with prednisolone at a dose 10mg or less per day can be entered into the trial)
- Patients with a creatinine clearance of less than 30ml/min (either measured or derived by the Cockcroft Gault formula [Appendix C] or alternative locally approved formula).
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Requirement for treatment with a strong CYP3A inhibitor or inducer (see Appendix F).
- Current treatment with two or more antiplatelet drugs
- Allergy or inability to tolerate uric acid reducing agents (eg allopurinol/rasburicase).
- Unwilling or unable to take PCP prophylaxis (eg cotrimoxazole).

*Anyone requiring anticoagulation treatment for greater than 6 months is not eligible for trial entry.
**Anyone who is HBsAg-ve/HBcAb+ve/HB DNA–ve should be referred to a liver disease specialist before the start of treatment with rituximab. During treatment, they should be monitored and managed to prevent HBV reactivation.

7.5 Inclusion criteria for 'genetically high risk' pathway

Patients must have a TP53 abnormality, confirmed by Leeds HMDS, and must meet all inclusion criteria in Section 7.3 with the exception of:

- Maximum age of 75 years old.
- Considered fit for treatment with FCR as determined by the treating clinician

There is no upper age limit for patients entering this pathway and FCR will not be given to patients who are eligible for the 'genetically high risk' pathway

7.6 Exclusion criteria for 'genetically high risk' pathway

Patients must meet all exclusion criteria in Section 7.4 with the exception of:

- TP53 abnormality
- Past history of anaphylaxis following exposure to rat or mouse derived CDR-grafted humanised monoclonal antibodies.

As noted above, to be eligible for the genetically high risk pathway, patients must have a TP53 abnormality, as confirmed by Leeds HMDS.

8. RECRUITMENT PROCESS

8.1 Recruitment setting

Participants will be recruited from multiple research centres from around the United Kingdom. Research centres will be identified via a feasibility assessment to determine the most appropriate centres to participate in the trial. Research centres will be required to have obtained ethical and management approvals and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

The trial originally had a recruitment target of 754 participants to be recruited to FCR or IR over 4 years. Following the addition of the I+V and I arms 822 participants are required to be randomised concurrently to FCR, I and I+V. Some of the FCR participants (those recruited after the addition of the I+V and I arms) count towards both targets, so the final recruitment target for the 'standard risk' patient pathway will be 1516 patients, as described in Section 14. It is anticipated that recruitment for the 'standard risk' patient pathway will be completed within 6 years of the trial opening

In addition, it is anticipated that a further 64 genetically high-risk participants with TP53 abnormalities will be randomised to I or I+V. These participants do not count towards the 'standard risk' randomisation total.

When the target of 1516 participants in the 'standard risk' pathway has been reached, the randomisation to the 'standard risk' pathway will close, while the 'genetically high risk' pathway for patients with TP53 abnormalities will stay open to allow sufficient time to recruit the required number of participants to meet the endpoints. It remains the responsibility of each participating centre to determine if they have adequate resource to continue recruiting patients into the trial. Safety of patients remains a priority and they should not be included into a trial unless they meet the inclusion and exclusion criteria.

8.2 Eligibility Screening

Potential participants will be identified by the clinical team at participating centres based on their diagnosis of CLL. Each trial research site will be required to maintain an ongoing log of all participants screened for eligibility who are not registered either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- age
- gender
- ethnicity
- reason for ineligibility for trial participation

or

- reason for declining participation

Non Registration Logs are required to be sent to the CTRU every 3 months or on request.

8.3 Informed consent and eligibility

Potential participants will be approached during standard clinic visits for management of their disease and will be provided with verbal and written details about the trial. The verbal explanation of the trial and Participant Information Sheet and Informed Consent Document will be provided by the attending medical staff for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial. Following information provision, participants will have as long as they need to consider participation (normally a minimum of 24 hours) and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study.

Assenting patients will then be invited to provide informed, written consent, be registered and be formally assessed for eligibility. The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996. If taking informed consent is delegated to another clinically qualified member of the trial team they must have received Good Clinical Practice (GCP) training and be approved by the Principal Investigator, as documented on the Authorised Personnel Log. Informed consent must be obtained and the participant must be registered prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with standard routine care at the participating site. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU. Re-consent may take place in person during a hospital appointment with the clinician obtaining re-consent, or remotely via telephone or video consultation and by posting, or emailing, re-consent forms. See Section 8.3.1 for more details

A record of the consent process including the date of consent and all those present will be kept in the participants' notes. The original consent form will be filed in the Investigator Site File, a copy of the consent form will be given to the participant and a copy will be returned to the Clinical Trials Research Unit (CTRU), at the University of Leeds.

Eligibility will be confirmed prior to randomisation by the Principal Investigator, or an appropriate medically trained delegate as detailed on the Authorised Personnel Log. Eligibility for the trial will be recorded in the participant's medical records and on the relevant CRF.

8.3.1 Remote Re-Consent Procedures

In light of Covid-19, it is the responsibility of the site PI, or delegated Co-Investigator, to make clinical decisions for the participants in the trial and to determine the best course of clinical action based on a risk-benefit assessment for each individual participant. This could include determining that taking re-consent remotely is in the best interests of the participant.

If a local decision is made for re-consent to take place remotely:

- The PI, or delegated clinician, should discuss the Informed Re-Consent Document with the participant via telephone or video consultation, making sure that the patient has been correctly identified by checking the relevant identifying information as specified in the local standard operating procedures for the site.
- It should be documented clearly in the medical notes:
  - That a telephone or video consultation has taken place between the PI (or delegated clinician) and the participant
  - Who was present at the discussion, and what was generally discussed
  - That the participant's identity has been correctly verified
- A minimum of two copies of the Informed Re-Consent Document should be sent to the patient's home address, via post ideally with a stamped address envelope, or email, for return of one signed copy to site (either via post, email, or brought in person to the clinic visit). The preferred course of action may include the PI, or delegated clinician, signing the re-consent form first, posting two signed re-consent forms to the participant and the participant signing and returning one fully signed copy to the site.
- The Informed Re-Consent Document signed by the participant should be checked by the site, and a copy that is signed by both the participant and the PI, or delegated clinician, forwarded to Leeds CTRU, at the University of Leeds. One copy of the re-consent form signed by both the PI, or delegated clinician, and the participant is sent or given to the participant, and the original signed re-consent form filed in the Investigator Site File.

Note that the term '*remote re-consent'* in this context means that the re-consent is documented on a paper form, but the participant and treating clinician will be in different locations when they have the re-consent discussions, and possibly when they sign the re-consent form.

8.3.2 Consent to the UK CLL Biobank

Participants who are eligible to take part in the main trial will also be eligible to have a number of biological samples sent to the UK CLL Biobank. Participation within the UK CLL Biobank will be discussed with participant at the same time as discussing their participation in the rest of the trial. Verbal and written details (the UK CLL Biobank Patient Information Sheet) will be provided to participants. Following information provision, participants will be given as long as they need to consider participation (normally a minimum of 24 hours) and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to have samples sent to the UK CLL Biobank.

Participants who wish to have biological samples sent to the UK CLL Biobank will be asked to sign an additional consent form. As for the main trial, a record of consent to this section of the trial, detailing the date of consent and all those present will be kept in the participants notes. The original UK CLL Biobank Consent Form will be filed within the Investigator Site File, a copy of the consent form will be given to the participant, a copy will be returned to the UK CLL Biobank at University of Liverpool and a copy will be returned to the CTRU at the University of Leeds.

8.3.3 Loss of Capacity Following Informed Consent

Where valid informed consent is obtained from the participant, and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the Principal Investigator and participant's carer / family with the participant's best interests foremost in the decision making process. Ongoing collection of safety and follow-up data (where possible) will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

8.4 Registration

Note that where mention is made of 'HMDS' in this protocol, this refers to the central laboratory, Leeds HMDS.

Following confirmation of written informed consent, participants will be registered immediately into the trial by an authorised member of staff at the trial research site. Registration will be performed centrally using the CTRU automated registration and randomisation system. Authorisation codes and PINs, provided by the CTRU after site initiation, will be required to access the registration and randomisation system.

The following information will be required at registration:

- Personal authorisation codes and PIN
- Name of person making the registration
- Name of trial research site and site code
- Participant details, including initials and date of birth
- Confirmation of written informed consent
- Decision regarding consent to the UK CLL Biobank
- Decision regarding consent to the Quality of Life/Health Economics questionnaires

Direct lines for 24hr registration and randomisation
Tel: 0113 343 2290
or
https://lictr.leeds.ac.uk/webrand/

All participants will be allocated a trial number after they have been registered.

As trial-specific investigations are carried out at the central laboratory, Leeds HMDS and the results of these determine which pathway a participant is randomised to, recruitment is a two-step process involving:

1. An initial registration of all potential participants
2. Followed by randomisation for eligible participants.

Refer to additional details in section 7 (Eligibility').

Sites should note that samples arriving to Leeds HMDS on Tuesday-Friday will typically be reported in 7-10 working days (however, this could be longer if the material is poor quality, e.g. >24 hours old on arrival, or the TP53 result is borderline or difficult to interpret and a repeat analysis is required).

Following registration, all participants will have a peripheral blood sample and, if their lymphocyte count is less than 10 ($x10^9$/L), a bone marrow aspirate, sent to Leeds HMDS. **If the participant's lymphocyte count is >10 ($x10^9$/L) a bone marrow aspirate is not required for HMDS (or for the UK CLL Biobank).** Leeds HMDS will provide a report following analysis of the samples and confirmation of these test results are required in order to proceed to randomisation. In certain situations (for example if a patient urgently needs treatment), Leeds HMDS may provide confirmation of TP53 abnormality status after reviewing a TP53 report issued by a different accrediated laboratory. In all cases, Leeds HMDS retain responsibility for confirming TP53 abnormality status, whether that is via analysing the samples or reviewing a report from a different accrediated laboratory. Leeds HMDS can still process samples from patients with Covid-19 with appropriate additional precautions

Randomisation of eligible participants will not take place until Leeds HMDS have confirmed that the participant has a suitable phenotype and confirmed TP53 abnormality status, as this will determine which pathway a participant is randomised to, the 'genetically high risk' pathway or to the 'standard risk' pathway.

Where a site uses Leeds HMDS in standard care, it is the site's responsibility to inform Leeds HMDS that the participant is registered into the trial. Trial participants will be identified as such on reports from Leeds HMDS.

8.5 Randomisation

Leeds HMDS must confirm that all participants are suitable for the trial, and which pathway the participants are eligible for, prior to randomisation. See Section 7.2 for further information about interpreting HMDS forms.

Participants without TP53 abnormalities (deletion or mutation) will be randomised on a 1:1:1 basis to receive either FCR, I or I+V.

Participants with TP53 abnormalities (deletion and/ or mutation) will be randomised on a 1:1 basis to receive either I or I+V.

Following registration and confirmation of eligibility, participants will be randomised into the trial by an authorised member of staff at the trial research site. Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system. Authorisation codes and PINs, provided by the CTRU after site initiation, will be required to access the registration and randomisation system.

The following information will be required at randomisation:

- Personal authorisation codes and PIN
- Name of person making the randomisation
- Name of trial research site and site code
- TP53 abnormality status

- Level of TP53 abnormality – refer to section 7.2 (*Actions to take based on Leeds HMDS reports determining eligibility*)
- Participant details, including trial number and date of birth
- NHS number
- Confirmation of eligibility (including of phenotype and of which pathway the participant is eligible for)
- Stratification factors (see list below)
- Confirmation that HMDS samples have been analysed and participant is eligible
- Confirmation that Quality of Life/Health Economics questionnaires have been completed (for participants who provided consent for this)

Direct lines for 24hr registration and randomisation
Tel: 0113 343 2290
or
https://lictr.leeds.ac.uk/webrand/

A computer-generated minimisation program that incorporates a random element will be used to ensure treatment groups are well-balanced for the following characteristics, details of which will be required for randomisation:

Genetically high risk pathway	**Standard risk pathway**
Binet Stage (A progressive or B, C)	Binet Stage (A progressive or B, C)
Age (≤65 years, >65 years)	Age (≤65 years, >65 years)
Gender (Male, Female)	Gender (Male, Female)
Level of TP53 abnormality (less than 20% ; ≥ 20%)	Centre

Participants randomised to the 'genetically high risk' pathway will not be stratified by centre.

After randomisation the local hospital will:
- Provide each participant with a Trial ID card which they should carry with them at all times and present to medical staff should they be admitted to hospital during their time on trial.

9. TRIAL MEDICINAL PRODUCT MANAGEMENT

Within the trial the following are classed as Investigational Medicinal Products (IMPs):

Fludarabine

Fludarabine Oral Tablets
Composition: Fludarabine phosphate 10mg

Generic off the shelf supply of fludarabine as determined by individual hospital sites; please refer to the most recent Summary of Product Characteristics (SmPC) for the brand being used.

Fludarabine Solution for Infusion
Composition: Fludarabine phosphate 50mg
Generic off the shelf supply of fludarabine as determined by individual hospital sites; please refer to the most recent SmPC for the brand being used.

Cyclophosphamide

Cyclophosphamide Oral Tablets
Composition: Cyclophosphamide monohydrate BP 53.50mg equivalent to 50mg anhydrous cyclophosphamide.
Generic off the shelf supply of Cyclophosphamide as determined by individual hospital sites; please refer to the most recent SmPC for the brand being used.

Cyclophosphamide Solution for Infusion
Composition: Cyclophosphamide monohydrate, powder for solution for injection or infusion.
Generic off the shelf supply of Cyclophosphamide as determined by individual hospital sites; please refer to the most recent SmPC for the brand being used.

Rituximab

Rituximab solution for infusion
Composition: Rituximab 100mg/10ml or 500mg/50ml
Off the shelf supply. Please refer to the most recent SmPC.

Ibrutinib

Ibrutinib Oral Capsules
Composition: hard gelatine capsules containing 140mg of ibrutinib per capsule
Supplied free of charge by Janssen. Please refer to the most recent SmPC.

Venetoclax

Venetoclax oral tablets
Composition: tablets containing either 10, 50 or 100mg
Supplied free of charge by Abbvie. Please refer to the most recent SmPC.

See section 12.1.4 for the IMPs Reference Safety Information for pharmacovigilance purposes

9.1 Supply of IMPs

9.1.1 Supply of ibrutinib

Ibrutinib will be supplied free of charge from Janssen for use in this clinical trial. Once received the trial specific ibrutinib should be kept at controlled room temperature (15°C - 25°C) and ring-fenced within a secure pharmacy location. Ibrutinib capsules will come packaged with 92 capsules/bottle.

Participants randomised to IR should be dispensed ibrutinib at each visit. Ibrutinib will be dispensed monthly in line with rituximab cycles for the first 6 months of treatment and 3 monthly thereafter. In order to keep dispensing in line with the trial follow up schedule it is permissible to either dispense 3 months of ibrutinib with the final cycle of rituximab or to dispense 1 month of ibrutinib with the final cycle of rituximab and a further 2 month supply at the End of Treatment visit.

For participants randomised to Ibrutinib monotherapy, a suggested dispensing schedule is as follows:

- monthly for the first three months
- and 3 monthly thereafter,

- or less frequently if required locally.

As a result of the Covid-19 pandemic, based on a clinical risk-benefit assessment by the investigator, prescriptions can be brought forward and/or provided to cover an extended period of time, and if is not possible for the participant to visit the hospital to collect their IMP in person, the treatment can be delivered to the participant by following the local Trust policy.

Participants randomised to I+V see next section.

9.1.2 Supply of venetoclax

Venetoclax will be supplied free of charge from Abbvie for use in this clinical trial. Venetoclax should be kept at controlled room temperature (15°C - 25°C) and ring-fenced within a secure pharmacy location.

If the Covid-19 risk is high, based on a clincal risk-benefit assessment by the investigator, it is acceptable to temporarily defer the initiation of venetoclax and dose escalation and continue the patient on ibrutinib monotherapy until the Covid-19 risk is acceptable

Venetoclax is prescribed weekly for the first four dose escalations and monthly from 400mg onwards to coincide with monthly ibrutinib prescriptions.

A suggested dispensing scheduled is: Venetoclax and ibrutinib prescribed monthly for three months and three-monthly thereafter.

Ibrutinib is prescribed monthly for the first six months, which overlaps with the venetoclax prescriptions from month three onwards. At all stages prescriptions can be more frequent if required locally.

As a result of the Covid-19 pandemic, based on a clinical risk-benefit assessment by the investigator, prescriptions for ibrutinib and for the maintenance dose of venetoclax (400mg dose) can be brought forward and/or provided to cover an extended period of time, and if is not possible for the participant to visit the hospital to collect their IMP in person, the treatment can be delivered to the participant by following the local Trust policy.

9.1.3 Supply of fludarabine, cyclophosphamide and rituximab

Fludarabine, cyclophosphamide and rituximab will be off the shelf supplies. There is no requirement to ring-fence off the shelf general hospital supplies of these IMPs. It is permissible to use pre-prepared bags/syringes of F, C or R as per standard hospital practice. All IMPs supplied from hospital stock (F, C and R) should be prepared in accordance with local practice. Use of National Dose Banding Tables is permitted but not mandated.

9.2 IMP Preparation

The reconstitution of fludarabine (IV), cyclophosphamide (IV) and rituximab should be under conditions approved by the local pharmacy.

9.3 IMP Labelling

Ibrutinib and venetoclax supplies will contain a study specific label, in line with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006). The pharmacy will be responsible for completing individual participant details on each label.

Pharmacy will be responsible for labelling fludarabine, cyclophosphamide and rituximab in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994. The pharmacy will be responsible for producing these labels.

Please refer to the FLAIR Pharmacy and IMP Study Site Operating Procedure for full details of the trial IMP management requirements.

9.4 IMP Accountability

The batch number and expiry date of all fludarabine, cyclophosphamide, rituximab, ibrutinib and venetoclax dispensed within the trial should be recorded on the trial specific dispensing log found within the Pharmacy Site File.

As ibrutinib and venetoclax are being supplied for use in this clinical trial full accountability of stock is also required on the trial specific Accountability Log found within the Pharmacy Site File.

9.5 Ibrutinib or Venetoclax Product Quality Complaints

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product.

All initial PQCs must be reported to CTRU by the study site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event (SAE), the study-site personnel must report the PQC and the SAR to CTRU. A sample of the suspected product should be maintained for further investigation if requested.

10. TREATMENT DETAILS

The following section of the protocol describes treatment for participants with FCR, IR, I and I+V.

10.1 Routine tests before treatment

Before commencing/continuing treatment participants will be assessed for suitability for treatment as described in the following sections:

- Rituximab, section 11.6 (FCR and IR participants)
- Ibrutinib, section 11.7 (IR, I and I+V participants)
- Venetoclax, section 11.8 (I+V participants)

10.2 Treatment regimen details

Participants eligible for the ‘genetically high risk’ pathway will be randomised to receive either I or I+V.

Participants eligible for the 'standard risk' pathway will be randomised to receive either FCR, I or I+V.

The IR arm was closed to recruitment from protocol version 7.0 onwards but remains in the protocol for participants randomised before this.

10.2.1 Fludarabine, cyclophosphamide and rituximab (FCR)

Participants randomised to FCR will receive 6 cycles of treatment; each cycle is repeated every 28 days.

FCR will be given according to the following regimen

Fludarabine	Oral*	24mg/m^2/day	Days 1 to 5
Cyclophosphamide	Oral*	150mg/m^2/day	Days 1 to 5
Rituximab	Intravenous	375mg/ m^2	Day 1 **(Cycle 1)**
Rituximab	Intravenous	500mg/m^2	Day 1 **(Cycle 2-6)**

G-CSF (as per standard dosing) for days 7 to 13 is recommended for all subsequent cycles in participants who have had to have a previous dose delay due to neutropenia (see Section 10.8.2).

The treatment of participants with a BSA > 2.2m^2 should be as per your local policy. (see appendix D for an example body surface area calculation).

*Participants should be questioned regarding nausea and vomiting or diarrhoea occurring with the prior cycle of therapy and if this is present then the fludarabine and cyclophosphamide should be given via the intravenous route from the next cycle onwards due to concerns over drug absorption. Intravenous fludarabine (25mg/m^2/day on days 1-3) and cyclophosphamide (250mg/m^2/day on days 1-3) regimens is recommended if the oral regimen is not tolerated.

See further information in section 10.4 on the administration of FCR

If a participant misses a dose of FC, the dose should be taken later provided the participant remembers within 12 hours. If the participant does not remember within 12 hours, the missed dose should be omitted. Doses should NOT be doubled to make up for missed doses.

10.2.2 Ibrutinib and rituximab (IR)

Cycles of rituximab are repeated every 28 days for a total of 6 cycles. Ibrutinib will be given the day before rituximab for the first dose and will be given daily for either: 6 years, until the MRD stopping rules are reached or until disease progression, whichever is earliest (see section 11 for further details).

Ibrutinib and rituximab (IR)

Rituximab	Intravenous	375mg/m^2	Day 1 **(Cycle 1)**
Rituximab	Intravenous	500mg/m^2	Day 1 **(Cycle 2-6)**
Ibrutinib	Oral	420mg	Daily from Day 0 Cycle 1 for 6 years, until the MRD stopping rules are reached or until disease progression

G-CSF (as per standard dosing) for days 7 to 13 is recommended for all subsequent cycles of rituximab in participants who have had to have a previous dose delay due to neutropenia (see section 10.8.2).

The treatment of participants with a BSA > 2.2m^2 should be as per your local policy. See Appendix D for an example body surface area calculation.

See section 10.3.1 for information on restarting treatment due to MRD relapse. See further information in section 10.4 on the administration of rituximab and section 10.5 on the administration of ibrutinib.

10.2.3 Ibrutinib monotherapy (I)

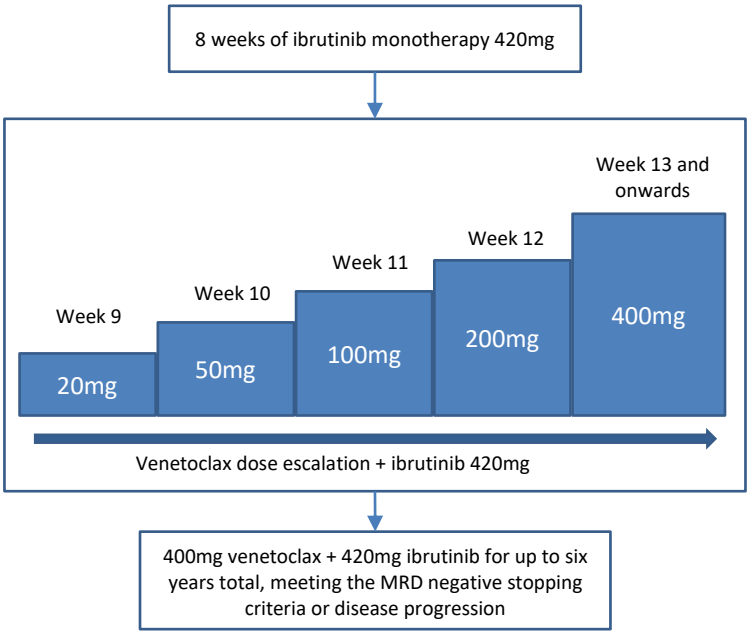
Participants randomised to I will receive 420mg ibrutinib daily for 6 years, until the MRD stopping rules are reached or until disease progression, whichever is earliest (see section 11 for further details). See section 10.3.2 for information on restarting treatment due to MRD relapse. See further information in section 10.5 on the administration of ibrutinib.

10.2.4 Ibrutinib and venetoclax (I+V)

Participants randomised to I+V will receive 420mg ibrutinib daily as monotherapy for 8 weeks (56 days treatment) before combining with weekly dose escalations (20mg, 50mg, 100mg, 200mg and 400mg) of venetoclax from weeks 9-13. Combination therapy of ibrutinib (420mg) and venetoclax (400mg) is then given daily until six years post randomisation, disease progression or the MRD negative stopping criteria is reached.

If the Covid-19 risk is high, based on a clincal risk-benefit assessment by the investigator, it is acceptable to temporarily defer the initiation of venetoclax and dose escalation and continue the patient on ibrutinib monotherapy until the Covid-19 risk is acceptable.

