CiproPAL (Ciprofloxacin Prophylaxis in Acute Leukaemia): A randomised trial to assess the use of ciprofloxacin prophylaxis to prevent bacterial infection in children treated on the induction phase of the ALLTogether1 treatment protocol

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Name & Role:	Signature:	Date authorised:
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Please note: This trial protocol must not be applied to patients outside the CiproPAL trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

We thank the patient representatives who reviewed the protocol for their comments on the trial design and input into the patient information sheets.

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1. PROTOCOL SUMMARY

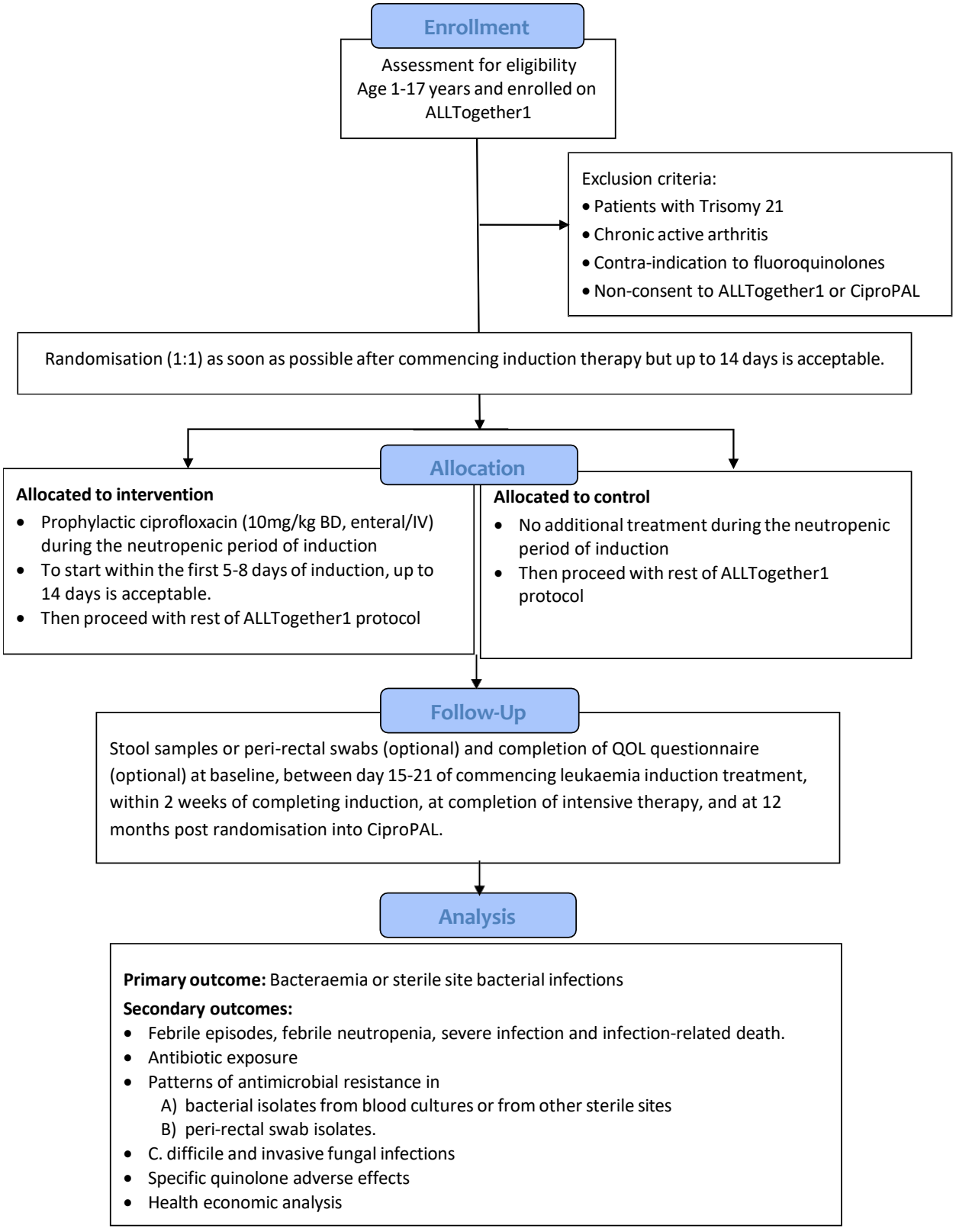
1.1. Summary of Trial Design

Title:	CiproPAL (Ciprofloxacin Prophylaxis in Acute Leukaemia): A randomised trial to assess the use of ciprofloxacin prophylaxis to prevent bacterial infection in children treated on the induction phase of the ALLTogether1 treatment protocol
Short Title/acronym:	CiproPAL
EUDRACT no:	2021-000341-40
Sponsor name & reference:	University College London – 129038
Funder name & reference:	National Institute for Health Research (NIHR) – NIHR130848
ISRCTN no:	ISRCTN21195635
Clinicaltrials.gov no:	NCT04678869
Design:	Multi-centre, randomised open-label trial
Overall aim:	1. To assess the efficacy of ciprofloxacin prophylaxis in reducing infections during the induction phase of the ALLTogether1 Trial. 2. To evaluate the impact of ciprofloxacin prophylaxis on antimicrobial resistance, both of invasive infections and colonising organisms.
Primary endpoint:	Bacteraemia or sterile-site bacterial infection during the induction phase of ALLTogether1. See section 3.2 for further detail.
Secondary endpoints:	1. Febrile episodes, febrile neutropenia, severe infection (defined as the need for organ support or critical care intervention) and infection-related death. See section 3.2 for further details. 2. Antibiotic exposure, including for prophylactic, empiric and treatment relating to infections which result in an inpatient hospital stay. See section 3.2 for further details. 3. Patterns of antimicrobial resistance and their changes over time in A) bacterial isolates from blood cultures or from other sterile sites, B) stool or peri-rectal swab isolates. See section 3.2 for further details.

	4. Secondary infections: Clostridium difficile infections and invasive fungal infections. 5. Specific quinolone adverse effects, including tendinitis and tendinopathy, visual disturbance, seizures, polyneuropathy and hepatic dysfunction. 6. Health economic analysis. See section 17.2.3 for further details.
Target accrual:	1052 patients
Inclusion & exclusion criteria:	Inclusion: • Paediatric patients (1-17 years inclusive) with de-novo Acute Lymphoblastic Leukaemia treated on ALLTogether1 in the UK as soon as possible after commencing induction, preferably in the first 5-8 days of therapy, up to 14 days is acceptable. • Written informed consent. Exclusion: • Non-participants of the ALLTogether1 trial. • Patients with Down syndrome. • Patients with chronic active arthritis. • Patients with any other contraindication to fluoroquinolones.