When the venetoclax dose escalation is initiated, the venetoclax safety tests must be done in accordance with the protocol.



See section 10.3.3 for information on restarting treatment due to MRD relapse. See section 10.5 and 10.6 for information on the administration of ibrutinib and venetoclax.

10.3 Restarting treatment due to MRD relapse

See section 11.7 (ibrutinib) and 11.8 (venetoclax) for information on routine tests required before restarting treatment.

10.3.1 Ibrutinib and rituximab (IR)

IR participants that have stopped treatment due to MRD negativity will restart treatment with ibrutinib if they subsequently have MRD relapse (see section 11.14). Treatment will recommence at 420mg daily until either a total of six years treatment has been given, or disease progession (whichever is earliest). Participants will not be able to meet the MRD negativity stopping criteria a second time.

10.3.2 Ibrutinib monotherapy (I)

I participants that stop treatment due to MRD negativity will restart treatment if they subsequently have MRD relapse (see section 11.14). Treatment will restart at 420mg daily until either a total of six years of treatment has been given, or disease progession (whichever is earliest). Participants will not be able to meet the MRD negative stopping criteria a second time.

10.3.3 Ibrutinib and venetoclax (I+V)

I+V participants that stop treatment due to MRD negativity will restart treatment if they subsequently meet the MRD relapse criteria (see section 11.14). Treatment will recommence with 8 weeks of daily ibrutinib monotherapy (420mg). Starting at 9 weeks venetoclax is also administered and re-escalated weekly as per the original schedule (20, 50, 100, 200, 400mg) in section 10.2.4 and investigations in section 10.6. Assessment of tumour burden must be repeated before re-starting venetoclax (see section 10.6). A combination of ibrutinib (420mg) and venetoclax (400mg) will then continue daily until either a total of six years of treatment has been given, or disease progession (whichever is earliest). Participants will not be able to meet the MRD negative stopping criteria a second time.

10.4 Administration of rituximab (for FCR & IR)

If on Day 1 of the first treatment cycle the total lymphocyte count is >25 x 10^9/L (or if this dose is already split as part of standard care) rituximab dosage should be split, in view of concerns of cytokine release and severe immediate toxicity, as per one of the following schedules:

Dose split schedule A

- Cycle 1, 100mg is given on day 1 and the remainder of the 375mg/m^2 (i.e. 375mg/m^2 minus 100mg) is given on day 2
- Cycle 2-6. If the lymphocyte count remains above 25 x 10^9/l then, at the clinician's discretion, the rituximab dose can be split, with 100mg on day 1 and the remainder of the 500mg/m^2 on day 2. If the lymphocyte count is <25 x 10^9/l then the whole dose should be given on day 1 without splitting the dose.

Dose split schedule B

- Cycle 1, 50mg/m^2 is given on day 1 and the remainder of the 375mg/m^2 (i.e. 325mg/m^2) is given on day 2
- Cycles 2-6. If the lymphocyte count remains above 25 x 10^9/l then, at the clinician's discretion, the rituximab dose can be split, with 125mg/m^2 given on day 1 and 375mg/m^2 given on day 2. If the lymphocyte count is <25 x 10^9/l then the whole dose should be given on day 1 without splitting the dose.

Rituximab should be administered in an environment where full resuscitation facilities are immediately available, and under close supervision of an experienced haematologist/oncologist. Participants should receive premedication with paracetamol and anti-histamines 30-60 minutes prior to infusion of rituximab. Rituximab must not be administered as an intravenous bolus injection. Prednisolone can be administered prior to rituximab prior to cycle 1 as per standard care.

Infusion rates: Sites are permitted to follow local practice when determining the rituximab infusion rates although it is recommended that sites use the dose rates given in the most recent version of the SmPC.

It is recommended that the speed of infusion be halved if the following adverse events occur:

- Fevers > 38.5C
- Chills – mild, moderate
- Mucosal swelling – mild, moderate
- Hypotension (drop in systolic BP) > 30mmHg

Following the infusions it is recommended that the intravenous line should be continued for one hour so that drugs may be administered intravenously if necessary.

10.5 Administration of ibrutinib (IR, I and I+V)

420 mg (3 x 140mg capsules) of ibrutinib is administered orally once daily with approximately 240mls of water at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. For participants randomised to IR the first dose will be given in clinic the day before rituximab is administered and subsequent doses will be taken by the participant at home. For participants randomised to I or I+V the first dose of ibrutinib should be administered in clinic. Time spent in clinic after the dose is at the discretion of the local investigator.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If the dose is more than 6 hours late, the dose should not be taken and the participant should take the next dose at the scheduled time the following day.

If ibrutinib is missed for 7 days (or more) during a 28 day period, please report this using an F15 Protocol Violations CRF and fax immediately to CTRU. Where treatment is suspended for toxicity or surgery (or due to Covid-19) this is not a protocol violation.

There have been no cases reported of leukostasis in patients with CLL treated with ibrutinib, although patients with high number of circulating malignant cells (> 400,000 k/ul) should be closely monitored

In addition to the effective contraception for women of child bearing potential listed in appendix J it is recommended that hormonal contraception is supplemented with barrier method for participants treated with ibrutinib.

10.6 Administration of venetoclax (I+V)

Participants randomised to I+V will receive 420mg ibrutinib daily as monotherapy for 8 weeks before combining with weekly dose escalations (20mg, 50mg, 100mg, 200mg and 400mg) of venetoclax from weeks 9-13. Combination therapy of ibrutinib (420mg and venetoclax 400mg) is then given until: six years post randomisation, disease progression or the MRD negative stopping criteria is reached, whichever is earliest

If the Covid-19 risk is high, based on a clincal risk-benefit assessment by the investigator, it is acceptable to temporarily defer the initiation of venetoclax and dose escalation and continue the patient on ibrutinib monotherapy until the Covid-19 risk is acceptable.

When the venetoclax dose escalation is initiated, the venetoclax safety tests must be done in accordance with the protocol

Participants with high/medium tumour burden (eg, any lymph node with a diameter ≥5 cm or high absolute lymphocyte count (ALC) ≥25 x 10^9/L are at greater risk of TLS when initiating venetoclax.

Reduced renal function (creatinine clearance <80 mL/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment.

Before commencing venetoclax, a CT scan and lymphocyte count must be performed to assess tumour burden before starting treatment with venetoclax. The CT scan must be within 2 weeks (+/- 7 days) of starting treatment with venetoclax. If the participant is deemed to have a high tumour burden according to the following criteria, they should be hospitalised as per the requirements in appendix I. The tests required before treatment with venetoclax are described in section 11.8

Site is required to complete the tumour burden assessment CRF form (F27) and return this to CTRU by fax or secure email before administering the first dose of venetoclax.

Table 1 Tumour Burden

Tumour burden	Criteria
Low	All measurable lymph nodes with the largest diameter <5cm AND ALC <25 x10^9/L
Medium*	Any lymph node with the largest diameter ≥5cm but <10cm (assessed by CT) OR ALC ≥ 25 x 10^9/L
High	Any lymph node with the largest diameter ≥10cm (assessed by CT) OR ALC ≥25 x 10^9/L AND any lymph node with the largest diameter ≥5cm but <10cm (assessed by CT).

*Note that participants with a creatinine clearance of <80 ml/min must also be treated as per medium tumour burden

Each dose of venetoclax should be taken with approximately 240ml of water and at approximately the same time each day and with a meal. The tablets should not be chewed, crushed, or broken before swallowing. Further information on hydration for I+V participants is in Appendix I.

In cases of vomiting, if vomiting occurs within 15 minutes of taking the dose and all tablets are intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose is missed or forgotten, the patient should take the dose as soon as possible, ensuring the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

If venetoclax is missed for 7 days (or more) during a 28 day period, please report this using an F15 Protocol Violations CRF and fax immediately to CTRU. Where treatment is suspended for toxicity or surgery (or due to Covid-19) this is not a protocol violation.

In addition to the effective contraception for women of child bearing potential listed in appendix J it is recommended that hormonal contraception is supplemented with barrier method for participants treated with venetoclax.

10.7 Contra-indicated and Concomitant Therapies

10.7.1 Routine concomitant therapy

All patients are strongly recommended to receive co-trimoxazole 480mg/day (or equivalent as per standard care) as prophylaxis against pneumocystis carinii pneumonia (PCP). Participants who are allergic to co-trimoxazole should receive an alternative, such as dapsone (100mg OD) or nebulised pentamidine (monthly). PCP prophylaxis should continue throughout treatment and for at least 2 months afterwards. If patients receiving ibrutinib monotherapy prefer not to receive PCP prophylaxis then this should be discussed with the CI or CoI.

FCR participants should also receive aciclovir 400mg bd (or equivalent as per standard care) as prophylaxis for herpes virus reactivation. Prophylaxis should continue throughout FCR treatment and for at least 2 months after the last course of treatment.

For participants randomised to FCR, IR and I treatment with uric acid reducing agents (e.g. allopurinol 300mg/day or febuxostat) is recommended for at least the first 28 days of therapy and can be given after day 28 at the discretion of the Investigator. For participants who are allergic to allopurinol and febuxostat treatment with rasburicase is recommended prior to treatment instead.

In addition to the recommendation in the previous paragraph participants randomised to I+V must be given uric acid reducing agents (e.g. allopurinol 300mg/day or febuxostat) at least 72 hours prior to

the first dose of venetoclax as prophylaxis for TLS, this must continue until at least the end of the venetoclax dose escalation phase. Patients with a high tumour burden must be given more intensive prophylaxis against TLS (e.g. rasburicase (200 ug/kg)) and this must be initiated prior to starting venetoclax (20mg) and also prior to the 50mg dose and can be used up to 7 days depending on local policy. Further information on TLS prophylaxis is in Appendix I.

Additionally participants should increase oral hydration prior to the first dose and each dose escalation of venetoclax. IV hydration must be initiated for TLS high risk participants unable to increase oral fluid intake. IV hydration can be administered for any participant at the discretion of the treating clinician. See Appendix I for further details.

Participants should be prescribed anti-emetics as per local policy. Anti-infection prophylaxis (in addition to that required above) can be administered as per local practice.

All blood products should be irradiated for participants in the FCR arm, but this is not mandated in the other treatment arms.

After randomisation, but before starting the allocated schedule, Binet stage C participants (Hb <10g/dl and/or platelets $<100x10^9$/l not due to autoimmune phenomena) can be given a short course of prednisolone at the discretion of the local Investigator. If so patients should receive prednisolone 30mg/m^2 daily for 3 weeks, plus 1 week tailing off, followed 1 or 2 weeks later by the randomised therapy.

Non-live Covid-19 vaccines can be given in line with national Covid-19 guidance and guidance provided by AbbVie and Janssen.

10.7.2 Concomitant therapy to be used with caution whilst receiving ibrutinib and/or venetoclax

10.7.2.1 CYP Inhibiting/Inducing Drugs and ibrutinib and venetoclax

A full list of CYP3A inhibiting and inducing drugs and other cautionary medications is provided in appendix F.

Table 2 Guidance on the use of CYP3A inhibiting/inducing drugs & other cautionary medications/foods

	Examples	**Advice**
Stong CYP3A inhibitors	Ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, telithromycin, and voriconazole	Avoid whilst on ibrutinib or venetoclax treatment. Strongly recommend alternative with less potent enzyme inhibition but if required should be discussed with CI/Co-I before use and monitor patient closely for treatment-related toxicities. For ibutinib either interruption of ibrutinib or reduction to 140mg daily initiated. For venetoclax prohibited during dose escalation phase as may increase risk of TLS. If dose escalation has been completed and patient is on steady daily dose, reduce venetoclax dose by at least 75%. Resume treatment dose that was used before administration of the inhibitor 2-3 days after discontinuing the inhibitor.

Moderate CYP3A inhibitors	Erythromycin, ciproxacin, dronedarone, fluconazole, verapamil,and diltiazem	Avoid and consider alternatives but can be used with caution whilst on ibrutinib or venetoclax treatment If required should be discussed with CI/Co-I before use and monitor patient closely for treatment-related toxicities. For ibutinib either interruption treatment or reduce dose to 140mg daily. For venetoclax reduce dose by at least 50% (<=200mg) daily. Resume treatment dose that was used before administration of the inhibitor 2-3 days after discontinuing the inhibitor.
Weak CYP3A inhibitors	Azithromycin, fluvoxamine	Monitor participant closely for toxicity and follow dose modification guidance as needed.
Strong CYP3A inducers	Carbamazepine, phenytoin, St. John's wort, and rifampin	Should be avoided as may decrease plasma concentration of ibrutinib or venetoclax consider alternative treatments with less enzyme induction.
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, nafcillin	
Weak CYP3A inducers	Prednisolone, pioglitazone	
P-gp, BCRP and OATP1B1 substrates	Digoxin, methotrexate, rosuvastatin, dabigatran, everolimus, sirolimus	In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp). The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild P-gp and BCRP inhibitor *in vitro.* As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose and so other substrates should be avoided. Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor *in vitro* and so other substrates should be avoided. Contact CI/Co-I before administering P-gp, OATP1B1 or BCRP substrates to participants treated with venetoclax or ibrutinib. If a statin is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended.
Food	Grapefruit, Seville oranges (including marmalade), and starfruit	Avoid whilst on ibrutinib or venetoclax treatment

10.7.2.2 QT Prolonging Agents and ibrutinib

Any medications known to cause QT prolongation (see Appendix G) should be used with caution alongside treatment with ibrutinib; periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered and if needed the Chief Investigator or a Co-Investigator (see Section 1) may be contacted.

10.7.2.3 Anticoagulants and anti-platelet drugs and ibrutinib

Warfarin, or equivalent vitamin K inhibitors, and anticoagulants should not be given concomitantly whilst the participant is receiving ibrutinib. For participants requiring anticoagulant therapy LMW heparin should be considered instead. Patients requiring anticoagulation for greater than 6 months are not eligible for trial entry. Participants with new requirement for therapy during the trial whilst treated with ibrutinib should contact the CI/CoI for advice.

Anti-platelet drugs can be used with ibrutinib but can be associated with increased bruising and bleeding. Therefore patients on these agents should be monitored for any significant change in bruising or bleeding. Dual antiplatelet therapy is excluded at baseline. If a patient develops a need for dual antiplatelet therapy during the trial this should be discussed with the CI/CoI beforehand.

10.7.2.4 ACE inhibitors and ibrutinib-containing regimes

Based on the results of an interim analysis, ACE inhibitors are contra-indicated for participants taking ibrutinib in the FLAIR trial. For participants requiring antihypertensive therapy an alternative therapy should be given.

10.7.3.Surgery whilst receiving ibrutinib

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be stopped for at least 7 days prior to the intervention and not be restarted for at least 7 days after the procedure. Ibrutinib should be restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

For minor procedures (i.e. such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be stopped at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to withhold ibrutinib for these procedures.

For investigational procedures (e.g. colonoscopy, endoscopy) consideration should be given as to whether a biopsy or other instrumentation is likely to be taken and the extent of the biopsy. If a biopsy or other instrumentation is possible ibrutinib should be stopped 3 or 7 days before the procedure and not be restarted for at least 3 or 7 days after, depending on the extent of the biopsy.

For emergency procedures, ibrutinib should be withheld after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Participants randomised to IR, I and I+V must be provided with the advice card detailing the circumstances where ibrutinib should be withheld for surgery. It is recommended that sites reissue the advice card annually due to the prolonged treatment period. Please remind participants of the requirement to stop ibrutinib before any surgical procedures at each clinic appointment. The increased risk of bleeding whilst taking ibrutinib should be communicated to other hospital departments as per local practice.

Where the participant has had a minor or major procedure without stopping ibrutinib a protocol violation form should be completed.

10.8 Management of toxicity– delays and dose reductions

10.8.1 Rituximab

For participants randomised to FCR treatment delays due to FC toxicity (section 10.8.2) will also delay rituximab. For participants randomised to IR treatment delays due to I toxicity (section 10.8.3.1) may also delay rituximab, though rituximab may continue at the discretion of the investigator.

10.8.1.1.1 Infusion related adverse reactions

Halve the speed of infusion if the following adverse events occur:

- Fevers > 38.5C
- Chills – mild, moderate
- Mucosal swelling – mild, moderate
- Hypotension (drop in systolic BP) > 30mmHg

Participants who develop grade 3 or 4 dyspnoea, bronchospasm or hypoxia should have their rituximab infusion interrupted immediately. Infusion should not be started until resolution of symptoms and normalisation of laboratory tests. At this point the infusion can be resumed at no more than one-half the previous rate. If the same adverse symptoms occur for a second time, the decision to stop treatment should be seriously considered by the investigator in line with standard care.

10.8.2 Fludarabine and cyclophosphamide (FC)

10.8.2.1 Impaired renal function

- Fludarabine should not be given to participants with a creatinine clearance of less than 30ml/min (exclusion criteria). Participants with a creatinine clearance of less than 30ml/min can have a delay of treatment for up to 4 weeks but should cease fludarabine treatment if their creatinine clearance does not improve to above 30ml/min.
- At the treating clinician's discretion, participants with a creatinine clearance between 30-60ml/min should have 50% the dose of fludarabine. The cyclophosphamide dose does not need to be reduced when the creatinine clearance is above 30ml/min after this time.
- Levels of creatinine should be monitored carefully in further cycles and, eventually, doses may be gradually increased to the original protocol dose at the discretion of the treating clinician.
- Creatinine clearance should be calculated using a locally approved formula, or as described in appendix D.

10.8.2.2 Neutropenia

- At day 29 +/- 3 days, if the neutrophils are $<1.0 \times 10^9$/l due to trial chemotherapy, rather than due to bone marrow involvement, treatment should be delayed for up to two weeks, with 25% reduction in dose of FC at the subsequent cycle (except in the case of isolated neutropenia not on G-CSF when the full dose of chemotherapy may be used if G-CSF is being added for the first time).
- Participants who have a neutrophil count of $<1.0 \times 10^9$/l at day 29 +/- 3 days of any cycle of therapy should receive G-CSF for the next and all subsequent cycles of chemotherapy. It is recommended that G-CSF should be given once daily in accordance with standard practice/the SmPC from days 7 to 13 for each subsequent cycle of therapy.
- If further grade 3-4 neutropenia occurs after 25% dose reduction, a further reduction to 50% of the original doses of F and C is recommended.
- If at Day 29 +/- 3 days of any subsequent cycle the neutrophils are $>1.0 \times 10^9$/l with G-CSF support then the chemotherapy should be re-escalated to full-dose which should be given with continuing G-CSF support.

- At the second occurrence of neutropenia treatment should be delayed for up to two weeks, with 25% reduction in dose of all subsequent cycles.
- If treatment is delayed by longer than 2 weeks the participant's ongoing treatment within the trial should be discussed with the Chief Investigator or a Co-Investigator (Protocol Section 1).

Table 3 Management of neutropenia due to therapy:

Four weeks after last course (Day 29 +/- 3 days)	One week delay (~Day 36 +/- 3 days)	Two weeks delay (~Day 43 +/- 3 days)
Neut >1.0: Commence next cycle therapy as planned		
Neut <1.0: Delay next course of therapy and commence G-CSF once daily in accordance with standard practice/the SmPC	Neut >1.0: Commence next cycle of therapy without dose reduction but with G-CSF once daily in accordance with standard practice/the SmPC Days 7-13	
	Neut still <1.0: Continue G-CSF and delay next course therapy for a further week	Neut >1.0 Commence next cycle of therapy with 25 % dose reduction* of FC (not rituximab) with G-CSF once daily in accordance with standard practice/the SmPC Days 7-13
		Neut <1.0 Ongoing treatment to be discussed with the Chief Investigator or Co-Investigator

* If the participant has already dose reduced by 25% previously then a dose reduction to 50% of the original doses of fludarabine and cyclophosphamide is recommended.

10.8.2.3 Other haematological toxicities

- At Day 29 +/- 3days, if the platelets are <75 x 10^9/L due to trial chemotherapy, rather than due to bone marrow involvement, treatment should be delayed for up to two weeks, with 25% reduction in dose of FC of subsequent cycles.
- If on subsequent cycles of therapy the platelets are over 100 x 10^9/L at Day 29 +/- 3days then the chemotherapy doses should be re-escalated to 100% dose level.
- If further grade 3-4 haematological toxicity occurs after 25% dose reduction, a further reduction to 50% of the original doses of FC is recommended.
- If the platelet count was decreased prior to commencing the first course of therapy due to marrow involvement then the platelets should reach at least 75% of the pre-treatment level before the next, and subsequent, cycles of therapy (lower levels are permitted at the discretion of the local Investigator).

10.8.3 Ibrutinib

10.8.3.1 Dose Delay, Reduction and Discontinuation

The actions in the table below should be taken for the following toxicities:

• Grade 3 neutropenia (<1.0 x 10^9/L) with infection and/or fever (GCSF is permitted and use must be recorded in CRF).
• Grade 3 or 4 nausea, vomiting, or diarrhoea, if persistent despite optimal antiemetic and/or anti-diarrhoeal therapy.
• Any Grade 3 or greater non-haematological toxicity related to ibrutinib.
• Any other Grade 4 toxicity.

Table 4: Drug Discontinuation Actions for Ibrutinib

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily)
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart a further dose level lower (140 mg daily)
4th	Discontinue ibrutinib

Where ibrutinib is withheld it is permissible, at the discretion of the local Investigator, to continue rituximab or venetoclax.

Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Chief Investigator or Co-Investigator (see Section 1). Any situations where dose delays or reductions, as detailed above, are not considered appropriate must be discussed with the Chief Investigator or Co-Investigator (see Section 1).

Study drug may be held for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed or approved by the Chief Investigator or Co-Investigator (see Section 1).

Dose changes must be recorded on the relevant CRF.

10.8.3.2 Dose re-escalation

If the participant has tolerated the lower dose of ibrutinib for 2 months following a dose reduction, as outlined in Section 10.8.3 then the dose should be re-escalated by one dose level. The dose may continue to be re-escalated by one dose level every 2 months until the maximum dose of 420mg is reached.

If the participant has further toxicities following a dose re-escalation the lower dose should be continued for the duration of ibrutinib treatment.

Dose changes must be recorded on the relevant CRF.

10.8.3.3 Treatment-related Lymphocytosis

Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared to baseline and >5000 per microlitre that occurs in the setting of unequivocal improvement in at least one other disease-related parameter and is associated with agents known to inhibit BCR (Hallek 2012[13], NCCN 2012, Cheson 2012[14]). Given the known mechanism of action of BCR-inhibiting agents including ibrutinib, treatment-related lymphocytosis is an expected and frequent pharmacodynamics phenomenon observed with initiation (or re-initiation) of ibrutinib. Ibrutinib associated treatment-related lymphocytosis generally occurs within the first few weeks of therapy, peaks within the first few months, and resolves slowly. Asymptomatic treatment-related lymphocytosis should also not be considered an AE. Patients with treatment related lymphocytosis should remain on study treatment and continue with all study-related procedures.

10.8.4 Dose modifications for venetoclax

Dose delays due to I toxicity (section 10.8.3.1) may delay the onset of venetoclax treatment.

Within the first 24 hours after either the first dose or at any dose increase, if any criteria below are met, the guidelines in the table below should be followed.

Within the first 24 hours after either the first dose or at any dose increase, if any laboratory criteria below are met, the patient should be hospitalised for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.

Nephrology (or other acute dialysis service) should be contacted/consulted (per standard care to ensure emergency dialysis is available) on admission for any subject hospitalised prophylactically or in response to laboratory changes.

IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not <50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.

Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhoea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, urate, calcium and creatinine within 1 hour.

Vital signs should be taken at time of all blood draws or any intervention.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per standard care.

In addition to the recommendations in the table below:
For potassium increase ≥0.5 mmol/L from baseline (taken pre dose at that dose level), or any value >5.0 mmol/L, recheck potassium, phosphorus, urate, calcium and creatinine within 1 hour and follow first guideline.

For phosphorous increase of >0.5 mg/dL (0.16 mmol/L) AND >5.0 mg/dL (1.615 mmol/L) recheck potassium, phosphorus, urate, calcium and creatinine within 1 hour.

Table 5: **Venetoclax dose modifications within the first 24 hours after either the first dose or at any dose increase**

Abnormality	**Dose Modification and Management Recommendation**
Laboratory Events	
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5mmol/L increase from prior value (and within ULN)	• Hold venetoclax until resolution • Recheck potassium, phosphorus, urate, calcium, and creatinine in 1 hour. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour.

	• Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium <ULN, and no other evidence of tumour lysis. • At discretion of the investigator may recheck prior to hospitalisation. If stable or decreased, and still within normal limits, hospitalisation is at the discretion of the Investigator. Potassium, phosphorus, urate, calcium and creatinine must be rechecked within 24 hours.
Potassium > ULN	• Hold venetoclax until resolution • Perform ECG; administer calcium gluconate 100-200mg/kg IV slowly if there is evidence of life-threatening arrhythmias • Administer Kayexalate/Resonium 60g • Administer furosemide 20mg IV • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 hour. If potassium, < ULN 1 hour later, repeat potassium, phosphorus, urate, calcium and creatinine 1, 2 and 4 hours later, if no other evidence of tumour lysis.
Potassium ≥ 6.0mmol/L (6.0 mEq/L) and/or symptomatic (e.g. muscle cramps, weakness, paresthesias, nausea, vomiting and diarrhoea)	• Hold venetoclax until resolution • Perform ECG; administer calcium gluconate 100-200mg/kg IV slowly if there is evidence of life-threatening arrhythmias. • Administer Kayexalate/Resonium 60g • Administer furosemide 20mg IV • Administer insulin 0.1 U/kg IV + D25 2mL/kg IV • Administer sodium bicarbonate 1 to 2 mEq/kg IV. Rasburicase should not also be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, urate, calcium and creatinine every hour.
Hyperuricaemia	
Urate ≥ 8.0 mg/dL (476 μmol/L)	• Hold venetoclax until resolution • Consider rasburicase (as per local guidelines). Sodium bicarbonate should not also be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 hour.
Urate ≥ 10 mg/dL (595 μmol/L) **OR**	• Hold venetoclax until resolution

Urate ≥ 8.0 mg/dL (476 μmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	• Consider rasburicase (as per local guidelines). Sodium bicarbonate should not also be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service) • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 hour. • If urate <8.0 mg/dL (476 μmol/L) 1 hour later, repeat potassium, phosphorus, urate, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumour lysis
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) **OR** Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Hold venetoclax until resolution • Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Recheck potassium, phosphorus, urate, calcium, and creatinine in 1 hour. If calcium normalised 1 hour later, repeat potassium, phosphorus, urate, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumour lysis • Calculate corrected calcium and check ionised calcium if albumin low
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Hold venetoclax until resolution • Nephrology notification (dialysis required for phosphorus > 10 mg/dL (3.23 mmol/L)) • Recheck potassium, phosphorus, urate, calcium, and creatinine in 1 hour. If phosphorus < 5.0 mg/dL (1.615 mmol/L) 1 hour later, repeat potassium, phosphorus, urate, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumour lysis.
Creatinine	
Increase ≥ 25% from baseline	• Hold venetoclax until resolution • Start of increase rate of IV fluids • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 to 2 hours.

Note that the baseline for comparision is the pre dose value at that dose level.

The following dose modifications should also be implemented if the criteria are met at any time during treatment with venetoclax.

Ongoing dosing of venetoclax
Management of electrolyte changes from last value at intervals >24 hours after either the first dose or at any dose increase (eg, 48 or 72 hours) are as below.

If the patient is hospitalised, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
    - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).
- If a smaller potassium increase of 0.5-0.9 mmol/L is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, urate, calcium and creatinine in 24 hours and confirm no evidence of tumour lysis prior to further venetoclax dosing.
- For urate, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

Dose modifications for tumour lysis syndrome

If a participant experiences blood biochemistry changes suggestive of TLS as per the table above, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 6). When resuming treatment after interruption due to TLS, the instructions for prevention of tumour lysis syndrome should be followed (see prophylaxis in section 10.7 and appendix I, Table 14).

Table 6 Dose modification for TLS and other toxicities

Dose at interruption (mg)	Restart dose (mg[a])
400	300
300	200
200	100
100	50
50	20
20	10

[a] The modified dose should be continued for 1 week before increasing the dose

For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose escalation or more than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose escalation; see

Table 6).

Dose modifications for toxicities not addressed above
Treatment with venetoclax should be withheld for any grade 3 or 4 non-haematological toxicities, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with venetoclax may be restarted at the same dose. If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines in Table 6 should be followed when resuming treatment with venetoclax following resolution. A larger dose reduction may occur at the discretion of the physician. For patients who require dose reductions to less than 100 mg for more than 2 weeks, discontinuation of venetoclax should be considered.

Administer G-CSF or growth factors for neutropenia as indicated (recommended to keep the neutrophil count above 1 x 10^9/L)

Where venetoclax is withheld it is permissible, at the discretion of the local Investigator, to continue ibrutinib as per the dose modifications listed in section 10.8.3

10.9 Treatment compliance

All participants will be asked to complete a participant diary card for any oral treatment (FC, I, V) and asked to return any unused capsules/tablets at each follow-up visit.

10.10 Early discontinuation of protocol treatment

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of attending clinicians or the participants themselves. All participants discontinuing early from protocol treatment or prescribed alternative treatment **after randomisation will still attend for follow up assessments unless unwilling to do so and Case Record Forms (CRFs) will continue to be completed**. Participants discontinuing prematurely from protocol treatment should be treated in accordance with local policy, and there is no provision for participants to cross-over treatment arms as part of trial treatment.

10.11 Participant withdrawal of treatment

The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial, be that from further treatment and/or follow-up data collection, are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and site following the withdrawal of consent. It should be made clear to any participant specifically withdrawing consent for further data collection in a CTIMP that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future. It should also be noted that if it is the decision of the attending clinician to withdraw the participant from further involvement in the trial then this should be documented on the relevant CRF.

11. ASSESSMENTS / SAMPLES / DATA COLLECTION

11.1 Submission of trial data

Data will be collected using paper case record forms which will be provided by the CTRU at the University of Leeds.

CRFs must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific Authorised Personnel Log. The original 'wet ink' version of the completed CRFs should be returned to the CTRU at the address given in the Investigator Site File. During the Covid-19 pandemic, additional guidance from Leeds CTRU is in place permitting sites to return completed CRFs electronically.

It is the responsibility of staff at participating sites to obliterate all personal identifiable data on any hospital reports, letters, etc., prior to sending to CTRU. Such records should only include Trial Number, initials and date of birth to identify the participant. The exception to this is the participant consent form, where the participant name and signature must not be obliterated. If signed consent forms are posted to CTRU, they must be sent in a separate envelope and not accompanied by any CRFs containing clinical data. Likewise, if signed consent or re-consent forms are sent electronically to CTRU, they must be sent separately using a secure file transfer system and not accompanied by any CRFs containing clinical data.

Participating hospitals will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial.

See Key Contacts (Section 1) for addresses for sending samples for central analysis and CRFs.

11.2 Schedule of events

Table 7 Central Investigations

Investigation	Post registration/ Baseline	6 months post randomisation (I+V only)	3 months post-completion of FCR or R (FCR or IR only) or 9 months post randomisation (I and I+V) (for IWCLL criteria)	6 monthly from 12 months post rand until 7 years post rand or disease progression requiring treatment, whichever is earliest		Stopping treatment with ibrutinib (or venetoclax if ibrutinib stopped due to toxicity)	At disease progression
				All participants	Participants receiving ibrutinib (IR, I and I+V)		
Bone marrow aspirate to HMDS 0.5 – 2ml EDTA and 6 x films	✓[1]		✓[1]		✓[3]	✓[5]	✓[4]
Bone marrow aspirate to UK CLL Biobank	✓[1]		✓[1]				
Peripheral blood to Leeds HMDS for flow cytometry (MRD Flow and TP53 abnormality (TP53 deletion and TP53 mutation testing) 3 x 5ml EDTA and 6 x films Confirmation of eligibility for 'genetically high risk' or 'standard risk' pathway by Leeds HMDS is required before randomisation	✓[6]	✓	✓				✓
2 x 5ml EDTA blood to HMDS for flow cytometry (MRD Flow)				✓[2]		✓	
40ml anticoagulated blood to UK CLL Biobank	✓						✓
10ml clotted blood to the UK CLL Biobank	✓						
Saliva sample to UK CLL Biobank	✓						

[1] Only for participants with a lymphocyte count $<10x10^9/L$

[2] Samples to be taken **annually** for participants randomised to FCR, until one MRD positive sample has been taken or 8 years post randomisation, whichever is earlier

[3] Only to be sent at 6 months after MRD negative peripheral blood result to confirm MRD negativity.

[4] Performed if the only indication of progressive disease is cytopenia and/or lymphocytosis

[5] For participants stopping treatment upon completing 6 years of treatment i.e. not repeated if stopping due to MRD negativity.

[6] Testing for TP53 abnormalities (TP53 deletion and TP53 mutation) only at baseline.

Table 8 Local Investigations

Investigation	Pre registration	Post registration/ Baseline	Routine tests before treatment	At the end of FCR or R (FCR or IR only)	3 months post-completion of FCR or R (FCR or IR) OR at 9 months post randomisation (I or I+V)	6 monthly until 2 years post randomisation, then annually until 7 years post rand or disease progression requiring treatment, whichever is earliest	6 monthly from 12 months post rand until 7 years post rand or disease progression requiring treatment, whichever is earliest		Stopping treatment with ibrutinib (or venetoclax if ibrutinib stopped due to toxicity)
						All participants	All participants	Participants receiving ibrutinib (IR, I and I+V)	
Informed consent (main and UK CLL Trials Biobank), Demographic Data, * Medical History	✓		Participants will be assessed for their suitability for treatment to the timelines in section 11.6, 11.7, 11.8 . As a minimum tests should be performed to ensure dose reductions are implemented and concomitant medications administered in line with section 10 of the protocol.						
***Pregnancy test (serum or urine HCG)**		✓[1]							
***Assessment of Disease (clinical examination)**		✓[9]			✓		✓		✓
***WHO performance Status**		✓		✓	✓		✓		
***Laboratory tests (haematology)**		✓		✓	✓		✓		
Reticulocyte count test		✓		✓					
***Laboratory tests (biochemistry)**		✓		✓	✓				
LDH test and β2M test		✓							
Serum immunoglobulins and electrophoresis		✓			✓		✓		
Direct Coombs Test		✓		✓					
***Serology for Hepatitis B (HBsAg & HBcAb) and C (HCAb)**		✓							
ECG		✓[9]							
ECHO		✓[11]							
For all participants whilst on trial treatment, blood pressure monitoring at every clinic visit and manage hypertension (either prior to the trial or emergent on treatment) in accordance with the NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg		✓			✓[12]			✓[12]	
Quality of Life questionnaires		✓		✓[7]			✓		
Health Economic Assessment questionnaires		✓		✓[7]		✓			
RANDOMISATION		✓[3]							
Physical examination (Vital signs (systolic and diastolic BP, pulse rate, B symptoms), weight (kg), height (cm) and BSA (m^2))		✓							

Investigation	Pre registration	Post registration/ Baseline	Routine tests before treatment	At the end of FCR or R (FCR or IR only)	3 months post-completion of FCR or R (FCR or IR) OR at 9 months post randomisation (I or I+V)	6 monthly until 2 years post randomisation, then annually until 7 years post rand or disease progression requiring treatment, whichever is earliest	6 monthly from 12 months post rand until 7 years post rand or disease progression requiring treatment, whichever is earliest		Stopping treatment with ibrutinib (or venetoclax if ibrutinib stopped due to toxicity)
						All participants	All participants	Participants receiving ibrutinib (IR, I and I+V)	
CT scan (thorax, abdomen and pelvis)		✓[4]	✓[8]		✓[6]				✓[5]
Bone marrow trephine, assessed locally		✓[10]			✓				✓
Adverse events and Serious Adverse Events (SAEs)						**Monitor from randomisation until 30 days post-treatment)**			
Serious Adverse Reactions (SARs) / Suspected Unexpected Serious Adverse Reactions (SUSARs)						**Monitor throughout study (from randomisation until end of trial)**			
Adverse Events of Special Interest (AEoSI)						**Monitor throughout study (from randomisation until end of trial)**			
Treatment compliance with ibrutinib and venetoclax				✓	✓			✓	
Assess ongoing suitability for ibrutinib (+/-venetoclax) treatment (participants randomised to IR, I and I+V)				✓	✓			✓	

* * to confirm eligibility, must be completed prior to randomisation, [1] within 2 weeks prior to starting treatment, , [3] all eligibility criteria should be confirmed prior to randomisation, [4] within 12 weeks prior to starting treatment, the CT scan must be repeated if the participant has received high dose steroid treatment following the initial scan, [5] IR/I/I+V participants who had an abnormal CT scan at 3 months post randomisation should have a repeat scan at the end of ibrutinib/venetoclax, [6] Not necessary if clinically palpable nodes, see section 11.11, [7]I and I+V participants at 6 months post randomisation, [8] at 6-8 weeks after starting treatment for I+V patients only to assess tumour burden before venetoclax. [9] Within 4 weeks prior to starting treatment[10]Only if lymphocyte count $<10x10^9/L$ [11] Prior to randomisation to confirm eligibility and within 4 weeks prior to starting treatment. For participants with a history of hypertension (defined as on treatment for hypertension) and / or cardiac disease [12] For all participants whilst on CLL treatment: blood pressure monitoring and management in accordance with the NICE guidelines [NG136] to keep blood pressure below 140/90mmHg

11.3 Laboratory samples

- **Local investigations**
  Biological material samples for local analysis should be labelled using the standard hospital system and therefore will not be anonymised, this will allow the results of the investigations to be fed back to the participants' doctors.

- **Central investigations (Peripheral blood and bone marrow aspirate) to Leeds HMDS**
  Samples will be sent to the central laboratory, Haematological Malignancy Diagnostic Service (HMDS) at St. James's University Hospital in Leeds. All samples should be labelled with the participant's trial number, date of birth, name and trial time-point. A sample request form, found in the Investigator Site File, should be enclosed when returning samples to HMDS. If you need to send a sample to Leeds HMDS from a participant with confirmed or suspected Covid-19 infection, please specify this on the request form, so that Leeds HMDS is aware. Leeds HMDS can still process samples from patients with Covid-19 with appropriate additional precautions

  It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to conform with the 2018 Data Protection Act.

  Biological samples collected from participants as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

  Trial-specific samples must not be collected prior to taking consent and the patient being registered.

  Trephine samples are not required to be sent for central investigation although a copy of a local pathology report, from within 6 months prior to trial entry, is required to be returned to CTRU with the participant's baseline data. A further local trephine report is required alongside bone marrow aspirates collected for response assessments at 3 months post rituximab for participants randomised to FCR and IR and for participants randomised to I and I+V at 9 months post randomisation and at the end of I or I+V.

  Samples for Leeds HMDS should not be collected on a Friday. If samples are collected on a Friday, a next day courier must be organised by the trial site.

  HMDS safe boxes can be ordered directly through HMDS by emailing:
  leedsth-tr.HMDSClinicalTrials@nhs.net

- **Central investigations (anti-coagulated blood, clotted blood, bone marrow aspirate and saliva sample) to UK CLL Biobank**
  The UK CLL Biobank aims to identify biomarkers that predict therapeutic response to the treatments being evaluated. Participants entering the study are therefore requested to donate blood, bone marrow and saliva samples prior to commencement of therapy. Additional samples are requested at specific points thereafter. These samples will be used for a range of studies of direct relevance to the treatment of CLL. Data resulting from analysis of samples sent to the Biobank will be fed back to the Clinical Trials Research Unit for integration with the clinical data set. Details of what samples to collect when and where to send them are given in Section 11. It should be noted that the UK CLL Biobank is a generic resource which is available to serve all national CLL trials.

As such, it has its own ethical approval for the purposes described above, including Participant Information Sheet and Consent Form, which should be used in addition to those provided for the main study.
Samples for the UK CLL Biobank must not be taken before consent using the specific UK CLL Biobank consent form is obtained and should be returned to the UK CLL Biobank using the specific kits provided.

Samples for the UK CLL Biobank must not be collected on a Friday. Sample collection kits can be requested by emailing: ukctbb@liverpool.ac.uk

11.4 Pre-Registration Assessments

Please note that assessments performed specifically for the trial **must not** be performed until **after** consent has been received. Where a test has been performed as part of local care and is within the required time-frame it does not have to be repeated but cannot be used for trial purposes until the participant has given consent.

- **Informed consent**
- **Demographic data:** (Participant initials, date of birth, hospital number, NHS number, gender)
- **Complete medical history:** (detailed history of CLL and other ongoing medical conditions)

Participants should now proceed to registration (see Section 8.4).

11.5 Post-registration/Baseline Assessments (all participants)

Once the participant has been registered, the following assessments should be performed. All assessments should be performed within 4 weeks of the start of treatment unless otherwise noted. Some of these assessments may have been conducted as part of routine clinical practice prior to registration and it is permissible to use these results where they have been performed within the required timescales.

* denotes tests which must be performed to confirm eligibility.

Once eligibility is confirmed the participant may be randomised, but all other assessments must be performed before the start of treatment. Eligibility tests should be repeated if they fall out of the required time window.

An echocardiogram (ECHO) must be done prior to randomisation to confirm eligibility and within 4 weeks prior to starting treatment for all participants who have a history of hypertension (defined as on medication for hypertension) and / or cardiac disease. Refer to Section 11.5.1 for more details about the cardiac monitoring requirements, and which anti-hypertensives are contra-indicated.

If the participant has a reduced ejection fraction identified during screening, and, in the opinion of the PI, meets the following exclusion criterion, then the participant should be excluded from the trial:

- *Symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)*

A participant can only be randomised after the central laboratory, Leeds HMDS, have confirmed the TP53 abnormality status, as this determines if a patient is eligible for the 'genetically high risk' or the 'standard risk' pathway.

* ***Complete medical history:*** *(Detailed history of CLL, baseline clinical conditions* ***within 4 weeks*** *prior to starting treatment)**
* ***Pregnancy test:*** *(Serum or urine HCG in women of child bearing potential* ***within 2 weeks*** *prior to starting treatment)**
- **Complete physical examination:** (Systolic and diastolic blood pressure, pulse rate, height, weight, body surface area, B symptoms **within 4 weeks** prior to starting treatment).
* ***WHO performance status*** *(Appendix A)* (within* ***4 weeks*** *prior to starting treatment).*
- **Local Haematology and Biochemistry:** (**All tests within 4 weeks** prior to starting treatment)
    * *FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes, reticulocyte count)**
    * *U&E's (calcium (adjusted), urea, urate, serum creatinine, calculated creatinine clearance)**
    * *LFT's (bilirubin, alkaline phosphatase, ALT or AST) **
    - Other biochemical tests (LDH, β_2M)
    - Serum immunoglobulins and electrophoresis
    - Direct Coombs test
* ***Serology for Hepatitis B and C* (HBsAg, HBcAb & HCAb) (within 12 weeks*** *prior to starting treatment and before randomisation)*
* ***ECHO (within 4 weeks prior to starting treatment)**** For participants with a history of hypertension (defined as on treatment for hypertension) and / or cardiac disease
- ***Blood pressure*** Take/ document blood pressure and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Participants with hypertension (either prior to the trial or emergent on treatment) should be managed according to NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg

- **Central investigations:**

  In addition, the following samples will be sent for central analysis,

    - ***Peripheral blood (3 x 5ml EDTA and 6 x films)**, to Leeds Haematological Malignancy Diagnostic Service, (HMDS) (address below) for flow cytometry, and TP53 deletion ('17p deletion') and TP53 mutation status. Confirmation that baseline samples have been analysed at HMDS is required prior to randomisation. **

    - **Bone marrow aspirate (0.5 – 2ml EDTA and 6 x films) (only for participants with a lymphocyte count <10x10^9/L):** The <u>first</u> draw of bone marrow aspirated should be put in EDTA and used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL). The marrow aspirate should be sent to:

      Haematological Malignancy Diagnostic Service
      Level 3, Bexley Wing
      St. James's University Hospital
      Beckett Street
      Leeds, LS9 7TF

  Sites should note that samples arriving to HMDS on Tuesday-Friday will typically be reported in 7-10 working days (however, this could be longer if the material is poor quality, e.g. >24 hours old on arrival, or the TP53 deletion result is borderline or difficult to interpret and a repeat analysis is required).

Only for participants who have provided consent, the second draw of bone marrow aspirate should be sent to:

UK CLL Biobank
1st floor William Henry Duncan Building,
6 West Derby Street
University of Liverpool
L7 8TX

For participants who have provided consent to participate in the UK CLL Biobank the following samples should also be sent.

- **40ml anticoagulated blood** to:

UK CLL Biobank
1st floor William Henry Duncan Building,
6 West Derby Street
University of Liverpool
L7 8TX

- **10ml clotted blood** to the UK CLL Biobank (address above)
- **Saliva sample** to the UK CLL Biobank (address above)

- **An anonymised copy of the bone marrow trephine report, performed within 6 months of trial entry, should be returned to the CTRU with the Baseline CRFs.** This assessment does not need to be performed if lymphocyte count $>10x10^9/L$
- **Chest X-ray (if required)**
- **CT-scan (thorax, abdomen and pelvis) (performed within 12 weeks of the start of treatment. The CT scan must be repeated if the participant has received high dose steroid treatment following the initial scan)**
- **Electrocardiogram (ECG) (performed within 4 weeks prior to starting treatment)**
- **Assessment of disease**
- Must be performed **within 2 weeks** prior to the participant starting treatment. Clinical assessment of lymph node disease; the size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions. Binet staging, liver and spleen examination).

11.5.1 Cardiac monitoring requirements (also see Appendix H)

Please follow the tables below for the cardiac monitoring requirements for new participants, participants already on treatment, and for participants who meet the MRD re-starting criteria. Note that blood pressure monitoring and management is for all participants on trial treatment, and the ECHO is for those participants with a history of hypertension (defined as on medication for hypertension) and / or cardiac disease or who develop hypertension whilst on trial treatment.

Under some circumstances the preferred course of action may include blood pressure monitoring performed at GP practices and/ or at participants' homes, however it is important to ensure the results are documented clearly in the participant's notes. If blood pressure monitoring is performed at GP practices and/ or at participants' homes, it remains the responsibility of the PI (or delegated Co-Investigator) to assess the blood pressure results and determine any required action in line with the protocol (e.g. requesting GP to initiate or adjust anti-hypertensives) and ensure this is clearly documented

*Cardiac abnormalities identified from these cardiac monitoring measures should be managed by the Principal Investigators. Should the site PIs require guidance, the site should contact the Chief Investigator and / or Co-Investigators listed in Section 1 of the protocol (copying in the CTRU_FLAIR@leeds.ac.uk email in all correspondence)

See Appendix H for a Summary of the NICE guidance and note that 'ACE inhibitors' should not be given concurrently with ibrutinib-based regimens in the study based on the results of an interim analysis (see sections 4.5.9 and 10.7.2.4). Also note the cautionary advice about diltiazem and verapamil in Section 10.7.7 (Concomitant therapy to be used with caution whilst receiving ibrutinib and / or venetoclax)

Common examples of 'ACE inhibitors' include (but not limited to): Ramipril, Perindopril, Lisinopril, Enalapril. A more complete list of ACE inhibitors is included in Appendix L.