Number of sites:	20 UK Primary Treatment Centres
Treatment summary:	Eligible patients who consent to take part in CiproPAL and who are already enrolled in ALLTogether1 will be randomised (1:1) to the interventional arm or control arm of the trial. Patients randomised to the interventional arm will receive prophylactic ciprofloxacin (10mg/kg twice a day, enteral or intravenously) from randomisation to the end of induction. Specifically, prophylactic ciprofloxacin should commence as soon as possible after randomisation (preferably within the first 5-8 days of induction therapy, but up to day 14) and continue until neutrophil recovery sufficient for the commencement of consolidation (ANC >0.5x10^9/L). See section 8.2 for further details. Patients randomised to the control arm will receive no additional treatment during induction. Such patients should receive the standard of care, as per local policy.

	Any febrile episodes should be treated according to local guidelines. For patients in the interventional arm (receiving prophylactic ciprofloxacin), ciprofloxacin prophylaxis should be stopped for the duration of any treatment with broad spectrum antibiotics, empirically or for a defined infection, and re-started afterwards. If antibiotic coverage is rationalised to treat a specific infection, for example teicoplanin for a Coagulase negative Staphylococcus central line infection, then ciprofloxacin should be restarted. If there are any uncertainties regarding restarting ciprofloxacin please contact UCL CTC who will enquire with the trial management group (TMG).
Duration of recruitment:	42 months
Duration of follow up:	Patients will be actively followed up for 12 months, with ongoing longer-term follow-up until the end of trial is declared.
Definition of end of trial:	The end of trial will be declared when the last patient has completed the follow-up for ALLTogether1 (this is estimated to be December 2031).

1.2. Trial Schema



2. INTRODUCTION

2.1. Background

2.1.1. What is the problem being addressed?

Treatment-related mortality (TRM) accounted for almost half of all deaths of children being treated for Acute Lymphoblastic Leukaemia (ALL) in the most recent UK trial, UKALL2003, with 30% of all deaths due to infection (infection-related mortality; IRM).(1) IRM occurred primarily in the first five weeks (induction) of the UKALL2003 protocol.(1) The majority of IRM is due to bacterial sepsis, with Gram negative organisms the most common cause.(1,2)

Prophylactic fluoroquinolone antibiotics have been reported to reduce episodes of fever and microbiologically documented infections (MDI), in adults with acute leukaemia in a meta-analysis of 95 studies.(4) The current NICE guideline on neutropenic sepsis states "For adult patients (aged 18 years and older) with acute leukaemias … offer prophylaxis with a fluoroquinolone during the expected period of neutropenia".(5) An updated systematic review drew on 23 trials of fluoroquinolone prophylaxis to estimate a risk ratio of bacteraemia in the treatment group of 0.56 (95% CI 0.41-0.76) across 29 trials in adult and paediatric populations, with moderate heterogeneity (I-sq 58%).(6)