Table A: for new participants

Who For	Time-point	Requirement	Action(s)
For all new participants	At screening (within 4 weeks of starting treatment) and throughout trial treatment	Take/ document blood pressure at every clinic visit and monitor patients as appropriate to ensure blood pressure is below 140/90mmHg	Participants with hypertension (either prior to the trial or emergent on treatment) should be managed according to NICE Guidelines* (NG136; published August 2019) to keep the blood pressure below 140/90mmHg https://www.nice.org.uk/guidance/ng136 https://www.nice.org.uk/guidance/ng136/resources/visual-summary-pdf-6899919517 *Note that 'ACE inhibitors' should not be given whilst a participant is being treated with an ibrutinib-containing regime
For new participants **with** hypertension **and / or** previous cardiac disease	Screening (within 4 weeks of starting treatment)	Perform echocardiogram	If the participant has a reduced ejection fraction identified during screening and, in the opinion of the PI, meets the following exclusion criterion, then the participant should be excluded from the trial: *Symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)*

Table B: for participants currently on trial treatment at the time of protocol v9.0 implementation, and for those participants who meet the MRD re-starting criteria

Who For	Time-point	Requirement	Action(s)
For all participants on trial treatment	At next scheduled clinic visit after implementation of protocol version 9.0 and through-out trial treatment	Take/ document blood pressure at every clinic visit and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg	Participants with hypertension (either prior to the trial or emergent on treatment should be managed according to NICE Guidelines* (NG136; published August 2019) to keep the blood pressure below 140/90mmHg https://www.nice.org.uk/guidance/ng136 https://www.nice.org.uk/guidance/ng136/resources/visual-summary-pdf-6899919517 *Note that 'ACE inhibitors' should not be given whilst a participant is being treated with an ibrutinib-containing regime
For participants **with** hypertension **and/or** previous cardiac disease on trial treatment on ibrutinib-containing arms at the time of protocol v9.0 implementation , and for	At the next scheduled clinic visit after implementation of protocol version 9.0	Perform echocardiogram	Clearly document in participant's notes/ source data all relevant details, including if the participants have left ventricular hypertrophy Monitor as appropriate*

those participants who meet the MRD re-starting criteria			

11.5.2 Pre-randomisation Questionnaires

For participants who have provided consent to complete Quality of Life and Health Economics questionnaires, these should be completed before the participant is randomised.

- **Quality of Life questionnaires (including Health Economic assessments)**

11.6 Routine tests before each cycle of FCR or R (FCR, IR participants)

Participants will be assessed for their suitability for treatment within 1 week prior to Day 1 of each cycle of FCR or R (for participants randomised to IR) according to standard clinical practice. As a minimum tests will be performed to ensure dose reductions are implemented, and concomitant medications administered, in line with Section 10 of the protocol.

Participants should be weighed prior to each cycle of treatment but the BSA (example calculation in Appendix D) should only be re-calculated if the weight changes by greater than 10% (loss or gain).

Participants who were HBsAg-ve/HBcAb+ve/HB DNA–ve at trial entry should have been referred to a liver disease specialist before the start of treatment with rituximab. During treatment, they should be monitored and managed to prevent HBV reactivation.

Treatment compliance will also be assessed.

Blood pressure: Whilst on trial treatment, take/ document blood pressure at every clinic visit and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Blood pressure monitoring can also be performed at GP practices and/ or at participants' homes if it is not safe for the participant to attend the clinic. Participants with hypertension (either prior to the trial or emergent on trial treatment should be managed according to NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg. Refer to Section 11.5.1 for more details.

11.7 Routine tests for participants treated with ibrutinib (IR, I, I+V participants)

Participants will be assessed for their suitability for treatment within one week prior to the start of the each of the first three months of ibrutinib. As a minimum tests will be performed to ensure dose reductions are implemented in line with section 10.8 of the protocol. After the first three months of treatment participants should then be assessed for treatment suitability three-monthly until 12 months of treatment where this may be increased to six-monthly for the remainder or ibrutinib treatment.

Participants randomised to IR and I+V will already be tested more frequently as a consequence of treatment with R and V respectively.

Blood pressure: Whilst on trial treatment, take/ document blood pressure at every clinic visit and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Blood pressure monitoring can also be performed at GP practices and/ or at participants' homes if it is not safe for the participant to attend the clinic. Participants with hypertension (either prior to the trial or emergent on trial treatment) should be managed according to NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg. Refer to Section 11.5.1 for more details.

11.8 Routine tests for participants treated with venetoclax (I+V participants)

Before giving the first dose of venetoclax, a CT scan and lymphocyte count must be performed to assess the participant's tumour burden within two weeks of starting treatment with venetoclax.

Pre-dose: Assess blood biochemistries (specifically creatinine, urate, potassium, phosphorus, and calcium) prior to initiating venetoclax to evaluate kidney function and correct pre-existing hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia to normal levels. Reassess blood chemistries before starting each subsequent dose escalation of venetoclax. Pre dose bloods should be within 24 hours of dosing.

Post dose: All patients will have blood biochemistry at 6-8 hours after each dose escalation and this must be evaluated before the patient leaves hospital. Wherever possible this time point should be at 8 hours post dose.

Blood biochemistry should also be carried out for low/medium tumour burden at 24 hours post dose at the 20 mg and 50 mg doses.

For participants with high tumour burden, monitor blood chemistries in the hospital at 4, 6-8, 12 and 24 hours after initiating venetoclax at the 20 mg and 50 mg doses; subsequent dose escalations can be administered in the outpatient setting with monitoring of blood chemistries at 6-8 hours and at 24 hours after initiating venetoclax.

Table 9 Monitoring schedule during venetoclax dose escalation phase

Tumour Burden/renal function		**Blood Biochemistry Monitoring[a,]**
		Setting and Frequency of Assessments
Low	All lymph nodes <5 cm AND ALC <25 x10^9/L	Outpatient 1. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 2. Pre-dose and 6 to 8 hours at subsequent dose escalations
Medium	Any lymph node 5 cm to <10 cm OR ALC ≥25 x10^9/L	Outpatient 3. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 4. Pre-dose and 6 to 8 hours at subsequent dose escalations 5. Consider hospitalisation for participants with creatinine clearance <80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any lymph node ≥10 cm OR ALC ≥25 x10^9/L	In hospital at first dose of 20 mg and 50 mg 6. Pre-dose, 4, 6-8, 12 and 24 hours Outpatient at subsequent dose escalations 7. Pre-dose, 6 to 8 hours and 24 hours

AND any lymph node ≥5 cm	

[a.] Evaluate blood biochemistries (potassium, urate, phosphorus, calcium, and creatinine); review in real time.

Electrolyte abnormalities should be corrected promptly. The next dose of venetoclax after the 20mg and 50mg dose should not be administered until the 24 hour blood chemistry results have been evaluated. Further laboratory assessments are at the discretion of the treating investigator or standard practice.

Hospitalisation: Participants with high tumour burden (as per table 1, section 10.6) or otherwise assesed as at high risk of TLS based on investigator assessment, require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring through the first 24 hours. Consider hospitalisation for subsequent dose escalations based on reassessment of risk. See Section 10.8.4 for Recommendations for Initial Management of Electrolyte Abnormalities and Appendix I for Prevention of Tumour Lysis.

After the venetoclax dose escalation phase, laboratory assessments to confirm suitabality for further treatment should be performed at least monthly for the first 3 months (4, 5, 6 months post randomisation if no delays), can be increased to three-monthly for the next 4 assessments (9, 12, 15, 18 months post randomistaion) and six-monthly thereafter (24, 30, 36 months etc. Assessments should include: platelets, ANC neutrophils, creatinine, phosphorus, calcium, urate and potassium as a minimum.

11.9 Evaluations at the end of FCR or R (FCR and IR participants only)

This visit should be at Day 28 of the final cycle of FCR/R treatment. The following investigations should be undertaken:

- **WHO performance status** (Appendix A)
- **Local haematology and biochemistry (carried out locally) :**
    - FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes, reticulocyte count)
    - U&E's (calcium (adjusted), urea, urate, serum creatinine)
    - LFT's (bilirubin, alkaline phosphatase, ALT or AST)
    - Direct Coombs Test
- **Quality of Life Questionnaires (including Health Economic assessments):** only for participants who provided consent to complete these

  Most participants will complete treatment with FCR/R at 6 months post-randomisation. However, if treatment is ended early (>28 days before 6 months post randomisation) or delayed (>28 days after 6 months post randomisation) the Quality of Life and Health Economics questionnaires must be completed at the end of FCR/R AND at 6 months post randomisation. Whilst it is preferred that questionnaires are completed in clinic to promote compliance sites may post this questionnaire to participants if the 6 month post-randomisation time point does not align with a clinic visit.
- **Treatment compliance**

11.10 Evaluations at six months post randomisation (I and I+V only)

- **Quality of Life Questionnaires (including Health Economic assessments):** only for participants who provided consent to complete these.
- **Treatment compliance**
- **Central investigations (I+V patients only)**
  In addition, the following samples will be sent for central analysis,
  - **Peripheral blood (3 x 5ml EDTA and 6 x films)**, to Haematological Malignancy Diagnostic Service, (HMDS) (address below) for flow cytometry
  - **Blood pressure:** For those participants on trial treatment, take/ document blood pressure at every clinic visit and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Blood pressure monitoring can also be performed at GP practices and/ or at participants' homes if it is not safe for the participant to attend the clinic. Participants with hypertension (either prior to the trial or emergent on trial treatment) should be managed according to NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg. Refer to Section 11.5.1 for more details.

11.11 Evaluations 3 months after the end of FCR or R (FCR and IR) or 9 months post randomisation (I and I+V)

Participants randomised to FCR or IR will be evaluated for response to treatment and assessment of minimal residual disease 3 months after the end of FCR or R (for participants randomised to IR), according to the IWCLL Response Criteria (Appendix B). This visit should be timed 3 months after Day 1 of the participant's final cycle of treatment.

Participants randomised to I or I+V will be assessed at 9 months post randomisation (if Covid-19 risk is not acceptable, this assesment can be done as soon as feasible after this date)

The following investigations should be undertaken:

Blood pressure: For those participants on trial treatment, take/ document blood pressure at every clinic visit and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Blood pressure monitoring can also be performed at GP practices and/ or at participants' homes if it is not safe for the participant to attend the clinic. Participants with hypertension (either prior to the trial or emergent on trial treatment) should be managed according to NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg. Refer to Section 11.5.1 for more details.

- **Complete physical examination:** (systolic and diastolic blood pressure, pulse rate, height, weight, body surface area (Appendix D) and WHO performance status (Appendix A)).
- **Local haematology** (Hb, WBC with differential count, neutrophils, lymphocytes, platelets).
- **Serum immunoglobulins**
- **Central investigations:**
  In addition, the following samples will be sent for central analysis:
  - **Peripheral blood (3 x 5ml EDTA and 6 x films)** to Haematological Malignancy Diagnostic Service, (HMDS) for flow cytometry should be sent to:

Haematological Malignancy Diagnostic Service
Level 3, Bexley Wing

St. James's University Hospital
Beckett Street
Leeds, LS9 7TF

Additionally, if the participant has a lymphocyte count **<10x10^9/L** then the following samples should also be sent for central analysis:

- **Bone marrow aspirate (0.5 – 2ml EDTA and 6 x films):** The first draw of bone marrow aspirated should be put in EDTA and used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL). The marrow aspirate should be sent to:

  Haematological Malignancy Diagnostic Service
  Level 3, Bexley Wing
  St. James's University Hospital
  Beckett Street
  Leeds, LS9 7TF

  For consenting participants only, the second draw of bone marrow aspirated should be sent to:

  UK CLL Biobank
  1st floor William Henry Duncan Building,
  6 West Derby Street
  University of Liverpool
  L7 8TX

- **An anonymised copy of the bone marrow trephine report should be sent to the CTRU.**
- **CT-scan (thorax, abdomen and pelvis). If there is clinically palpable disease (nodes or spleen) it is not necessary to perform the CT scan.**
- **Assessment of disease**
  Clinical assessment of lymph node disease should be performed. The size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions. Liver and spleen examination.

11.12 6 monthly evaluations from 12 months post-randomisation

All participants will be evaluated every 6 months from 12 months post-randomisation until 1 year after treatment has ended or 7 years post randomisation, whichever is later. All participants will end six monthly follow up at disease progression if this is sooner. Where necessary due to Covid-19 risk, telephone/ video consultations can take place and the missed assesments can be done as soon as feasible.

11.12.1 6 monthly evaluations for participants randomised to FCR

The following investigations should be undertaken for participants randomised to FCR:

- **WHO performance status** (Appendix A)
- **Local haematology and biochemistry**
  - FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes).
  - LFTs (ALT or AST, bilirubin)

- **Serum immunoglobulins**

- **Assessment of disease**
    - Clinical assessment of lymph node disease should be performed. The size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions.
    - Liver and spleen examination

- **Quality of Life and Health Economic questionnaires**

- **Central investigations (performed annually at 12, 24, 36, 48, 60, 72 and 84 months post-randomisation):**
  The following samples are needed for central investigations and should continue to be taken and sent on a 12 monthly basis:

    - **2 x 5ml blood** in EDTA to Haematological Malignancy Diagnostic Service, (HMDS) for flow cytometry

      Haematological Malignancy Diagnostic Service
      Level 3, Bexley Wing
      St. James's University Hospital
      Beckett Street
      Leeds, LS9 7TF

      NB: For participants randomised to FCR the central investigations listed above are only required until 1 MRD positive result is received.

Where necessary due to Covid-19 risk, telephone/ video consultations can take place and the missed assesments can be done as soon as feasible.

11.12.2 6 monthly evaluations for participants randomised to IR, I or I+V

- **Blood pressure:** For those participants on trial treatment**,** take/ document blood pressure at every clinic visit and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. The preferred course of action may include blood pressure monitoring to be performed at GP practices and/ or at participants' homes, until it is safe for participants to attent visits at the hospital. Participants with hypertension (either prior to the trial or emergent on trial treatment should be managed according to NICE Guidelines (NG136; published August 2019) to keep the blood pressure below 140/90mmHg. Refer to Section 11.5.1 for more details.

- **WHO performance status** (Appendix A)
- **Local haematology and biochemistry**
    - FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes).
    - LFTs (ALT or AST, bilirubin)
- **Serum immunoglobulins**

- **Assessment of disease**
    - Clinical assessment of lymph node disease should be performed. The size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions.
    - Liver and spleen examination

- **Treatment compliance**

- **Central investigations:**
  The following samples are needed for central investigations and should continue to be taken and sent on a 6 monthly basis:

    - **2 x 5ml blood** in EDTA to Haematological Malignancy Diagnostic Service, (HMDS) for flow cytometry

      Haematological Malignancy Diagnostic Service
      Level 3, Bexley Wing
      St. James's University Hospital
      Beckett Street
      Leeds, LS9 7TF

  For participants receiving ibrutinib, ongoing treatment is determined by the MRD results as described in section 11.13 and 11.14.

If any of these visits and assessments are missed due to Covid-19, these can be re-scheduled for when the Covid-19 risk is acceptable. Where necessary due to Covid-19 risk, telephone/ video consultations can take place.

- **Quality of Life questionnaires:** completed 6 monthly
- **Health Economic questionnaires:** completed 6 monthly until 2 years post randomisation, then annually until 7 years post rand or disease progression requiring treatment, whichever is earliest
-

11.13 MRD negativity stopping rules

Participants randomised to I, IR and I+V will receive treatment for up to 6 years. Treatment will be stopped if the participant has toxicity requiring cessation, progressive disease or if they become MRD negative during the first 3 years of treatment. The MRD stopping rules due to MRD negativity are based on a stopping algorithm. Participants will have MRD measured in the peripheral blood every 6 months and once an MRD negative result is obtained the time from randomisation to the first MRD negative result will be calculated and treatment will continue for that same time period again before being stopped.

The first MRD test that will count for the MRD negative stopping criteria is at 12 months post-randomisation (i.e. the 9 month post-randomisation MRD test will not trigger the stopping process). The additional MRD peripheral blood sample at 6 months post randomisation in the I+V group will not be included in assessing MRD negativity for implementation of these stopping rules.

Participants that have an MRD negative peripheral blood result will have another sample taken 3 months later. If both samples are MRD negative then a bone marrow aspirate and peripheral blood test will be carried out at after a further 3 months (6 months after the first MRD negative result). If any of these assessments are missed due to Covid-19, these can be re-scheduled for when the Covid-19 risk is acceptable. The treatment stop date will still be calculated from the first MRD Negative test, considering that the following two peripheral blood samples and the bone marrow aspirate are MRD Negative prior to the participant stopping treatment.

Participants who become MRD negative will be categorised and treated as follows:

- If a participant becomes MRD negative in the peripheral blood (later confirmed in the marrow) after one year of treatment they will stop treatment after two years of treatment (approximately 2 years post-randomisation).
- If a participant becomes MRD negative in the peripheral blood after 18 months of treatment they will stop treatment after 3 years of treatment (approximately 3 years post-randomisation).
- If a participant becomes MRD negative in the peripheral blood after 24 months of treatment they will stop treatment after 4 years of treatment (approximately 4 years post-randomisation).
- If a participant becomes MRD negative in the peripheral blood after 30 months of treatment they will stop treatment after 5 years of treatment (approximately 5 years post-randomisation)

Participants will need to have an MRD negative result prior to their 3 years post-randomisation assessment to meet the MRD stopping algorithm criteria.

In order for treatment to be stopped participants must remain MRD negative in their peripheral blood throughout the period between their first MRD negative result and stopping treatment, and MRD negativity must be confirmed by bone marrow aspirate six months after (or as soon as feasible after six months when Covid-19 risks are acceptable) the first MRD negative peripheral blood result. If the bone marrow aspirate is MRD positive then the participant will continue treatment for the remainder of the six years.

If after an MRD negative peripheral blood result there is an MRD positive peripheral blood sample prior to the bone marrow aspirate, the participants will be treated as MRD positive and continue treatment. If at a later timepoint the participant has an MRD negative peripheral blood result, the time from randomisation to MRD negativity must be recalculated based on the later MRD negative result.

If a single MRD positive peripheral blood result is observed following a MRD negative bone marrow aspirate and followed by a further MRD negative peripheral blood result, please contact the CI or Co investigator and CTRU for advice. This is to account for the possibility of false positives.

When treatment is stopped the investigations described in section 11.15 are to be carried out.

11.14 MRD relapse in participants who stopped treatment due to MRD negativity

Once participants have stopped treatment due to MRD negativity (section 11.13) they will be monitored every 6 months for MRD relapse by peripheral blood samples sent to Leeds HMDS. If an MRD positive result is recorded, a further blood sample should be taken three months later, followed by a blood sample and bone marrow aspirate three months after that to confirm MRD status (6 months after the first MRD positive result). If all the results are MRD positive then the participant will recommence their randomised treatment (either I (if I or IR arm) or I+V, as it was before stopping treatment) until they have received a total of six years of treatment. If, following an MRD positive blood result, an MRD negative blood (or bone marrow aspirate) result is recorded the participant will revert to six monthly MRD testing.

Participants who relapse at the MRD level at or after 6 years since randomisation will not recommence treatment.

Participants that restart treatment due to MRD relapse will receive a total of 6 years of treatment, irrespective of their MRD status.

As a minimum participants must meet the following criteria to recommence treatment:

- ALT ≤3 ULN or AST ≤3 ULN
- Total bilirubin ≤1.5 ULN
- Creatinine clearance >30ml/min (either measured or derived by the Cockcroft Gault formula (appendix C) or alternative locally approved formula).

All restarting participants will be required to carry out the baseline assessments described in section 11.5 and 11.5.1 before recommencing treatment (including CT scan). It is not necessary to repeat the following investigations:

- Serology for hepatitis B & C
- TP53 deletion and TP53 mutation (collectively referred to as TP53 abnormalities)
  ECG

It is important to follow the cardiac monitoring requirements for re-starting patients who have a history of hypertension (defined as on medication for hypertension) and / or cardiac disease or who develop hypertension following trial treatment. Refer to Section 11.5.1.

Participants will follow the assessment schedule in 11.7 and 11.8 for their allocated treatment. IR participants will not restart R so must follow section 11.7 for assessing suitability for ibrutinib monotherapy (I). Participants that restart treatment will be evaluated after the end of treatment as detailed in section 11.15.

11.15 Evaluations at the end or treatment with ibrutinib (+/- venetoclax) (IR, I and I+V)

End of treatment investigations will be carried out at the point treatment ends and this includes:

- Participants that have not stopped treatment due to MRD negativity and stop treatment at 6 years post randomisation
- Participants that have met the MRD negative stopping criteria and stop treatment
- Participants that have restarted treatment due to MRD relapse and complete 6 years of treatment in total
- Participants that stop treatment early due to toxicity

The following samples will be sent for central analysis:

- **Bone marrow aspirate** (**0.5 – 2ml EDTA and 6 x films**) Bone marrow aspirate should be put in EDTA and used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL). The marrow aspirate and should be sent to:

  Haematological Malignancy Diagnostic Service
  Level 3, Bexley Wing
  St. James's University Hospital
  Beckett Street
  Leeds, LS9 7TF

Participants that are stopping treatment due to MRD negativity will already have had a bone marrow aspirate at six months after the first MRD negative peripheral blood result (or as soon as feasible after six months when Covid-19 risks are acceptable). The bone marrow aspirate should not be carried out

again at the point of stopping treatment. Participants stopping treatment due to toxicity do not need to perform a bone marrow aspirate.

- **2 x 5ml blood in EDTA** to Haematological Malignancy Diagnostic Service, (HMDS) for MRD flow cytometry. Participants stopping treatment due to toxicity do not need to collect this sample if blood has been sent to HMDS within the last six months.

- **An anonymised copy of the bone marrow trephine report should be sent to the CTRU.**

- **Assessment of disease**
  Clinical assessment of lymph node disease should be performed. The size of the largest lymph nodes in each nodal area should be measured in centimetres in 2-dimensions. If the CT scan 9 months post randomisation was abnormal then the CT scan should be repeated at the end of treatment.

11.16 Evaluations at disease progression

Participants will be evaluated at disease progression. If the only sign of progression is either progressive cytopenia(s) and/or lymphocytosis then it is necessary to send a bone marrow sample to HMDS to confirm the abnormalities are due to disease progression. The following investigations should be undertaken.

- **40 ml anti-coagulated blood** (for participants who have provided consent to participate in the UK CLL Trials Biobank only) sent to:

  UK CLL Biobank
  1st floor William Henry Duncan Building,
  6 West Derby Street
  University of Liverpool
  L7 8TX

- **Bone marrow aspirate (performed if the only indication of progressive disease is cytopenia and/or lymphocytosis).** The first draw of bone marrow aspirated should be put in EDTA and used for MRD flow cytometry (the less the marrow is diluted with blood the more accurate the assessment of involvement by CLL). The marrow aspirate should sent to:

  Haematological Malignancy Diagnostic Service
  Level 3, Bexley Wing
  St. James's University Hospital
  Beckett Street
  Leeds, LS9 7TF

- **Peripheral blood (3 x 5ml EDTA and 6 x films)** to Haematological Malignancy Diagnostic Service, (HMDS) for flow cytometry should be sent to:

  Haematological Malignancy Diagnostic Service
  Level 3, Bexley Wing
  St. James's University Hospital

Beckett Street
Leeds, LS9 7TF

11.16.1 Treatment post disease progression

Following disease progression, participants should be treated in accordance with local policy. There is no provision for participants to cross-over to other trial treatments.

All further treatment received for CLL should be recorded in the CRFs.

11.17 Definition of disease progression

11.17.1 Definition of disease progression

Disease progression will be defined using the IWCLL criteria given in Appendix B. Progressive disease during or after therapy is characterised by at least one of the following:

- Increasing Lymphadenopathy
- An increase in the liver and/or spleen size by 50% or more or *de novo* appearance of hepatomegaly or splenomegaly due to CLL.
- An increase in the number of blood lymphocytes by 50% or more with at least 5000 B-lymphocytes per microliter (if the patient is still receiving ibrutinib then lymphocytosis in isolation does not define progression; see Sections 11.12 & 11.12.2 and please contact the C.I. or other clinician from Section 1 [page 2]).
- Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible this diagnosis should be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) attributable to CLL.

For participants randomised to IR, I or I+V the above criterion should be considered alongside section 11.17.2.

11.17.2 Additional definition of disease progression for participants randomised to IR, I or I+V

Ibrutinib may cause blood lymphocytosis with concomitant reduction in lymphadenopathy and/or splenomegaly. In this setting an increase in blood lymphocyte counts, by itself, does not indicate an increased tumour burden, but may rather reflect a re-distribution of leukaemia cells from the lymphoid tissues to the blood. In such cases, increased blood lymphocytosis is not a sign of treatment failure or progressive disease. Such a treatment-related lymphocytosis usually occurs within the first few months of initiating therapy with ibrutinib and can be very marked. Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation is blood lymphocyte count of >50% compared to baseline and >5000 per microlitre.

11.18 Quality of Life

For all participants who have consented to complete the Quality of Life questionnaires, the questionnaires will be completed in clinic (or posted to participants) at the following timepoints: prior to randomisation; at end of treatment with R (FCR/IR); 6 months post-randomisation (I, I+V); and then every 6 months from 12 months post-randomisation until 7 years post-randomisation. Participants will be given an envelope to seal their questionnaires in before returning to their clinical team in order to preserve the confidentiality of the results. See Section 14.3 for full details.

11.19 Annual follow up

Participants will be followed up on an annual basis from 7 years post randomisation, or from disease progression requiring treatment, whichever is earliest, until death.

Other treatments for CLL before disease progression (e.g. consolidation) are not permitted. Please contact CTRU for more information. Participants should not enter another clinical trial without contacting the CI/CTRU.

11.20 Assessment of efficacy

As described in section 11.11, all participants will have a formal assessment of response, including minimal residual disease status, by IWCLL Criteria 3 months after the end of therapy with FCR or R (for participants randomised to receive IR) or at 9 months post randomisation (for participants randomised to I and I+V).

For participants randomised to IR, I or I+V a formal assessment of response, including minimal residual disease status, by IWCLL Criteria, will also be made when treatment with ibrutinib/ibrutinib + venetoclax is stopped as described in section 11.17.

11.21 Response to treatment

Disease will be evaluated according to the IWCLL criteria given in Appendix B. Disease progression is defined by the IWCLL criteria as given in Appendix B and section 11.17.

11.22 Adverse and Serious Adverse Events

Complete the relevant CRF for all AEs occurring from randomisation until 30 days after treatment and report via the usual data management routes.

Complete the SAE CRF for all SAEs and SARs occurring in the trial. SAEs should be reported from the time of randomisation until 30 days post treatment and SARs reported from randomisation throughout the trial. All SAEs and SARs must be faxed to the CTRU within 24 hours of becoming aware of the event (see Section 12).

Complete the SUSAR CRF for all SUSARs occurring in the trial from the time of randomisation throughout the trial and fax to the CTRU within 24 hours of becoming aware of the event:

11.23 Pregnancies

All pregnancies, suspected pregnancies and pregnancies in the female partners of male participants must be reported immediately to the CTRU using the Pregnancy Reporting Form. The CTRU will then notify Janssen and/or Abbvie of this information for participants exposed to ibrutinib or venetoclax. Female participants who become pregnant should be withdrawn from the trial treatment immediately. CTRU will follow the pregnancy up to outcome and any congenital abnormality or birth defect resulting from the pregnancy should be reported as a Serious Adverse Event.

11.24 Deaths

All deaths must be recorded on the Notification of Death CRF and sent to the CTRU within 24 hours of notification to the site trial research team. The date of death and cause of death will be collected.

All deaths should be assessed to determine whether they meet the criteria of a SAE, SAR or SUSAR. Definitions and reporting requirements for SAEs, SARs and SUSARs can be found in Section 12.

11.25 Definitions of the end of trial

The end of the trial is defined as the date of the collection of the last participant's last data item. Long term follow up will continue via the CLL Long-term Follow-up Study.

11.26 Participant Transfer

If a participant is being transferred to a different site, the Participant Transfer form needs to be completed and returned to CTRU.
If the transfer is to another site participating in FLAIR:

- Copies of CRFs, consent form and any other relevant correspondence is sent to the new hospital, with originals kept at the original site. Data from before the date of transfer is questioned with the original site, data after the transfer date is questioned with the new site. Both sites must ensure that the participant transfer is recorded on the participant log in the Investigator Site File and the Pharmacy Site File

If the transfer is not to a site that is participating in FLAIR:

- Any further treatment for CLL received by the participant will be off trial.
- If the participant agrees to be followed up at the new site, it is the responsibility of the original site to gather follow up data from the new site in order to complete the CRFs. The original site will keep all trial documentation and ensure that the participant transfer is recorded on the participant log in the Investigator Site File and the Pharmacy Site File.
- If the participant does not want to be followed up at the new site, a Participant Withdrawal form must be completed by the original site and returned to CTRU.

11.27 Protocol violations

Protocol violations should be reported immediately to the CTRU using the Protocol Violations CRF. Protocol violations that need to be reported include:

- Breaches of the eligibility criteria
- Drug administration errors related to the study drugs
- Non-adherence to the protocol in relation to concomitant therapy or surgery whilst receiving ibrutinib or venetoclax.

If the protocol violation is also associated with an event which meets the criteria of an SAE or SUSAR this should also be reported in accordance with Section 12 of the protocol.

12. PHARMACOVIGILANCE PROCEDURES

12.1 General definitions

12.1.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence in a participant or clinical trial subject administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment and can include;

- any unintentional, unfavourable clinical sign (including an abnormal finding) or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

In addition the following criteria may be used in order to collect protocol-defined *reportable adverse events* which do not meet the criteria for serious (Section 12.1.3):

- requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

12.1.2 Adverse Reaction (ARs)

An adverse reaction is:

- any untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

When determining whether an event is attributable to the trial drug the following guidance should be followed:

- Not related to the study drug: the adverse event is not related to the use of the study drug.
- Possibly related to the study drug: the adverse event might be due to the study drug. Alternative explanations e.g. concomitant medication(s) or concomitant disease(s) are inconclusive and the relationship to time is reasonable; therefore, the causal relationship cannot be excluded.
- Yes, related to the study drug: the adverse event is listed as a possible adverse reaction in the relevant reference safety information and cannot be reasonably explained by an alternative explanation e.g. concomitant medication(s) or concomitant disease(s). The relationship in time is very suggestive of a causal relationship (e.g. it is confirmed by dechallenge and rechallenge).

12.1.3 Serious Adverse Events (SAEs)/Serious Adverse Reactions (SARs)

A Serious Adverse Event (SAE) is defined in general as ‘any untoward medical occurrence or effect that:

- results in death,
- is life-threatening,
- requires or prolongs hospitalisation,
- is significantly or permanently disabling or incapacitating,
- constitutes a congenital anomaly or a birth defect or
- Other important medical event

Medical judgement should be exercised in deciding whether an event is serious (see protocol section 12.5 for Responsibilities). These characteristics must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

Where an SAE is deemed to have been related to an IMP used within the trial the event is termed as a Serious Adverse Reaction (SAR). Any suspected transmission via a medicinal product of an infectious agent is also considered a SAR.

12.1.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the characteristics of being unexpected, the nature and severity of which is not consistent with the information about the medicinal product. The expectedness of an adverse event

will be determined by whether or not it is listed in the reference safety information (RSI) for that product supplied in the Investigator Site File or the latest updated version as instructed by the CTRU.

12.1.5 Adverse Events of Special Interest

These following events will be reported within 24 hours of the research team becoming aware of the event. They should be reported in the same way as SAEs as detailed in Section 12.4 using the relevant CRF.

If the event also meets the criteria and reporting timeframe for an SAE/SUSAR you do not need to report the event separately as an Adverse Event of Special Interest (AEoSI).

All Events of Special Interest will be submitted within 24 hours of the research team becoming aware of the event even if they do not meet the seriousness criteria for an SAE/SUSAR.

AE of special interest	Definition/ Detail
Major Haemorrhage	Defined as any haemorrhagic event that is Grade 3 or greater in severity, or that results in one of the following: o intraocular bleeding causing loss of vision o the need for a transfusion of two or more units of red cells or an equivalent amount of whole blood, hospitalisation o prolongation of hospitalisation.
Intracranial Haemorrhage	Any intracranial haemorrhage adverse event, including subdural hematoma/haemorrhage, epidural hematoma/haemorrhage and intracerebral haemorrhage, of any grade severity, will be captured as an event of special interest as described above. If the participant experiences any ophthalmological adverse event of Grade 2 or greater they should be referred for further ophthalmological examination.
Tumour Lysis Syndrome	As per Howard Criteria in the table below.

Table 10 Howard Criteria for Laboratory and Clinical TLS

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Urate >8.0 mg/dL (475.8 μmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter) in adults or >6.5 mg/dL (2.1 mmol/liter) in children	

Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 μmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hr

* In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.
† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams perdeciliter).
‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 μmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin et al (2007).

12.2 Operational definition and reporting AEs

All adverse events, both related and unrelated to the treatment of CLL, will be collected for all participants and will be evaluated for duration and intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Published: June 14, 2010

AEs will be collected from randomisation until 30 days after the last dose of treatment with FCR, IR, I or I+V.

Information about AEs, whether volunteered by the participant, discovered by the investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the CRF.

All adverse events, regardless of causality, seriousness or severity must be recorded using medical terminology in the participant's medical records. Records should capture the details of the duration and severity of each episode, the action taken with respect to the study drug(s), the Investigator's evaluation of causality and the subject outcome.

12.3 Operational definition – Serious Adverse Events

12.3.1 Events not classed as SAEs

The following events **will not** be recorded as SAEs within this trial:

- Disease progression
- Protocol mandated hopsitalisation for TLS prophylaxis
- Deaths attributable to CLL beyond 30 days of the last administration of the study agent
- **Hospitalisation for:**
  - Routine treatment or monitoring of the studied indication not association with any deterioration in condition.
  - Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition.
  - Admission to hospital or other institution for general care, not associated with any deterioration in condition.
  - Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission.

12.3.2 Expected SAEs

When determining whether an SAE is expected or not, please refer to the version of the reference safety information contained within the SmPC/IB (detailed section 12.1.4) supplied in the Investigator Site File or the latest updated version as instructed by the CTRU.

12.4 Recording and reporting SAEs, SARs and SUSARs

All SAEs / SARs / SUSARs occurring whilst on trial must be recorded on the SAE or SUSAR Form and faxed to the CTRU within 24 hours of the research staff becoming aware of the event. All SAEs / SARs / SUSARs will be collected from the time of randomisation until 30 days post treatment. SARs and SUSARs will be reportable, if the research staff become aware of the event, from the time of randomisation and for the duration of the trial. Once all resulting queries have been resolved, CTRU will request for the original form to be posted to the CTRU and a copy to be retained on site.

For each SAE / SAR / SUSAR, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- seriousness criteria
- action taken
- outcome
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether or not the event would be considered expected or unexpected
- Other medical information deemed relevant by CTRU

Any follow-up information should be faxed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

Fax Number for reporting SAEs and SUSARs:
0113 343 1487

12.5 Responsibilities

Principal Investigator:

1. Checking for SAEs when participants attend for treatment.
2. Medical judgment in assigning to SAEs:
   - Seriousness
   - Causality
   - Expectedness
3. To ensure all SAEs are recorded and reported to the CTRU and to provide further follow up information as soon as available.
4. To report SAEs to local committees in line with local arrangements.
5. To ensure all measures required for adverse event management are recorded in the source documentation

CTRU:

1. Expedited reporting of SUSARs to Competent Authority (MHRA in UK), REC and Sponsor within required timelines.
2. Preparing annual Developmental Safety Update Reports (DSURs) for Competent Authority, REC, Sponsor, AbbVie and Janssen.
3. Notifying Investigators of SUSARs that occur within the trial.
4. To report all SAEs occurring in participants receiving ibrutinib to Janssen.
5. To report all SAEs occurring in participants receiving venetoclax to AbbVie
6. Report all pregnancies in participants receiving ibrutinib, or partners of participants receiving ibrutinib to Janssen.
7. Report all pregnancies in participants receiving venetoclax, or partners of participants receiving venetoclax to AbbVie
8. To supply periodic line listings of SAEs to the Sponsor.

Chief Investigator (or nominated individual in CIs absence):

1. Medical review of all SAEs for seriousness, expectedness and causality.
2. Review and assign code for all SAEs using the MedDRA Body System Organ Class coding, prior to submission of DSURs.
3. Review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and CI / Sponsor review with regards to SUSAR status, local assessment will not be overruled, but CI / Sponsor may add comments prior to expedited reporting.

Janssen:

1. Inform CTRU/Chief Investigator of any new information, which becomes available during the course of the Study, which may affect the overall safety profile of ibrutinib

AbbVie:

1. Inform CTRU/Chief Investigator of any new information, which becomes available during the course of the Study, which may affect the overall safety profile of venetoclax

TSC:

1. In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:

1. In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues which would not be apparent on an individual case basis.
2. In accordance with the Trial Terms of Reference for the DMEC, real time review of any Suspected Unexpected Serious Adverse Reactions (SUSARs) and Serious Adverse Reactions (SARs) which result in death.

12.6 Safety Monitoring Plan

Table 11

Risks associated with trial interventions ☐ **LOW** ≡ Comparable to the risk of standard medical care ☒ **MODERATE** ≡ Somewhat higher than the risk of standard medical care ☐ **HIGH** ≡ Markedly higher than the risk of standard medical care	
Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):* Fludarabine, cyclophosphamide and rituximab will all be given within their licensed indications and FCR is the standard treatment for previously untreated patients with CLL. These drugs all have a well established safety profile and the risks of receiving these treatments within the trial are no higher than that of standard medical care. Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase, a key molecule in B-cell receptor signalling. It is licenced as monotherapy for untreated CLL and for patients that have previously had at least one prior treatment for CLL. In this trial ibrutinib will be administered alongside venetoclax. Venetoclax is an oral inhibitor of B-cell lymphoma-2 (Bcl-2) protein, leading to the programmed cell death of CLL cells. Venetoclax is unlicenced. Tumour lysis syndrome (TLS) has been identified as a significant risk early in the drug development and since the adoption of debulking and dose escalation (as will be used in the trial) this risk appears to have been successfully mitigated. The trial will carefully monitor patients randomised to I+V, particularly around dose escalation.	

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		**How will these risks be minimised?**	
IMP	**Body system/Hazard**	**Activity**	**Frequency**
Fludarabine	Anaemia Thrombocytopenia Neutropenia	Full blood count/assessment for suitability for treatment. Dose reductions and delays to be implemented in accordance with Section 10.8.2	Prior to each cycle of treatment
	Nausea Vomiting Diarrhoea	Participants questioned regarding symptoms during treatment and, where indicated, anti emetics administered as per local policy in accordance with Section 10.2.2	As indicated, per local policy

	Infection	Prophylaxis against pneumocystis carinii pneumonia (PCP) and herpes virus reactivation in accordance with Section 10.5.2	Throughout treatment
	Renal function	Patients with a creatinine clearance <30ml/min are excluded from the trial. Impaired renal function should be managed in accordance with Section 10.6.2	Eligibility assessment and throughout treatment
Cyclophosphamide	Anaemia Thrombocytopenia Neutropenia	Full blood count/assessment for suitability for treatment. Dose reductions and delays to be implemented in accordance with Section 10.6.2	Prior to each cycle of treatment
	Nausea Vomiting	Participants questioned regarding symptoms during treatment and, where indicated, anti-emetics administered as per local policy in accordance with Section 10.2.	As indicated, per local policy
Rituximab	Infusion related reactions	Participants with a lymphocyte count >25 x 10^9/L to have their initial dose split in accordance with Section 10.4. If the lymphocyte count remains >25 x 10^9/L at subsequent cycles the dose may be split at the clinician's discretion.	Prior to each treatment cycle.
		Rituximab to be administered under the supervision of a haematologist or oncologist and infusion rates reduced if infusion reactions occur.	Throughout treatment.
	Anaemia Thrombocytopenia Neutropenia	Full blood count/assessment for suitability for treatment. Dose reductions and delays to be implemented in accordance with Section 10.8.1.	Prior to each cycle of treatment
	Infection	Patients with an active infection or who have a positive serology for hepatitis B or C are excluded from the trial.	Eligibility assessment
Ibrutinib	Hypertension Cardiac	Screening ECHO and monitoring hypertension in accordance with NICE guidelines NG136 (published August 2019) to keep the blood pressure below 140/90mmHg ACE inhibitors not to be used with ibrutinib More details in Section 11.5.1 and statement below	Eligibility assessment Throughout treatment

	Cardiac	Patients with symptomatic cardiac failure not controlled by therapy or unstable angina not adequately controlled by current therapy are excluded from the trial.	Eligibility assessment
	Thrombocytopenia Neutropenia	Full blood count/assessment for suitability for treatment. Dose reductions and delays to be implemented in accordance with Section 10.8.3.	Throughout treatment
	Haemorrhage Bleeding	Patients on concomitant warfarin or equivalent vitamin K inhibitors are excluded from the trial. Participants who require these after starting ibrutinib will be discussed with the CI/CoI beforehand in accordance with Section 10.7.1.3	Eligibility assessment and throughout treatment
		Patients who have had major surgery within 4 weeks prior to randomisation are excluded from the trial. When a patient requires surgery during ibrutinib then the drug will be interrupted around the surgery. It will be stopped at least 7 days prior to the procedure and will only be restarted at least 7 days following the operation in accordance with Section 10.7.2.	Eligibility assessment and throughout treatment.
	Nausea Vomiting Diarrhoea	Participants questioned regarding symptoms during treatment and, where indicated, anti-emetics administered. Dose reductions and delays implemented in accordance with Section 10.8.3.	Throughout treatment
	Drug interactions with CYP3A inhibitors and inducers	Use of CYP3A inhibitors and inducers to be given in accordance with Section 10.7.1.	Throughout treatment
	Compliance with treatment (ibrutinib will be taken by participants at home)	Participants with concurrent diseases or mental disorders that may interfere with their ability to participate in the study are excluded from the trial.	Eligibility assessment
		Participants will be given a diary card to record treatment errors and will return unused capsules at each study visit.	Throughout treatment
		Participants will be given instructions to take home to provide details of how ibrutinib should be taken.	Before the start of treatment

		Participants will be asked to report any dosing errors immediately to their treating hospital.	Throughout treatment
	Infection	PCP prophylaxis is strongly recommended during treatment as per 10.7. Other anti-infective prophylaxis as per standard of care.	Throughout treatment
Venetoclax	Tumour lysis syndrome (TLS)	Tumour burden is assessed before venetoclax, dose escalation, uric acid prophylaxis at least 72 hours prior (if high risk= rasburicase), hospitalisation for 20 and 50mg if high risk, increased oral hydration before first dose and IV hydration for high risk or unable to take oral hydration, monitor electrolytes following initial dose and dose escalation, prompt management of electrolyte disturbances as provided in protocol.	Throughout treatment
	Neutropenia	Guidelines on neutropenia in section 10.8.4. GCSF is permitted.	Throughout treatment
	Thrombocytopenia	Full blood count/assessment for suitability for treatment. Dose reductions and delays to be implemented in accordance with Section 10.8.4.	Throughout treatment
	Infection	PCP prophylaxis is strongly recommended during treatment as per 10.7. Other anti-infective prophylaxis as per standard of care.	Throughout treatment
	Reduced spermatogenesis	Male participants should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility	Before first treatment
	Teratogenicity	Venetoclax should not be administered to pregnant women. Women of child bearing potential must have a negative pregnancy test at baseline and agree to use medically approved contraception (appendix J) until 12 months after rituximab or 30 days after treatment with ibrutinib or venetoclax.	Exclusion criteria and then throughout treatment

		Male participants must agree to use medically approved contraception (appendix J) and refrain from sperm donation from initial study drug administration until 30 days and 90 days, respectively, after the last dose of study drug.	
	Drug interactions with CYP3A inhibitors and inducers, P-gp, BCRP and OATP1B1 substrates	Use of CYP3A inhibitors and inducers, P-gp, BCRP and OATP1B1 substrates to be given in accordance with Section 10.7.1.1	Throughout treatment
	Compliance	As per ibrutinib	Throughout treatment

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. IDMC, independent data review,...)

A Data Monitoring and Ethics Committee (DMEC) will be convened for the trial, who will meet on an annual basis and will review interim unblinded safety information for the trial as agreed by the committee at their initial meeting. Safety information will be reviewed at least 3 monthly intervals for at least the first year of the trial, and at least 6 monthly for the remainder of the trial. This 3 monthly safety review will continue for at least the first year of I+V treatment. The DMEC will also review SUSARs and SARs that result in death in real time. The DMEC will, in light of these reports, have the authority to recommend trial closure to the Trial Steering Committee (TSC) should they have concerns over the safety or ethics of the trial. The TSC have the authority to recommend appropriate action including amendments to or closure of the trial at any time.

Participant data will be entered on to a validated database and monitored for completeness and quality by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. A validation check program will be incorporated into the trial database to verify the data, and discrepancy reports will be generated for resolution by the investigator. Priority validations will be incorporated into the validation programme to ensure that any discrepancies related to participant rights, or the safety of participants, are expedited to sites for resolution.

13. ENDPOINTS

13.1 IR vs. FCR endpoints

13.1.1 Primary endpoint

- Progression-free survival of IR vs. FCR

13.1.2 Secondary endpoints

- Overall survival of IR vs. FCR
- Proportion of participants with undetectable MRD with IR vs. FCR
- Pattern of MRD relapse, retreatment and MRD response over time in participants stopping treatment with IR
- Response to therapy with IR vs. FCR
- Safety and toxicity of IR

- Health related quality of life in IR vs. FCR
- Cost-effectiveness of IR vs. FCR

13.2 I+V vs. I vs. FCR endpoints

13.2.1 Primary endpoints

- Progression-free survival of I+V vs. FCR
- Proportion of participants achieving MRD negativity in I+V vs. I at 2 years

13.2.2 Secondary endpoints

- Progression-free survival of I+V vs. I
- Progression-free survival of I vs. FCR
- Overall survival of I+V vs. FCR, I+V vs. I, and I vs. FCR
- Proportion of participants with undetectable MRD with I+V, I and FCR
- Pattern of MRD relapse, retreatment and MRD response over time in participants stopping treatment with I+V and I
- Response to therapy with I+V vs. FCR, I+V vs. I, and I vs. FCR
- Safety and toxicity of I+V and I
- Health related quality of life in I+V vs. FCR, I+V vs. I, and I vs. FCR
- Cost-effectiveness of I+V vs. FCR, I+V vs. I, and I vs. FCR

13.3 Genetically high risk randomisation endpoints (patients with TP53 abnormalities)

13.3.1 Primary endpoint

- Proportion of participants achieving MRD negativity in I+V vs. I at 2 years

13.3.2 Secondary endpoints

- Progression-free survival of I+V vs. I
- Overall survival of I+V vs I
- Proportion of participants with undetectable MRD negativity in I+V and I
- Response to therapy with I+V vs. I
- Safety and toxicity of I+V and I
- Health-related quality of life in I+V vs. I
- Cost effectiveness of I+V vs I

13.4 Study definitions

- Progression-free survival: Time from randomisation to first documented evidence of disease progression (as defined by IWCLL criteria (Appendix B)) or death from any cause. Participants who do not progress will be censored at the last date they were known to be alive and progression free.
- Overall survival: Time from randomisation to date of death from any cause. Participants not known to have died will be censored at the date they were last known to be alive.
- Minimal residual disease: A negative MRD is defined as the presence of <0.01% CLL cells in the bone marrow (Appendix B). Achievement of MRD negativity is defined as a MRD negative

result at any time over the length of the trial. Analyses will also be conducted based on MRD levels measured in the peripheral blood, although this will not be the measure of primacy. The additional MRD peripheral blood sample in the I+V group will not be included when making comparisons between randomised groups.

- Response: Response criteria are defined by the standard IWCLL criteria (Appendix B). For participants randomised to FCR and IR, response to therapy will be assessed at 3 months post-treatment. For participants randomised to I or I+V, response to therapy will be assessed at 9 months post-randomisation. Response will also be assessed at the end of trial treatment.
- Safety and toxicity: Reported based on adverse events, as graded by CTCAE V5.0, and determined by routine clinical assessments at each centre.
- Quality of life: The EORTC QLQ-C30 and EORTC QLQ-CLL16 will be used to measure participant-assessed QoL prior to randomisation, at 6 months post-randomisation (3 months post-treatment for participants randomised to FCR or IR), and then at 6 monthly visits.
- Cost-effectiveness: The SF-12 and EQ-5D will be used to produce quality adjusted life years (QALYs). NHS resource use and participants' out of pocket expenses will be collected via the Case Record Forms, as well as health economics patient questionnaires. The SF-12 and EQ-5D will be collected prior to randomisation, 6 months post-randomisation (3 months post-treatment for participants randomised to FCR or IR), and then at 6 monthly visits. The health economics questionnaires will be collected at the same time-points up until 2 years post-randomisation. After this point, the health economics questionnaires will be collected annually

14. STATISTICAL CONSIDERATIONS

14.1 Sample size for the 'standard risk' pathway

1524 participants will be randomised to the 'standard risk' pathway of the trial. An additional 64 patients will be randomised to the 'genetically high risk' pathway (refer to Section 14.2 for more details)

771 participants were randomised to FCR and IR in total (stage I and II), and 822 participants are required to be randomised concurrently to FCR, IR/I and I+V (stage II and III).

The total sample size is dependent on when the amendment to include the I and I+V arms opened to recruitment. When stage I completed recruitment, at the end of August 2017, 633 participants were randomised to receive FCR and IR. A further 138 IR and FCR participants were randomised by the end of stage II. Since the trial is designed to randomise participants in a 1:1:1:1 ratio in stage II, 277 participants were randomised across all four arms, leading to 979 participants recruited in total by the end of stage II. At the end of stage II the IR arm ceased recruitment and randomisation has continued in a 1:1:1 ratio to FCR, I and I+V.

In the amended trial, 274 participants are required per arm, which is 822 participants over 3 arms. Of these 274 participants per arm, 69 participants in FCR/I+V and 70 participants in I were randomised in stage II, leaving 205 participants remaining to be randomised to FCR/I+V and 204 participants remaining to be randomised to I in stage III (614 in total).

To summarise:

- 633 participants were randomised in stage I (1:1 to FCR and IR),
- 277 participants were randomised in stage II (1:1:1:1 to FCR, IR, I and I+V), and
- 614 will be randomised in stage III (1:1:1 to FCR, I and I+V)

Table 12 outlines the treatment arms that will be recruiting patients over each stage in the trial. A dotted line indicates that the participants recruited to those arms will be used for more than one comparison.

Table 12: Diagram of trial stages and treatment groups for 'standard risk' pathway

Trial Stage	**I**	**II**	**III**
Approximate time	Q3 2014 - Q2 2017	Once 377 participants have been randomised to each of FCR and IR (stage I and II) (Q3 2017 - Q3 2018)	Once 274 participants have been randomised concurrently to each of FCR, I+V and I (stage II and III) (Q3 2018 – Q2 2020)
Arms to assess IR vs. FCR endpoints (N=771)			
FCR (N=377)	(N=316)	(N=69)	
IR (N=377)	(N=317)	(N=69)	
Arms to assess I+V vs. FCR and I endpoints (N=822)			
FCR (N=274)		(N=69)	(N=205)
I (N = 274)		(N=70)	(N=205)
I+V (N=274)		(N=69)	(N=204)

Sample size required for IR vs. FCR primary endpoint

The primary endpoint will be PFS. The German CLL8 trial[15] showed a median PFS rate of 4.5 years for participants randomised to FCR. To assess a superiority hazard ratio of 0.75 (to a median PFS of 6 years) with an overall 5% significance and 80% power, assuming a 4 year recruitment and 4 year follow-up period, 355 participants are required per arm (710 participants overall). Accounting for a 5% dropout rate, which is based on previous CTRU trials in similar populations, 748 participants are required in order to observe 379 events.

A formal interim analysis on progression free survival will be carried out and reported to the Data Monitoring and Ethics Committee (DMEC) when half of the required number of events (191) have been observed in both FCR and IR arms combined or 109 events have been observed in FCR alone, whichever is earlier. This is in order to allow large differences between the randomisation arms to be reported early.

The O'Brien and Fleming alpha-spending function [16] will be used to adjust for multiple testing in order to conserve the overall type I error, which recommends that the interim results are compared to a p-value of 0.005, and the final results are then compared to a p-value of 0.048. In order to account for the interim analysis, the O'Brien and Fleming method recommends increasing the maximum required sample size and number of events by a factor of 1.008. Therefore **754 participants will be recruited to the IR vs. FCR comparison and 382 events are required.**

Sample size required for I+V and I-related primary endpoints

<u>PFS of I+V vs. FCR</u>

To assess a superiority hazard ratio of 0.69 (for a median PFS increase of 4.5 to 6.5 years) with an overall 5% significance and 80% power, assuming a 2.5 year recruitment period and 3.5 years of follow-up, 260 participants are required per arm. Allowing for a 5% dropout rate, 274 participants are required to be concurrently randomised to each of FCR and I+V in order to observe 232 events. 822 participants are therefore required to be concurrently randomised to FCR, I and I+V.
Note that the clinically relevant effect size is larger than it was for the IR vs. FCR comparison (HR=0.75). This is due to evidence published in the New England Journal of Medicine comparing I with chlorambucil[17] , demonstrating that ibrutinib monotherapy leads to a very good PFS (90% at 18 months) and overall survival (98% at 2 years), and a clinically relevant improvement with I+V would be better than that with I alone, or equally effective with a much shorter duration of therapy. In addition, there is evidence emerging that this magnitude of difference is more than realistic given the synergy seen between venetoclax and other therapies in vivo, including with monoclonal antibodies (rituximab and obinutuzumab) and with chemotherapy (bendamustine+rituximab) and that there is emerging in vitro evidence for synergy between I and V. A similar trial assessing IR vs. FCR in the same population currently being run in the US (ECOG1912) has powered for a much larger difference, assessing a HR of 0.67. Given the exceptional activity of I and the synergy expected between I and V, powering for a hazard ratio of 0.69 compared to FCR is desirable to ensure that the trial is not over-powered.

A formal interim analysis on progression free survival will be carried out and reported to the DMEC when half the required number of events (116) have been observed in FCR and I+V participants combined or 69 events have been observed in FCR alone, whichever is earlier. This is in order to allow large differences between the randomisation arms to be reported early. The O'Brien and Fleming alpha-spending function will be used to adjust for multiple-testing due to the planned interim analysis, which recommends that the interim results are compared to a p-value of 0.005, and the final results are then compared to a p-value of 0.048.

MRD negativity in I+V vs I

At the time of implementation, the MRD levels in the I comparator arm were not known, so in order to assess the adequacy of the proposed sample size a range of power calculations have been carried out. In the I alone arm, the MRD negativity rate is likely to be low (less than 10%). With 260 patients in each of the arms, and a 5% two-sided significance level, there is 90% power to detect an improvement from 10% to 20% in I+V (OR=2.3). If the MRD negativity rate is only 5% with I alone, there is 90% power to detect an improvement to 13% in I+V (OR=2.9). A large increase in MRD negativity would be required in order to justify the use of V, and therefore the planned number of patients is more than adequate to answer this question.

A formal interim analysis will be carried out on the co-primary efficacy endpoint of the proportion of participants who are MRD negative at any time up to 2 years post-randomisation in the comparison of I+V vs. I. The interim analysis will occur 2 years after the 274th participant was randomised and will include the first 274 randomised participants only.

To account for multiple testing and conserve the overall type I error, the O'Brien and Fleming alpha spending function will be used. This recommends that the interim results are compared to a p-value of 0.005, and the final results are then compared to a p-value of 0.048.

Multiple comparisons

Adjustment for multiple primary outcomes is not required despite I+V being compared to both FCR and I. In order for I+V to be considered superior, it needs to be significantly better than both of the control groups, and for this reason there is no inflation of the type I error rate.

14.2 Sample size for 'genetically high risk' pathway

MRD negativity in I+V and I participants with TP53 abnormalities.

Genetically high risk participants with TP53 abnormalities will be included in a separate randomisation (1:1, I or I+V). It is reported that 7-10% of front-line patients have a TP53 abnormality. In addition, the eligibility criteria can be relaxed for the genetically high risk randomisation as patients will not need to be fit for FCR and therefore older or less fit patients could be included, increasing the numbers expected. If we estimate that 64 participants will be randomised, this would generate a large sample of important data for this rare group of genetically high risk, poor prognosis participants .

MRD is chosen as the primary endpoint since it is MRD negativity that drives the stopping algorithm and is the key advantage of the addition of V, and this is also the primary endpoint currently for the I vs I+V randomisation in the main trial. In the MD Anderson trial[11] based on 2 year follow-up, 15 participants who were treatment naïve high risk (17p del or TP53 mutated) received ibrutinib, and none of these became MRD negative. Therefore, MRD negative rates at 2 years with I alone are expected to be very low. It is unlikely that the MRD negativity rate will exceed 5%. To assess an improvement in MRD negativity at 2 years using a two-sided alpha of 5% with 80% power based on a two-group chi-squared test of equal proportions:

N=60 would detect an improvement from 5% to 33% (OR=9.4)

If MRD with I alone is only 2%, to assess an improvement in MRD negativity at 2 years using a two-sided alpha of 5% with 80% power based on a two-group chi-squared test of equal proportions, N=60 would detect an improvement to 27% (OR=18).

The CLARITY Trial, assessing I+V on 54 participants with relapsed/refractory CLL, presented early results at ASH 2017[12]. 20% of the participants were 17p deleted. The trial showed MRD negativity at just 6 months after combined I+V in 37% in peripheral blood and 32% in bone marrow. These rates were similar in 17p deleted participants (4/7 in PB and 2/7 in BM). Therefore the rate of MRD negativity in newly diagnosed patients at 2 years is anticipated to be higher than this. The level of difference that is anticipated with the numbers available and 80% power is realistic given the expectation of MRD negativity with the addition of venetoclax, and also is reasonable to assess in a rare group.

Assuming a 5% loss to follow-up rate, 64 participants are required (32 per arm) to assess these differences..

14.3 Planned recruitment rate

In order to recruit 754 participants to the original IR vs. FCR comparison, the recruitment target is 7 patients per month for the first 6 months whilst centres are opening to recruitment and 17 patients per month thereafter.

Following the addition of the I+V and I arms to the 'standard risk' pathway, the number of centres increased, with an anticipated recruitment rate of approximately 30 patients a month in order to complete recruitment within approximately 2.5 years of the I+V and I arms opening.

It is anticipated that, once all sites are open following the protocol amendment, that approximately 5 patients per month will be randomised to the 'genetically high risk' pathway.

14.4 Quality of Life

Participants who are willing and able to read and complete the quality of life questionnaires will be asked to complete the EORTC QLQ-C30 and CLL specific module, EORTC QLQ-CLL16, at baseline, at the end of FCR or R treatment (for those randomised to FCR or IR), at 6 months post-randomisation (for those randomised to I or I+V), and then 6 monthly starting from 12 months post-randomisation until one year after 6 years of treatment have been received, or until disease progression requiring treatment, whichever is earliest.

The EORTC QLQ-C30 is a multi-dimensional tool for cancer patients which addresses aspects of patients' functioning and symptoms as well as their overall quality of life. The EORTC QLQ-CLL16 is approaching the final stage of its development, and aims to specifically address the health-related quality of life of CLL patients.

14.5 Health Economics

The objectives of the economic analyses are to assess:

- The cost-effectiveness of IR compared to FCR
- The cost-effectiveness of I+V compared to both FCR and I
- The cost-effectiveness of I compared to FCR
- The cost-effectiveness of I compared with I+V in participants with TP53 abnormalities (TP53 deletion and TP53 mutation)

The focus of the economic evaluations will be the development of decision analytic cost effectiveness models. The economic models will identify the incremental cost-effectiveness ratios. The exact structure of the cost-effectiveness models will be established in discussions with the clinicians on the study team. It is likely that the models will be Markov or semi-Markov state models. Where possible the transition rates for the models will be estimated from the data from the RCT. For model parameters for which data could not be collected within the study, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature (Weinstein et al 2003).

As economic evaluations are designed to inform resource allocation decisions, the models will use quality adjusted life years (QALYs) outcome measures. The estimation of QALYs requires the production of utility weights for health states, the EQ-5D and SF12 will be used for this purpose. NHS resource use associated with each treatment modality will be collected from hospital records. Data of use of community based health and social care (for example, home help or residential care) will be collected using a patient self questionnaire at six monthly intervals. The patient questionnaire will be designed to allow tick-box completion where ever possible.

Unit costs for health and social service resources will be obtained from national sources such as the PSSRU, the BNF and NHS Reference Cost database. Where national costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimates in the analysis.

In line with recommended best practice, the models will adopt the perspective of the UK NHS and Personal Social Services budget. The time horizon of the analysis will be lifetime. There remains some uncertainty regarding the correct approach to discounting costs and benefits. The analysis will follow the recommendations current at the time. Under current recommendations this would mean that costs and outcomes would be discounted at 3.5% per annum [Brouwer et al 2005; Claxton et al 2006).

The non-parametric bootstrap method will be used to produce stochastic sensitivity analyses of the incremental cost effectiveness ratios. In addition to presenting the expected incremental cost effectiveness ratios, we will present the scatterplots on the cost effectiveness plane, the 95% cost effectiveness ellipses and the cost effectiveness acceptability curves (Drummond et al 2005).

15. STATISTICAL ANALYSIS

15.1 General considerations

Statistical analysis is the responsibility of the CTRU Statisticians. The analysis plan outlined in this section will be reviewed and separate final statistical analysis plans for the IR vs. FCR comparison, I+V vs. I and FCR comparisions and 'I vs. I+V TP53 deleted/TP53 mutated comparison will be written before any analysis is undertaken. The final and any interim analysis plans will be written in accordance with current CTRU Standard Operating Procedures and will be finalised and agreed by the following people (where appropriate): Trial Statistician, CTRU Scientific Lead/Supervising Statistician, Chief Investigator, Head of Trial Management, Senior Trial Manager and Senior Data Manager. Any changes to the finalised analysis plans, and reasons for changes, will be documented.
All analyses will be conducted on the intention-to-treat (ITT) population (as defined further in the statistical analysis plans), where participants will be included according to the treatment they were randomised to. A per-protocol analysis, where participants will be included according to the treatment they received, will be considered for the primary endpoints if there are a considerable number of protocol violators. The safety population will consist of all participants who receive at least one dose of trial treatment.

An overall two-sided 5% significance level will be used for efficacy endpoint comparisons. For the primary endpoints, these will be adjusted to account for the planned interim analyses as described in Section 14.1.

The impact of the Covid-19 pandemic on trial conduct, treatment compliance and treatment effect estimates will be described in an addendum to the trial statistical analysis plans.

15.2 Frequency of analyses

Interim reports for all trial arms will be presented to the DMEC in strict confidence at approximately yearly intervals whilst patients are receiving trial treatment. Summaries will be presented for the IR vs. FCR, I+V vs. I and FCR, and I+V vs. I (in TP53 deleted/TP53 mutated participants) comparisons separately with only concurrently randomised participants being compared. The DMEC, in the light of the interim reports and of any advice or evidence they wish to request, will if necessary report to the Trial Steering Committee if there are concerns regarding the safety of the trial treatment.

IR vs. FCR analyses

A formal interim analysis on the primary efficacy endpoint of progression-free survival of IR vs. FCR, will be carried out when either half the required number of events have been observed i.e. when 191 events have been observed in the FCR and IR arms over stages I-II combined, or when 109 events are recorded in FCR alone, whichever occurs first. The latter is based on the number of number of events expected in FCR based on the planned clinically relevant difference, and an earlier analysis will be triggered if there are fewer events in IR than expected. This is in order not to delay the analysis should the IR PFS rate be better than anticipated. The outcome will be compared to a p-value of 0.005. This is likely to take place after recruitment into the IR vs. FCR comparison has completed.

The final analysis of IR vs. FCR in terms of PFS will be carried out when either 382 events have been observed in these arms in patients recruited over stages I-II and there is sufficient follow-up, or when 218 events are recorded in FCR alone, whichever occurs first. This is anticipated to be 4 years after the final participant has been randomised to the IR vs. FCR comparison. Secondary endpoints for comparisons including FCR and IR will be analysed at this point, and the PFS, OS and MRD relapse analyses will subsequently be updated as per a separate publication policy document, subject to funding. This is likely to take place after recruitment into all additional trial arms have completed, so it will not impact on the continuation of the trial.

I+V vs. FCR and I+V vs. I analyses

A formal interim analysis on the I+V vs. FCR co-primary efficacy endpoint of progression-free survival will be carried out when half the required number of events have been observed i.e. when 116 events have been observed in the concurrent FCR and I+V arms combined or 69 events have been observed in FCR, whichever is earlier. The outcome will be compared to a p-value of 0.005. This interim analysis is in order to allow large differences between I+V and FCR to be reported early. This is likely to take place after recruitment has completed.

Final analysis of I+V vs. FCR in terms of PFS will be carried out when at least 232 events have been observed in these arms over stages II and III, or 137 events have been observed in FCR, whichever is earlier, and there is sufficient follow-up. This is anticipated to be 3.5 years after the close of recruitment.

A formal interim analysis will be carried out on the co-primary efficacy endpoint of the proportion of participants who are MRD negative at any time up to 2 years of post-randomisation in the comparison of I+V vs. I. The interim analysis will occur 2 years after the 274th participant was

randomised and will include the first 274 randomised participants only. This analysis will not include any PFS or OS data to preserve co-primary endpoint of PFS in FCR vs. I+V. The outcome will be compared to a p-value of 0.005.

The final analysis of MRD negativity will be initially carried out at 2 years after the close of recruitment to the standard risk pathway. The outcome will be compared to a p-value of 0.048. Short term secondary endpoints for comparisons including I+V and I will also be analysed at this point. The MRD negativity analysis will be updated at the time of the final analysis on PFS, since participants can become MRD negative at any time during the course of their treatment.
The long-term endpoints relating to PFS, OS and MRD relapse and re-treatment will be analysed at the time of the final analysis on PFS and as outlined in a separate publication policy document.

I vs. I+V in participants with TP53 abnormalities analyses

The analysis of MRD negativity will be initially carried out at 2 years after the close of recruitment to this genetically high risk pathway.. Short term secondary endpoints for comparisons including I+V and I will also be analysed at this point. The MRD negativity analysis will be updated annually, since participants can become MRD negative at any time during the course of their treatment.

The long term endpoints relating to PFS, OS and MRD relapse and re-treatment will be analysed at the time of the final analysis on PFS for the main trial and updated as per a separate publication policy document.

15.3 Analyses of IR vs. FCR endpoints

All analyses of endpoints relating to the original trial arms will be based on the 754 participants specified in the original sample size, concurrently randomised during stages I-II.

15.3.1 Primary endpoint analyses

The analysis of the primary endpoint will be based on the ITT population. An analysis based on the per-protocol population will also be carried out if there are a substantial number of protocol deviators, to assess the sensitivity of the outcomes.

- **Progression-free survival (PFS) of IR vs. FCR**

An interim analysis on PFS will be carried out when 191 events have been observed in the FCR and IR arms for participants randomised to stages I and II, or 109 events have been observed in FCR alone, whichever is earlier. The final analysis on PFS will be assessed once 382 events have been observed in the FCR and IR arms for participants randomised to stages I and II (i.e. 382 participants have progressed/died out of the 754 recruited participants), or 218 events have been observed in FCR alone, whichever is earlier. Participants not having progressed or died at the time of the analysis will be censored at the last date they were known to be alive and progression-free. Cox's regression analysis will be used to analyse the PFS accounting for the trial stage and minimisation factors, excluding centre, and Kaplan-Meier curves will be presented. The assumptions of the model will be checked, and if the hazards are found to be non-proportional alternative analysis methods will be used.

15.3.2 Secondary endpoint analyses

- **Overall survival (OS) of IR vs. FCR**

Cox's regression analysis will be used to analyse overall survival accounting for the trial stage and minimisation factors, excluding centre, and Kaplan-Meier curves will be presented. Participants not known to have died at the time of the analysis will be censored at the last date they were known to be alive.

- **Proportion of participants with undetectable minimal residual disease (MRD) with IR vs. FCR**

The proportion of participants who are MRD negative in the bone marrow at any time during the trialwill be summarised by treatment arm. In addition, the proportion of participants who are MRD negative in the peripheral blood at 3 months post-treatment and then at any later time during the trial will be summarised by timepoint, treatment group and overall.

The time to participants becoming MRD negative in the IR arm will be summarised, and a Kaplain-Meier curve presented.

- **Pattern of MRD relapse, re-treatment and MRD response over time in participants stopping treatment with IR**

Participants randomised to IR who have an MRD negative result in the peripheral blood at any timepoint between 12 and 30 months post-randomisation will be eligible to stop treatment with ibrutinib prior to the 6 years post-randomisation timepoint if they confirm MRD negativity in the bone marrow. The proportion of participants who confirm MRD negativity in the bone marrow and subsequently stop treatment due to reaching the MRD stopping rule criteria will be summarised. Time to MRD negativity will be summarised and Kaplan-Meier curves presented. In addition, MRD negativity will be summarised by timepoint.

Time to MRD relapse for participants who stop treatment based on MRD negativity and then go on to relapse at the MRD level will be assessed using a median survival estimate and a Kaplan-Meier curve. The proportion of participants who reach the MRD stopping rules who then go on to relapse at the MRD level will be summarised by timepoint.

The proportion of participants who re-achieve MRD negativity in the peripheral blood following retreatment with ibrutinib for MRD relapse will be summarised.

- **Response to therapy with IR vs. FCR**

The proportion of participants with each class of response as defined by the IWCLL criteria at 3 months post-treatment with FCR or R and at the end of therapy with ibrutinib, will be summarised by treatment group and overall. The proportion of participants achieving a Complete Response (CR+CRi) and an Overall Response (at least a PR) at any time during the trial will be summarised by treatment arm and overall. Treatment arms will be compared using a binary logistic regression model, adjusted for the trial stage and minimisation factors excluding centre.

- **Safety and toxicity of IR vs. FCR**

Safety analyses will summarise the AR, SAE, SAR and SUSAR rates per participant, by treatment received and overall. Suspected relationship to the protocol treatment will be presented along with other causality, outcome and event duration. ARs will be presented by CTCAE toxicity grade (V5.0) Individual AR/SAE line listings will be reported by treatment arm and MedDRA System Organ class (where applicable). Treatment related mortality rates will be presented by treatment received.

- **Health related quality of life of IR vs. FCR**

Mean Quality of Life (QoL) scores and 95% CIs adjusted for the baseline score will be calculated for all domains of the EORTC QLQ-C30 and CLL specific module, EORTC QLQ-CLL16, for each treatment group and at each assessment time-point and overall.

- **Cost-effectiveness of IR vs. FCR**

A cost-effectiveness analysis will be carried out by a designated Health Economist at the University of Leeds. Further details are provided in Section 14.4 and a separate analysis plan will be written before the analysis is performed.

15.4 Analyses of I+V vs I and FCR endpoints, or I+V vs I endpoints in 'genetically high risk' randomisation

All analyses of endpoints relating to the I+V, I and FCR trial arms will be based on the 822 standard risk participants concurrently randomised during stages II-III.

All analyses relating to the I+V and I trial arms for the TP53 abnormalities endpoints will be based on the 'genetically high risk' participants included in that randomisation.

15.4.1 Primary endpoint analyses

For both primary endpoints, the analyses will be based on the ITT population. An analysis based on the per-protocol population will also be carried out if there are a substantial number of protocol deviators to assess the sensitivity of the outcomes.

- **Progression-free survival (PFS) of I+V vs. FCR**

An interim analysis on PFS will be carried out when 116 events have been observed in the FCR and I+V arms for participants randomised concurrently during stages II and III, or 69 events have been observed in FCR alone, whichever is earlier. The final analysis on PFS will be assessed once 232 events have been observed in the FCR and I+V arms recruited concurrently during stages II-III, or 137 events have been observed in FCR alone, whichever is earlier. This is anticipated to be approximately 3.5 years after the final participant has been randomised. Participants not having progressed or died at the time of the analysis will be censored at the last date they were known to be alive and progression-free. Cox's regression analysis will be used to analyse the PFS adjusting for the minimisation factors and trial stage, excluding centre, and Kaplan-Meier curves will be presented. The assumptions of the model will be checked, and if the hazards are found to be non-proportional alternative analysis methods will be used.

- **Proportion of participants with undetectable minimal residual disease (MRD) in I+V vs. I, and I vs. I+V in participants with TP53 abnormalities**

An interim analysis on MRD negativity will be carried out 2 years after the 274th participant was randomised and will include the first 274 randomised participants only.

For the standard risk pathway final analysis and the genetically high risk pathway, the proportion of concurrently randomised participants who are MRD negative in the bone marrow at any time during the trial will be summarised by treatment arm and compared using a binary logistic regression model adjusted for the minimisation factors and trial stage, excluding centre. The analysis will initially be carried out at 2 years after the close of the appropriate randomisation. In addition, the proportion of participants who are MRD negative in the peripheral blood at 9 months post-randomisation and then at any later time during the trial will be summarised by timepoint, treatment group and overall. The additional MRD peripheral blood sample in the I+V group at 6 months will not be included when making comparisons between randomised groups.

Time to MRD negativity in participants who become MRD negative in the bone marrow at any time during the trial, will be summarised and Kaplan-Meier curves will be presented.

15.4.2 Secondary endpoint analyses

- **Progression-free survival (PFS) of I+V vs. I, and I+V vs. I in participants with TP53 abnormalities**

Cox's regression analysis will be used to analyse PFS of I vs. I+V in patients randomised concurrently, adjusting for the minimisation factors and trial stage, excluding centre, and Kaplan-Meier curves will be presented. The results of this comparison will be confounded by the MRD stopping rule, since participants receive differing amounts of treatment depending on their MRD response, and therefore this analysis will be interpreted with caution.

- **Progression-free survival (PFS) of I vs. FCR**

Cox's regression analysis will be used to analyse PFS of I vs. FCR in patients randomised concurrently, accounting for the minimisation factors and trial stage, excluding centre, and Kaplan-Meier curves will be presented.

- **Overall survival (OS) of I+V vs. FCR, I+V vs. I I vs. FCR, and I+V vs. I in participants with TP53 abnormalities**

Cox's regression analysis will be used to analyse overall survival in patients randomised concurrently accounting for the minimisation factors and trial stage, excluding centre, and Kaplan-Meier curves will be presented.

- **Pattern of MRD relapse, re-treatment and MRD response over time in participants stopping treatment with I+V and I, and I+V vs. I in participants with TP53 abnormalities**

Participants who have an MRD negative result in the peripheral blood at any timepoint between 12 and 30 months post-randomisation will be eligible to stop treatment prior to the 6 years post-randomisation timepoint if they confirm MRD negativity in the bone marrow. The proportion of participants who confirm MRD negativity in the bone marrow and subsequently stop treatment due to reaching the MRD negative stopping rule criteria will be summarised and compared for each treatment group using a binary logistic regression model adjusted for the minimisation factors and trial, stage, excluding centre. In addition, time to MRD negativity will be summarised and Kaplan-Meier curves presented.

Time to MRD relapse for participants who stop treatment based on MRD negativity and then go on to relapse at the MRD level will be assessed using Kaplan-Meier curves presented by treatment group. The proportion of participants who reach the MRD stopping rules who then go on to relapse at the MRD level will be summarised by treatment group and overall.

The proportion of participants who re-achieve MRD negativity in the peripheral blood following re-treatment with I of I+V for MRD relapse will be summarised by treatment group and overall.

- **Response to therapy with I+V vs. FCR, I+V vs. I, I vs. FCR and I+V vs. I in participants with TP53 abnormalities**

For each comparison, the best response for each participant at either 3 months post-treatment with FCR, 9 months post randomisation (for participants randomised to I or I+V) or the end of treatment (for I or I+V) will be summarised by treatment group and overall. The proportion of participants achieving a Complete Response (CR+CRi) and an Overall Response (at least a PR) at any stage during the trial will be summarised by treatment arm and overall and treatment arms will be compared

using a binary logistic regression model, adjusted for the minimisation factors and stage, excluding centre.

- **Safety and toxicity**

Safety analyses will summarise the AR, SAE, SAR and SUSAR rates per participant, by treatment received and overall for all participants randomised to stages II and III. Suspected relationship to the protocol treatment will be presented along with other causality, outcome and event duration. ARs will be presented by CTCAE toxicity grade (V5.0) Individual AR/SAE line listings will be reported by treatment arm and MedDRA System Organ class (where applicable). Treatment related mortality rates will be presented by treatment received.

- **Health related quality of life of I+V vs. FCR, I+V vs. I, I vs. FCR (if appropriate) and I+V vs. I in participants with TP53 abnormalities**

For each comparison, mean Quality of Life (QoL) scores and 95% CIs adjusted for the baseline score will be calculated for all domains of the EORTC QLQ-C30 and CLL specific module, EORTC QLQ-CLL16 for each treatment group and at each assessment time-point and overall.

- **Cost-effectiveness of I+V vs. FCR, I+V vs. I and I vs. FCR and I+V vs. I in participants with TP53 abnormalities**

A cost-effectiveness analysis will be carried out by a designated Health Economist at the University of Leeds. Further details are provided in Section 14.4 and a separate analysis plan will be written before the analysis is performed.

15.5 Subgroup and exploratory analyses for standard risk participants only

Exploratory analyses will be carried out, comparing the primary and key endpoints in those participants who have been randomised concurrently, to assess the heterogeneity of the treatment effect amongst different subgroups of interest. These analyses will be dependent on the number of participants observed with each event of interest. The following subgroups will be assessed if appropriate:

- Stratification factors:
  - Gender: Males, females
  - Age: <65, ≥65
  - Binet stage: Progressive A, B or C

- IGVH mutation status:
  - Stereotyped B-cell receptor subset 2 (BCR subset 2) cases
  - VH unmutated, (excluding BCR subset 2)VH mutated (excluding BCR subset 2)
- Genetic analysis:
  - NOTCH-1
  - SF3B1
  - 11q
  - 13q
  - Trisomy 12
  - CD38
  - CD49d

Subgroup analyses may, by chance, generate false positive or negative results. Those carried out will be interpreted with caution and treated as hypothesis generating.

16. DATA MONITORING

16.1 Data Monitoring and Ethics Committee

An independent Data Monitoring and Ethics Committee (DMEC) will review the safety and ethics of the study.

Detailed unblinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals and the committee will be required to review the formal interim analysis reports when half the required number of events have been observed (Section 15.2). The DMEC will also review cumulative unblinded safety data along with individual SAE/SAR listings every 3 months for at least the first year. The subsequent frequency of review will be determined by the committee members.

Suspected Unexpected Serious Adverse Reactions (SUSARs) and Serious Adverse Reactions (SARs) which result in death will be reviewed at least 3-monthly by the DMEC (and reviewed in real-time by the Chief Investigator).

16.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to participant notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports. Remote monitoring methods (including virtual/telephone review of source data) may be used to verify source data and will approved by CTRU.

16.3 Clinical governance issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

17. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

17.1 Quality assurance

The trial will be conducted in accordance with the principles of Good Clinical Practice in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (*and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland),* and through adherence to CTRU Standard Operating Procedures (SOPs).

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP of the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a potential serious breach (as defined by Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. A "serious breach" is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial.

For further information, the Investigator should contact the Senior Trial Manager at the CTRU.

17.2 Ethical considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 2000. Informed written consent will be obtained from the participants prior to registration into the trial. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The trial will be submitted to and approved by a Research Ethics Committee (REC) and the appropriate local R&D department for each participating centre prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

18. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth, postcode, NHS ID, hospital ID
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- participant name will be collected on the consent form when a participant is randomised into the trial, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU

If a participant withdraws consent from further trial treatment and / or further collection of data, their data and samples will remain on file and will be included in the final study analysis.

The trial staff at the participating site will be responsible for ensuring that any data / documentation sent to the CTRU is appropriately anonymised as per instructions given by CTRU in accordance with the trial procedures to conform with the 2018 Data Protection Act.

19. ARCHIVING

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility

and site data and documents will be archived at the participating centres. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. If a participant withdraws consent for their data to be used, it will be confidentially destroyed.

20. STATEMENT OF INDEMNITY

This trial is sponsored by The University of Leeds and The University of Leeds will be liable for negligent harm caused by the design of the trial. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to participants under this duty of care.

This is a clinician-led study, involving the use of an unlicensed drug. The University of Leeds does, under certain circumstances, provide indemnity for patient harm where no fault can be attributed. In addition usual product liability will be covered by the manufacturer under the Consumer Protection Act 1987.

21. STUDY ORGANISATIONAL STRUCTURE

21.1 Responsibilities

Chief Investigator - The Chief Investigator will have responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial in accordance with relevant GCP standards and CTRU SOPs.

UK CLL Biobank – The UK CLL Biobank will have responsibility for providing collection kits for Biobank samples and for processing and storing Biobank samples.

Janssen – Janssen will have responsibility for the investigational medicinal product supply.

AbbVie - AbbVie will have responsibility for the investigational medicinal product supply

21.2 Operational structure

Chief Investigator – The Chief Investigator is involved in the design, conduct, co-ordination and management of the trial

Trial Management Group - The TMG, comprising the Chief Investigator, CTRU team and co-investigators will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the REC and supporting applications for HRA Approval, (iv) submitting a CTA, and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) appointing and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Clinical Trials Research Unit - The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support REC, HRA Approval local R&D submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

Trial Steering Committee – The Trial Steering Committee, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair and not less than two other independent members. The Chief Investigator and other members of the TMG will attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC): The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet or communicate via teleconference approximately annually as well as reviewing unblinded safety data every 3 months (for at least the first year). The subsequent frequency of review will be determined by the committee

members. After each annual review, the DMEC will make their recommendations to the TSC about the continuation of the trial.

22. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to ICMJE Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigator. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

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APPENDIX A – PERFORMANCE STATUS SCALE

Activity performance description	Score
Fully active, able to carry out all normal activity without restriction.	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e. g. light house work, office work.	**1**
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	**2**
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	**3**
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	**4**

APPENDIX B – iwCLL RESPONSE CRITERIA

Definition of response, relapse, and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and marrow (Tables 3,4).

5.1. Complete remission (CR)

CR requires all of the following criteria as assessed at least 2 months after completion of therapy:

5.1.1. Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/µL). In clinical trials, the presence of minimal residual disease (MRD) after therapy should be assessed (see section 5.9). The sensitivity of the method used to evaluate for MRD should be reported.

5.1.2. Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.

5.1.3. No hepatomegaly or splenomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.

5.1.4. Absence of constitutional symptoms.

5.1.5. Blood counts above the following values: *5.1.5.1. Neutrophils more than 1.5 x 10^9/L (1500/µL) without need for exogenous growth factors.*

5.1.5.2. Platelets more than 100 x 10^9/L (100 000/µL) without need for exogenous growth factors.

5.1.5.3. Haemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.

5.1.6. For patients in clinical trials (Table 3), a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed in sections 5.1.1 through 5.1.5 demonstrate that a CR has been achieved.

Table 3. Recommendations regarding the response assessment in CLL patients

Diagnostic test	Section of guidelines	General practice	Clinical trial
History, physical examination	5.1.2, 5.1.3, 5.1.4, 5.2.2, 5.2.3, 5.3.1, 5.3.2	Always	Always
CBC and differential count	5.1.1, 5.1.5, 5.2.4, 5.3.3, 5.3.5	Always	Always
Marrow aspirate and biopsy	5.1.6	At cytopenia of uncertain cause	At CR or cytopenia of uncertain cause
Assessment for minimal residual disease	5.9	NGI	Desirable
Ultrasound of the abdomen*	5.1.2, 5.1.3, 5.2.2, 5.2.3, 5.3.1, 5.3.2	Possible, if previously abnormal	NGI
CT scans of chest, pelvis, and abdomen	5.1.2, 5.1.3, 5.2.2, 5.2.3, 5.3.1, 5.3.2	NGI	Recommended if previously abnormal and otherwise with a CR

General practice is defined as the use of accepted treatment options for a patient with CLL who is not enrolled in a clinical trial.
NGI indicates not generally indicated.
* Used in some countries to monitor lymphadenopathy and organomegaly.

To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.
In some cases, lymphoid nodules can be found, which often reflect residual disease.[55,56] These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician.
In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry (see section 5.9) or by immunohistochemistry (IHC).
5.1.7. A controversial issue is how best to categorize the response of patients who fulfill all the criteria for a CR (including the marrow examinations described in section 5.16) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity. We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (see section 5.1.6) should be performed with scrutiny and not show any clonal infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual disease or with noncytopenic CR.

5.2. Partial remission (PR)
PR is defined by the criteria described in sections 5.2.1, 5.2.2, or 5.2.3 (if abnormal before therapy), as well as one or more of the features listed in section 5.2.4. To define a PR, these parameters need to be documented for a minimal duration of 2 months (Table 4). Constitutional symptoms persisting for more than 1 month should be recorded.

Table 4. Response definition after treatment for patients with CLL, using the parameters of Tables 1 and 3

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Increase ≥50%
Splenomegaly	None	Decrease ≥50%	Increase ≥50%
Blood lymphocytes	< 4000/µL	Decrease ≥50% from baseline	Increase ≥50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			

Platelet count	> 100 000/µL	> 100 000/µL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Haemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/µL	> 1500/µL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

* CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡These parameters are irrelevant for some response categories.

5.2.1. A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.

5.2.2. Reduction in lymphadenopathy (by CT scans in clinical trials[57] or by palpation in general practice) as defined by the following: *5.2.2.1. A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.*

5.2.2.2. No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.

5.2.3. A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (in clinical trials) or palpation (in general practice).

5.2.4. The blood count should show one of the following results: *5.2.4.1. Neutrophils more than 1.5 x 10^9/L (1500/µL) without need for exogenous growth factors.*

5.2.4.2. Platelet counts greater than 100 x 10^9/L (100 000/µL) or 50% improvement over baseline without need for exogenous growth factors.

5.2.4.3. Haemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

PLEASE NOTE: FOR THE PURPOSES OF THIS TRIAL AN ADDITIONAL RESPONSE DEFINITION 'PARTIAL REMISSION WITH LYMPHOCYTOSIS' HAS BEEN ADDED IN SECTION 5.10 OF THIS APPENDIX.

5.3. Progressive disease

Progressive disease during or after therapy is characterized by at least one of the following:

5.3.1. Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse.[58] Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed:

Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates.

An increase by 50% or more in greatest determined diameter of any previous site.

5.3.2. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
5.3.3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes per microliter.
5.3.4. Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
5.3.5. Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) attributable to CLL.
5.3.5.1. During therapy. Cytopenias may occur as a side effect of many therapies and should be assessed according to Table 5. During therapy, cytopenias cannot be used to define disease progression. Each protocol should define the amount of drug(s) to be administered with such cytopenias.

Table 5. Grading scale for haematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/µL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

* Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.
†Platelet counts must be below normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 10^9/L (20 000/µL), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20 x 10^9/L [20 000/µL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches < 1 x 10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/µL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

5.3.5.2. After treatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100 000/µL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

5.4. Stable disease

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

5.5. Treatment failure

Responses that should be considered clinically beneficial include CR and PR; all others (eg, stable disease, nonresponse, progressive disease, or death from any cause) should be rated as a treatment failure.

5.6. Time to progression, progression-free survival, and overall survival

Time to progression (TTP) is defined as the time from study entry until objective disease progression (see section 5.3). Progression-free survival (PFS) is defined as the time from study entry until objective disease progression or death. Overall survival is defined as the time from study entry until death from any cause, and is measured in the intent-to-treat population.

5.7. Relapse

Relapse is defined as a patient who has previously achieved the above criteria (sections 5.1 and 5.2) of a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression (see section 5.3).

5.8. Refractory disease

Refractory disease is defined as treatment failure (as defined in section 5.5) or disease progression within 6 months to the last antileukemic therapy. For the definition of "high-risk CLL" justifying the use of allogeneic stem cell transplantation,[59] the disease should be refractory to a purine analog-based therapy or to autologous hematopoietic stem cell transplantation.

5.9. Minimal residual disease

The complete eradication of the leukemia is an obvious desired endpoint. New detection technologies, such as multicolor flow cytometry and real-time quantitative PCR, have determined that many patients who achieved a CR by the 1996 NCI-WG guidelines have detectable MRD. Although eradication of MRD may improve prognosis, prospective clinical trials are needed to define whether additional treatment intended solely to eradicate MRD provides a significant benefit to clinical outcome. The techniques for assessing MRD have undergone a critical evaluation and have become fairly standard.[60] Either 4-color flow cytometry (MRD flow) or allele-specific oligonucleotide PCR is reliably sensitive down to a level of approximately one CLL cell in 10 000 leukocytes. As such, patients will be defined as having a clinical remission in the absence of MRD when they have blood or marrow with less than one CLL cell per 10 000 leukocytes. The blood generally can be used for making this assessment except during the period within 3 months of completing therapy, particularly for patients treated with alemtuzumab, rituximab, and other antibodies targeting CLL. In such cases, it is essential to assess the marrow for MRD. Therefore, future clinical trials that aim toward achieving long-lasting CRs should include at least one test to assess MRD because the lack of leukemia persistence using these sensitive tests seems to have a strong, positive prognostic impact.[61–63]

5.10 Partial Remission (PR) with Lymphocytosis

Patient exhibits lymphocytosis but the following are observed in a criterion evaluable at baseline:

- ≥ 50% decrease in the sum products of up to 6 lymph nodes by CT or, if only one measureable lymph node at baseline, a ≥ 50% decrease in the longest diameter of the single lymph node by CT AND no increase in any other lymph node by CT. Note: In a small lymph node < 2cm, an increase of < 25% is not considered to be significant.
- No new enlarged lymph nodes by CT or physical examination.
- ≥ 50% decrease in the enlargement of liver or spleen size from baseline or normalization by CT.

Plus a response in at least one of the following criteria independent of growth factor support or transfusion*. If all criteria are normal at baseline, they must remain normal to be considered a PR:

- ANC > 1500/μL or ≥ 50% improvement over baseline

- Platelets > 100,000/μL or ≥ 50% improvement over baseline
- Haemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline

* Note: For a criterion to be considered a response, it must have been evaluable at baseline.

APPENDIX C – EXAMPLE CREATININE CLEARANCE (Cockcroft Gault Formula)

Creatinine clearance (ml/min) for males = (140-age) x weight[kg] x 1.23/serum creatinine (µmol/l)

Creatinine clearance (ml/min) for females = (140-age) x weight[kg] x 1.04/serum creatinine (µmol/l)

It is permissible to use another locally approved formula to calculate creatinine clearance.

APPENDIX D – EXAMPLE BODY SURFACE AREA CALCULATION

BSA [m2] = weight [kg]$^{0.425}$ x height [cm]$^{0.725}$ x 0.007184

It is permissible to use other BSA calculations in accordance with local practice.

APPENDIX E – INTERPRETATION OF MRD RESULTS

	Diagnosis	**Response assessment iwCLL guidelines**
	B-CLL - minimal residual disease present	MRD positive
	B-cell CLL – MRD-positive at iwCLL threshold (≥0.01%)	MRD positive
	B-cell CLL – MRD-negative at iwCLL threshold (<0.01%)	MRD negative
	"Other diagnosis – e.g. "See comments" or "inadequate sample"	Not known

According to the iwCLL criteria less than 1 CLL cell per 10,000 leucocytes (or less than 0.01%) is classified as MRD negative. It is possible to detect CLL cells at lower levels than this however the reproducibility of these results is not known and therefore they are **not** classified as MRD positive even though CLL cells may be detected.

APPENDIX F – INHIBITORS OR INDUCERS OF CYP3A AND OTHER CAUTIONARY MEDICATIONS

Examples of inhibitors and inducers of CYP3A are given below. Note that this is not an exhaustive list. Further information can be found at the following websites: http://www.medicine.iupui.edu/Flockhart/table.htm and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm. The general categorisation into strong, moderate, and weak CYP3a inhibitors is displayed below:

• A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. Strong inhibitors are capitalised in the list below.

• A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.

• A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

In addition to the medications listed in this table, participants receiving ibrutinib or venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

INHIBITORS		**INDUCERS**		**SUBSTRATES**
STRONG CYP3A INHIBITORS:	**MODERATE CYP3A INHIBITORS:**	**STRONG CYP3A INDUCERS:**	**MODERATE CYP3A INDUCERS:**	**SUBSTRATES OF P-GP**
boceprevir	aprepitant	avasimibe	bosentan	aliskiren
clarithromycin	amprenavir	carbamazepine	efavirenz	ambrisentan
cobicistat	atazanavir	phenobarbital	etravirine	colchicines
conivaptan	ciprofloxacin	phenytoin	modafinil	dabigatran etexilate
indinavir	crizotinib	rifabutin	nafcillin	digoxin
itraconazole	darunavir/ritonavir	rifampin	oxcarbazepine	everolimus
ketoconazole	dronedarone	St. John's Wort	troglitazone	fexofenadine
lopinavir	erythromycin			lapatinib
mibefradil	diltiazem	**WEAK CYP3A INDUCERS:**		loperamide
nefazodone	fluconazole	amprenavir		maraviroc
nelfinavir	fosamprenavir	aprepitant,		nilotinib
posaconazole	imatinib	armodafinil		ranolazine
ritonavir	verapamil	clobazamechinacea		saxagliptin
saquinavir		glucocorticoids (eg, prednisone)		sirolimus
telaprevir		nevirapine		sitagliptin
telithromycin		pioglitazone		talinolol
troleandomycin		rufinamide		tolvaptan
voriconazole*		vemurafenib		topotecan
WEAK CYP3A INHIBITORS:				**SUBSTRATES OF BCRP****
alprazolam	goldenseal			methotrexate
amiodarone	isoniazid			mitoxantrone
amlodipine	nilotinib			irrinotecan
atorvastatin	oral contraceptives			lapatinib
bicalutamide	pazopanib			rosuvastatin
cilostazol	ranitidine			sulfasalazine
cimetidine	ranolazine			topotecan
cyclosporine	suboxone			
fluvoxamine	tipranavir/ritonavir			**SUBSTRATES OF OATP1B1/B3****

INHIBITORS		INDUCERS	SUBSTRATES
fluoxetine	ticagrelor		atrasentan
ginkgo	zileuton		atorvastatin
			ezetimibe
			fluvastatin
			glyburide
			olmesartan
			rosuvastatin
			simvastatin acid
			pitavastatin
			pravastatin
			repaglinide
			telmisartan
			valsartan

* moderate CYP3A inhibitor per ibrutinib in vitro and clinical studies **Only affects venetoclax, not ibrutinib

APPENDIX G – QT PROLONGING AGENTS

Substantial evidence supports the conclusion that the drugs listed below prolong the QT interval and have a risk of *torsade de pointes* when used as directed in labeling.

amiodarone	Haloperidol
arsenic trioxide	Ibutilide
astemizole	Levomethadyl
bepridil	Mesoridazine
chloroquine	Methadone
chlorpromazine	Moxifloxacin
cisapride	Pentamidine
citalopram	Pimozide
clarithromycin	Probucol
disopyramide	Procainamide
dofetilide	Quinidine
domperidone	Sotalol
droperidol	Sparfloxacin
erythromycin	Terfenadine
flecainide	Thioridazine
halofantrine	Vandetanib

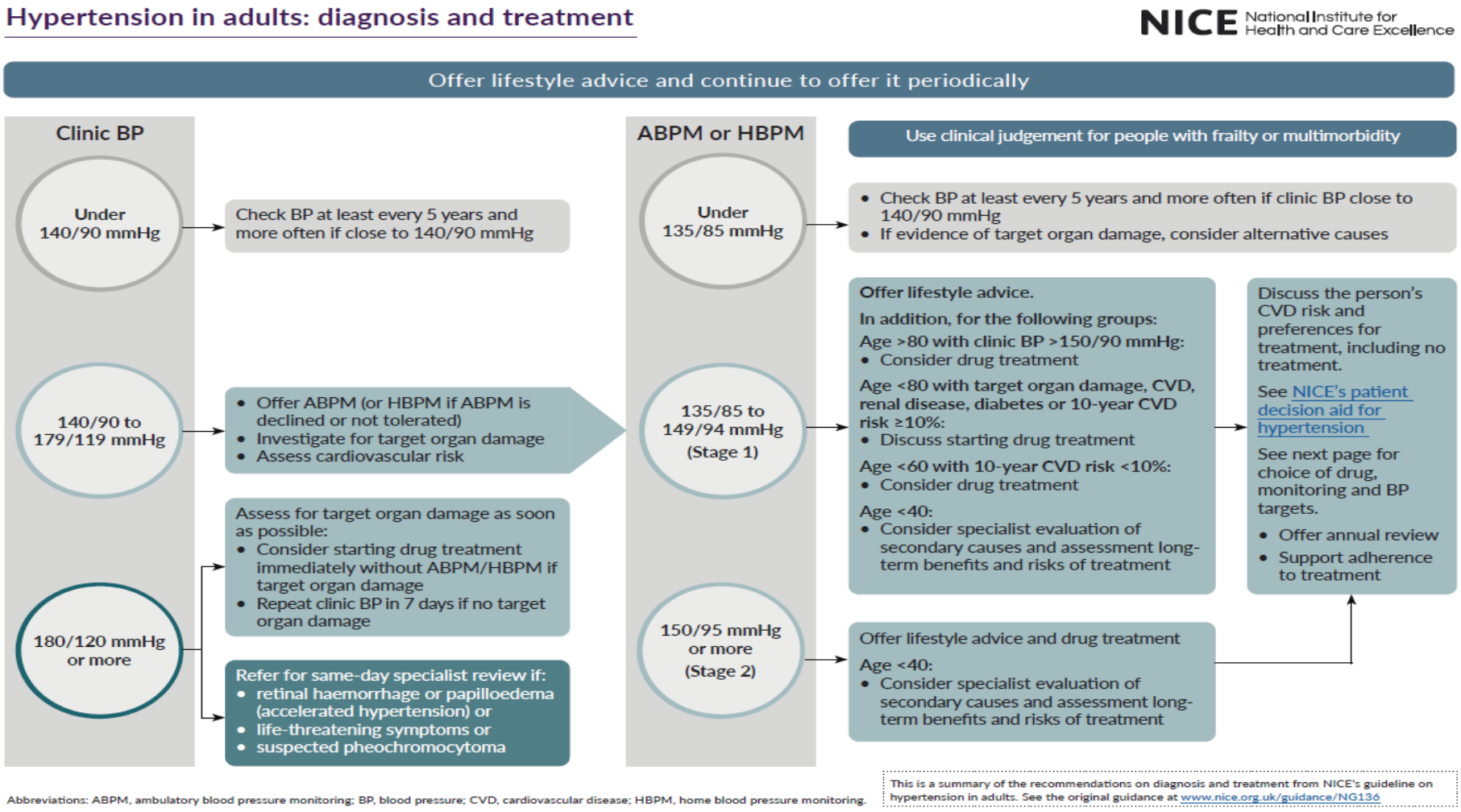
Source: http://www.azcert.org/medical-pros/drug-lists/list-01.cfm?sort=Generic_name

This list is not exhaustive and new information regarding drugs with dysrhythmic potential emerges on a regular basis. Please refer to the Arizona CERT website or similar sites for additional information on drugs with dysrhythmic potential.

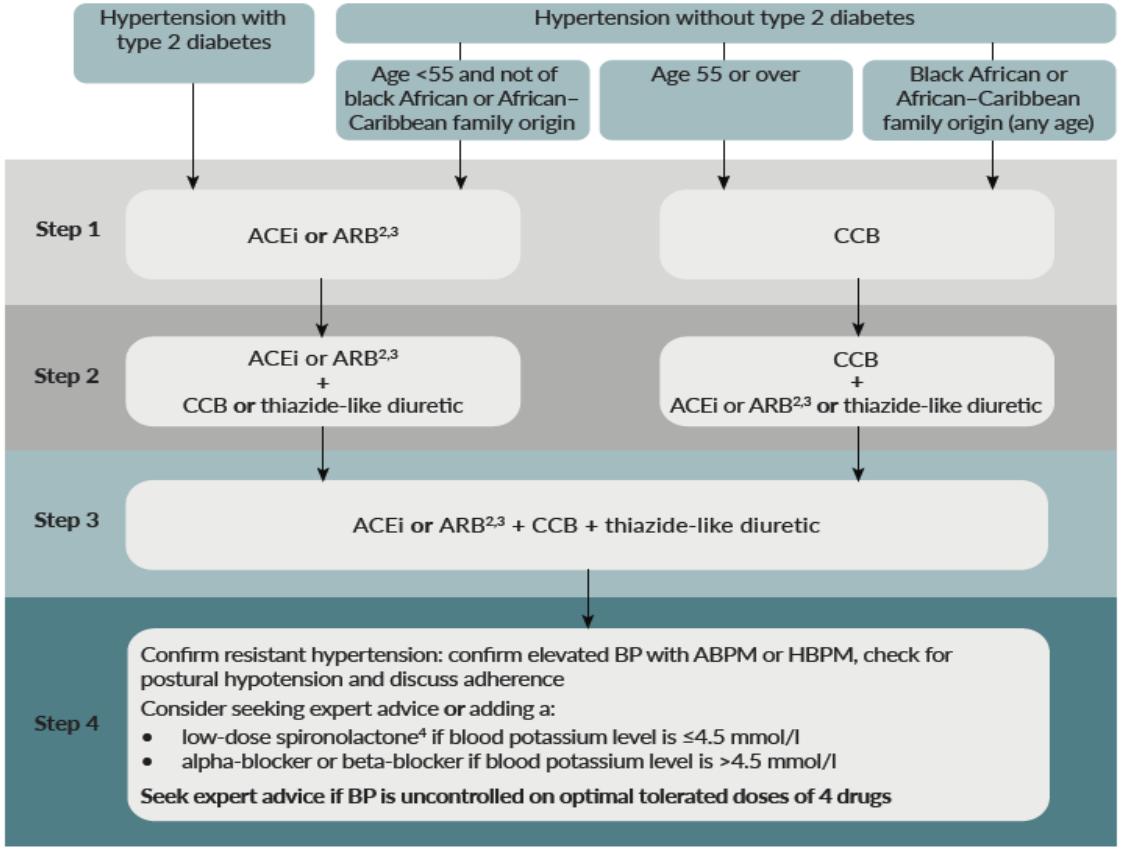
APPENDIX H – TREATING HYPERTENSION (NICE GUIDELINES, NG136)

Please do not prescribe ACE inhibitors for FLAIR participants taking ibrutinib for their CLL

Note the cautionary advice about diltiazem and verapamil in Section 10.7.1. (Concomitant therapy to be used with caution whilst receiving ibrutinib and / or venetoclax)



Choice of antihypertensive drug[1], monitoring treatment and BP targets



Monitoring treatment

Use clinic BP to monitor treatment.

Measure standing and sitting BP in people with:

- type 2 diabetes **or**
- symptoms of postural hypotension **or**
- aged 80 and over.

Advise people who want to self-monitor to use HBPM. Provide training and advice.

Consider ABPM or HBPM, in addition to clinic BP, for people with white-coat effect or masked hypertension.

BP targets

Reduce and maintain BP to the following targets:

Age <80 years:

- Clinic BP <140/90 mmHg
- ABPM/HBPM <135/85 mmHg

Age ≥80 years:

- Clinic BP <150/90 mmHg
- ABPM/HBPM <145/85 mmHg

Postural hypotension:

- Base target on standing BP

Frailty or multimorbidity:

- Use clinical judgement

[1] For women considering pregnancy or who are pregnant or breastfeeding, see NICE's guideline on hypertension in pregnancy. For people with chronic kidney disease, see NICE's guideline on chronic kidney disease. For people with heart failure, see NICE's guideline on chronic heart failure

[2] See MHRA drug safety updates on ACE inhibitors and angiotensin-II receptor antagonists: not for use in pregnancy, which states 'Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed', ACE inhibitors and angiotensin II receptor antagonists: use during breastfeeding and clarification: ACE inhibitors and angiotensin II receptor antagonists. See also NICE's guideline on hypertension in pregnancy.

[3] Consider an ARB, in preference to an ACE inhibitor in adults of African and Caribbean family origin.

[4] At the time of publication (August 2019), not all preparations of spironolactone have a UK marketing authorisation for this indication.

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEi, ACE inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; HBPM, home blood pressure monitoring.

BIHS British and Irish Hypertension Society
Committed to preventing cardiovascular disease

This visual summary builds on and updates previous work on treatment published by the BIHS (formerly BHS)

Published: August 2019

APPENDIX I – GLOSSARY OF TERMS

AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ß$_2$M	ß$_2$microglobulin
BCR	B-cell Receptor
BP	Blood Pressure
BSA	Body Surface Area
Btk	Bruton's Tyrosine Kinase
CLL	Chronic Lymphocytic Leukaemia
CR	Complete Response
CRi	CR with incomplete marrow recovery
CRF	Case Record Form
CT	Computerised Tomography
CTA	Clinical Trials Authorisation
CTC	Common Toxicity Criteria
CTRU	Leeds Clinical Trials Research Unit
DFS	Disease Free Survival
DMEC	Data Monitoring and Ethics Committee
ECG	Electro-Cardiogram
ECHO	Echocardiogram
FCR	Fludarabine, Cyclophosphamide and Rituximab
FISH	Fluorescent In Situ Hybridisation
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
Hb	Haemoglobin
HB	Hepatitis B
HC	Hepatitis C
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HMDS	Haematological Malignancy Diagnostic Service
I	Ibrutinib
IB	Investigators Brochure
IMP	Investigational Medicinal Product
IR	Ibrutinib plus Rituximab
I+V	Ibrutinib plus venetoclax
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
LDH	Lactate dehydrogenase
LDT	Lymphocyte Doubling Time
LFTs	Liver function tests
REC	Research Ethics Committee
MDS	Myelomdysplastic Syndromes
MHRA	Medicine and Healthcare Products Regulatory Agency
MRD	Minimal Residual Disease
NICE	National Institute for Health and Clinical Excellence
NR	No Response
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction

PD PFS PI	Progressive Disease Progression Free Survival Principal Investigator
Plts	Platelets
PR	Partial Response
PS SAE	Performance Status Serious Adverse Event
SAR SLL SmPC SUSARs	Serious Adverse Reaction Small Lymphocytic Leukaemia Summary of Product Characterstics Suspected Unexpected Serious Adverse Reactions
U&Es ULN	Urea & Electrolytes Upper limit of normal
WBC	White Blood Cells
WHO	World Health Organisation

APPENDIX J – TUMOUR LYSIS SYNDROME MANAGEMENT

Venetoclax can cause rapid reduction in tumour and thus poses a risk for tumour lysis syndrome (TLS) in the dose escalation phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of venetoclax and at each dose increase. The risk of TLS is a continuum based on multiple factors, including tumour burden and comorbidities. Participants with high tumour burden are a greater risk of TLS when initiating venetoclax. Reduced renal function further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment.

Participants with high tumour burden (at least one lesion ≥10 cm; or at least one lesion ≥5 cm plus ALC <25 x10^9/L will be hospitalised during the first 24-48 hours of treatment for TLS monitoring and hydration. Hospitalisation for participants lacking immediate access to a facility capable of correcting TLS promptly or for participants who are otherwise considered at risk for TLS is allowed at the discretion of the investigator.

In all participants, perform tumour burden assessments, including CT scan, assess blood biochemistry (potassium, urate, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.

In all participants, assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics (eg allopurinol) to participants prior to first dose of venetoclax to reduce risk of TLS. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalisation) as overall risk increases.

Table 13 TLS Recommended Prophylaxis Based on Tumour Burden (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)

Tumour Burden/ renal function		Prophylaxis		Blood Biochemistry Monitoring[c]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All lymph nodes <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient 1. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 2. Pre-dose and 6-8 hours at subsequent dose escalations
Medium	Any lymph node 5 cm to <10 cm OR ALC ≥25 x10^9/L OR Creatinine clearance <80 ml/min	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient 3. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 4. Pre-dose and 6 to 8 hours at subsequent dose escalations 5. Consider hospitalisation for participants with creatinine clearance

				60-80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any lymph node ≥10 cm OR ALC ≥25 x10^9/L AND any lymph node ≥5 cm	Oral (1.5-2 L). Intravenous (150-200 mL/hr as tolerated) is required if participant cannot tolerate oral hydration.	Administer more intensive prophylaxis against TLS (e.g. rasburicase)	In hospital at first dose of 20 mg and 50 mg 6. Pre-dose, 4, 6-8,12 and 24 hours Outpatient at subsequent dose escalations 7. Pre-dose, 6 to 8 hours and 24 hours.

a. Administer intravenous hydration for any patient who cannot tolerate oral hydration.
b. Start allopurinol or other uric acid reducing agent 72 hours prior to initiation of venetoclax.
c. Evaluate blood biochemistries (potassium, urate, phosphorus, calcium, and creatinine); review in real time.

Within the first 24 hours after either the first dose or at any dose increase, if any laboratory criteria below are met, the patient should be hospitalised for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.

Nephrology (or other acute dialysis service) should be contacted/consulted (per standard care to ensure emergency dialysis is available) on admission for any subject hospitalised prophylactically or in response to laboratory changes.

IV fluids (eg, D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not <50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.

Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhoea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, urate, calcium and creatinine within 1 hour.

Vital signs should be taken at time of all blood draws or any intervention.

The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per standard care

In addition to the recommendations in the table below:
For potassium increase ≥0.5 mmol/L from baseline (taken pre dose at that dose level), or any value >5.0 mmol/L, recheck potassium, phosphorus, urate, calcium and creatinine within 1 hour and follow first guideline.

For phosphorus increase of >0.5 mg/dL (0.16 mmol/L) AND >5.0 mg/dL (1.615 mmol/L recheck potassium, phosphorus, urate, calcium and creatinine within 1 hour.

Table 14 Venetoclax dose modifications within the first 24 hours after either the first dose or at any dose increase

Abnormality	Dose Modification and Management Recommendation
Laboratory Events	
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5mmol/L increase from prior value (and within ULN)	• Hold venetoclax until resolution • Recheck potassium, phosphorus, urate, calcium, and creatinine in 1 hour. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium <ULN, and no other evidence of tumour lysis. • At discretion of the investigator may recheck prior to hospitalisation. If stable or decreased, and still within normal limits, hospitalisation is at the discretion of the Investigator. Potassium, phosphorus, urate, calcium and creatinine must be rechecked within 24 hours.
Potassium > ULN	• Hold venetoclax until resolution • Perform ECG; administer calcium gluconate 100-200mg/kg IV slowly if there is evidence of life-threatening arrhythmias • Administer Kayexalate/Resonium 60g • Administer furosemide 20mg IV • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 hour. If potassium, < ULN 1 hour later, repeat potassium, phosphorus, urate, calcium and creatinine 1, 2 and 4 hours later, if no other evidence of tumour lysis.
Potassium ≥ 6.0mmol/L (6.0 mEq/L) and/or symptomatic (e.g. muscle cramps, weakness, paresthesias, nausea, vomiting and diarrhoea)	• Hold venetoclax until resolution • Perform ECG; administer calcium gluconate 100-200mg/kg IV slowly if there is evidence of life-threatening arrhythmias. • Administer Kayexalate/Resonium 60g • Administer furosemide 20mg IV • Administer insulin 0.1 U/kg IV + D25 2mL/kg IV • Administer sodium bicarbonate 1 to 2 mEq/kg IV. Rasburicase should not also be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.

	• Recheck potassium, phosphorus, urate, calcium and creatinine every hour.
Hyperuricaemia	
Urate ≥ 8.0 mg/dL (476 μmol/L)	• Hold venetoclax until resolution • Consider rasburicase (as per local guidelines). Sodium bicarbonate should not also be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 hour.
Urate ≥ 10 mg/dL (595 μmol/L) **OR** Urate ≥ 8.0 mg/dL (476 μmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	• Hold venetoclax until resolution • Consider rasburicase (as per local guidelines). Sodium bicarbonate should not also be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service) • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 hour. • If urate <8.0 mg/dL (476 μmol/L) 1 hour later, repeat potassium, phosphorus, urate, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumour lysis
Hypocalcemia	
Corrected calcium ≤ 7.0 mg/dL (1.75 mmol/L) **OR** Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	• Hold venetoclax until resolution • Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Recheck potassium, phosphorus, urate, calcium, and creatinine in 1 hour. • If calcium normalised 1 hour later, repeat potassium, phosphorus, urate, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumour lysis • Calculate corrected calcium and check ionised calcium if albumin low
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Hold venetoclax until resolution • Nephrology notification (dialysis required for phosphorus > 10 mg/dL(3.23 mmol/L)) • Recheck potassium, phosphorus, urate, calcium, and creatinine in 1 hour. • If phosphorus < 5.0 mg/dL (1.615 mmol/L) 1 hour later, repeat potassium, phosphorus, urate, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumour lysis.
Creatinine	

Increase ≥ 25% from baseline	• Hold venetoclax until resolution • Start of increase rate of IV fluids • Recheck potassium, phosphorus, urate, calcium and creatinine in 1 to 2 hours.

Note that the baseline for comparision is the pre dose value at that dose level.

Ongoing dosing of venetoclax

Management of electrolyte changes from last value at intervals >24 hours after either the first dose or at any dose increase (eg, 48 or 72 hours) are as below.

If the patient is hospitalised, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
    - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).
- If a smaller potassium increase of 0.5-0.9 mmol/L is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, urate, calcium and creatinine in 24 hours and confirm no evidence of tumour lysis prior to further venetoclax dosing.
- For urate, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

Section 10.6 describes dose modifications for non-biochemical toxicity (eg haematological).

Dose modifications for tumour lysis syndrome

If a participant experiences blood biochemistry changes suggestive of TLS as per the table above, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 16). When resuming treatment after interruption due to TLS, the instructions for prevention of tumour lysis syndrome should be followed (see prophylaxis in table 14 above).

Table 15 Dose modification for TLS and other toxicities

Dose at interruption (mg)	Restart dose (mg[a])
400	300
300	200
200	100
100	50
50	20
20	10

[a] The modified dose should be continued for 1 week before increasing the dose

For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose escalation or more than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose escalation; see Table 15).

Tumour burden assessment
The tumour burden assessed by the nodal disease and lymphocyte count at screening has been used to define each category as described below:

Table 16 Tumour burden assessment

Tumour burden	Criteria
Low	All measurable lymph nodes with the largest diameter <5cm AND ALC <25 $x10^9$/L
Medium	Any measurable lymph node with the largest diameter ≥5cm but <10cm OR ALC ≥ 25 x 10^9/L
High*	Any measurable lymph node with the largest diameter ≥10cm OR ALC ≥25 x 10^9/L AND any measurable lymph node with the largest diameter ≥5cm but <10cm

*Note that patients with creatinine clearance of <80ml/min are treated as per medium tumour burden as outlined in Table 13.

Downgrading tumour burden

- Patients with a high tumour burden before commencing venetoclax due to an absolute lymphocyte count ≥25 × 10^9/L AND a measurable lymph node with the largest diameter ≥ 5 cm but less than 10 cm by radiologic assessment may have a re- evaluation of their tumour burden based on their most recent ALC **for dose increases above 50 mg**. Based on those results, one of the following two options may be implemented:
    - If the patient's ALC decreases to < 25 × 10^9/L, the patient may be categorised as having a medium tumour burden and follow the management guidelines for medium tumour burden for subsequent dose increases (to 100, 200, 400 mg) of venetoclax
    - If the patient's ALC remains ≥ 25 × 10^9/L, the patient will remain as having a high tumour burden and continues to follow management guidelines for high tumour burden for subsequent dose increases of venetoclax
    - Re-assessment of the patient's tumour burden can occur prior to each subsequent dose increase

APPENDIX K – EXAMPLES OF MEDICALLY APPROVED CONTRACEPTION

For participants treated with ibrutinib or venetoclax it is recommended that hormonal methods of contraception should add a second barrier method (e.g. condom).

- combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
  o oral
  o intravaginal
  o transdermal

- progesterone-only hormonal contraception associated with inhibition of ovulation
  o oral
  o injectable
  o implantable

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [3]
- sexual abstinence [4]

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[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

APPENDIX L – TABLE OF ACE INHIBITORS

The below table shows a list of ACE inhibitors. Each of these medicines has different brand names so the generic and brand names are shown below, along with a web-link for more information. We have tried to include as complete a list as possible, however there may be other ACE inhibitors not listed here. Please also note that some ACE inhibitor medicines are also part of a combined tablet with a calcium-channel blocker medicine or water tablet' (diuretic) medicine (click on the hyperlinks to find out more).

Source: UK website called ''Patient'' https://patient.info/heart-health/ace-inhibitors

Generic Name	**Brand Names / Also Known As**	**Weblink**
Ramipril	Tritace Triapin (ramipril with felodipine) Altace	https://patient.info/medicine/ramipril-an-ace-inhibitor-tritace-triapin-altace
Lisinopril	Zestril; Zestoretic (lisinopril combined with hydrochlorothiazide)	https://patient.info/medicine/lisinopril-an-ace-inhibitor-zestril
Perindopril	Perindopril arginine; perindopril erbumine; perindopril tert-butylamine; Brand: Coversyl® Arginine; Combination brands: Coversyl® Arginine Plus (perindopril with indapamide)	https://patient.info/medicine/perindopril-an-ace-inhibitor-coversyl
Enalapril	Innovace; Innozide (contains enalapril with hydrochlorothiazide)	https://patient.info/medicine/enalapril-an-ace-inhibitor-innovace-innozide
Fosinopril	Fosinopril sodium	https://patient.info/medicine/fosinopril-an-ace-inhibitor
Imidapril	Tanatril	https://patient.info/medicine/imidapril-for-high-blood-pressure-tanatril
Quinapril	Accupro Accuretic (quinapril in combination with hydrochlorothiazide)	https://patient.info/medicine/quinapril-tablets-accupro
Trandolapril	No other names as far as we are aware	https://patient.info/medicine/trandolapril-an-ace-inhibitor
Captopril	Noyada	https://patient.info/medicine/captopril-an-ace-inhibitor-noyada

APPENDIX M – Covid-19 Risk Mitigation Plan

Participating sites must comply with their local public health rules and guidance produced by the Medicine and Healthcare products Regulatory Agency (MHRA) https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19.

A record must be kept of when specific COVID-19 local guidelines have been implemented. Please notify CTRU with details of the local guidance and dates of implementation for any alternate approaches as soon as possible. In the event that a participating site is impacted by the evolving COVID-19 pandemic in a way that results in an inability to perform study activities please inform CTRU as soon as possible.

Every effort should be made to follow the protocol. Protocol deviations cannot be preapproved.

If a participant is diagnosed with COVID-19 or is suspected to have COVID-19 the local area treatment and quarantine guidance should be followed. All adverse events (AEs) and serious adverse events (SAEs) must be reported in line with instructions for safety reporting documented in section 12.

Participant safety is paramount and the investigator should continue to reassess the risk/benefit of continued study involvement for each participant. Safety assessments are critical and should continue to be performed as per protocol. Safety assessments must be prioritised above all other assessments and all contingency measures explored to allow their continuation.

If a study participant is unable to attend clinic visits, and/or receive study intervention, the site staff must keep in close contact with the study participant(s), preferably through telephone or virtual consultations, to maintain awareness of their status. A telephone/virtual assessment should include a review of any new AEs or changes to any ongoing AEs, treatment compliance and any changes to concomitant medications. In advance of this assessment, please remember to review the participant's previous assessments to inform this follow-up discussion. Also, where applicable, please discuss study drug supply and review any questions participants may have regarding their study drug.

In the event that a study visit is delayed/postponed, or a telephone/virtual assessment is used in place of a study visit, the study site should document the circumstances, so that any missed assessments can be performed as soon as conditions permit.

Further information on collection of data during follow-up are outlined in separate guidance provided to sites.

The investigator must ensure that the conduct of study visits and any applicable study-related information during the COVID-19 pandemic are recorded in the participants' medical records.
If it is not possible to conduct study activities at the approved participating site and an alternative non-participating site is more appropriate, CTRU must be informed.

As a reminder, if a member of the participating site staff should become temporarily indisposed or unavailable, please ensure delegation of duties is properly revised and recorded on the authorised personnel log, as necessary