There are currently no other randomised trials addressing the use of prophylaxis in de novo paediatric ALL patients, though a randomised COG (Children's Oncology Group) study in more intensively treated AML or relapsed ALL found a halving in the rates of bacteraemia (44% vs. 22%) with levofloxacin prophylaxis. (7) Several non-randomised reports have suggested fluoroquinolone prophylaxis may be of benefit. Three small studies using ciprofloxacin showed a decrease in febrile episodes, intensive care admissions and bloodstream infections. Larger prospective cohort studies by the St Jude and Dana Faber groups (135 patients total) using levofloxacin demonstrated a significant (>50%) reduction in bacterial infections in induction and a non-significant decrease in TRM. (8–12)

2.1.2. Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

Recent studies in paediatric ALL have focussed upon treatment of relapsed or refractory disease, which, while important, are very rare events, and may have a small absolute gain compared to the potential for halving deaths from infections. Beyond the direct survival benefit, infections are important adverse experiences during treatment. Our patient and public involvement (PPI) group of patients and parents with ALL highlighted the importance of reducing serious infections given the impact on patients' health and family experiences. Our group spoke of their fear of infections, and how they have "a knock-on effect on everything else you're trying to do", including causing chemotherapy delays. The importance of this issue is also highlighted in responses to the James Lind Alliance Teenage and Young Adult Cancer Priority Setting Partnership. (3)

2.1.3. Rationale for antibiotic choice

Fluoroquinolones are particularly appropriate for prophylaxis due to their broad spectrum of activity, oral administration, low toxicity and lack of myelosuppression.(21,15) Three of

the largest studies of antibiotic prophylaxis in paediatric ALL have used levofloxacin.(7,11,12) Levofloxacin has activity against gram-positive organisms, particularly streptococcus, whilst maintaining activity against gram-negative organisms.(16) However, the European Medicines Agency currently recommends against levofloxacin use in children and adolescents due to a lack of safety data.(16,17) In addition, levofloxacin is not currently available in a liquid form or dispersible tablet in the UK, which precludes its use in a paediatric trial. Ciprofloxacin, however, is available in liquid form, as tablets, and as an intravenous infusion.

In 2019, the UK Medicines and Healthcare products Regulatory Agency (MHRA) introduced new guidance regarding fluoroquinolones. In particular, concerns related to musculoskeletal and nervous system side effects, including tendinitis or tendon rupture, muscular or joint symptoms, peripheral neuropathy and CNS side effects. A key feature of the guidance is the recommendation that fluoroquinolones are discontinued in the event of any evidence of such reactions; this is incorporated within this protocol. Additional considerations include the risk of prolongation of the QT interval, increased risk of seizures, effects on blood glucose control, increased sensitivity to sunlight, adverse effects in patients with G6PD deficiency and worsening of existing psychiatric disorders.

The most recent systematic review undertook a multiple treatment comparison (network meta-analysis) as part of the synthesis, and found no clear evidence of difference between the ciprofloxacin and levofloxacin though data were sparse with no direct comparative trials (RR bacteraemia 0.79, 95% credible limit 0.42 to 1.5). (6)

Therefore, we will use ciprofloxacin in CiproPAL. Although lacking some Gram-positive activity compared with levofloxacin, ciprofloxacin has excellent Gram-negative cover, which targets the organisms responsible for the majority of IRM. Furthermore, the professional community have experience with ciprofloxacin prophylaxis, increasing the acceptability and confidence in its use.

2.1.4. Assessment of resistance

There is concern that prophylactic antibiotics could lead to the development of antimicrobial resistance (AMR). This was highlighted by our PPI group as of particular importance to them as well as clinicians. Although prophylaxis has not been associated with immediate harm, it may increase the presence of resistant bacteria, and community antibiotic resistance. (8,13) The recent COG trial and St Jude cohorts did not show any increase in resistance, but reported over a relatively short period of time. (7,11) The longer-term effects on local microbiology and resistance rates are a significant concern. Fluoroquinolones have been implicated in the pathogenesis of Clostridium difficile infection (CDI), and while programmes to restrict their use exist, the North American studies using prophylaxis demonstrated reduced episodes of CDI, possibly through reduction in overall antibiotic usage. (7,11,14)

Resistance will be monitored as part of CiproPAL, addressing AMR monitoring of invasive infections, and during the randomised phase of CiproPAL, through AMR monitoring of colonising organisms. Colonisation of patients on CiproPAL will be assessed with stool samples or peri-rectal swab cultures at timelines specified in section 9 of the protocol. See sections 3 and 9 for further details of resistance testing.

2.1.5. Trial organisation

CiproPAL is an add-on randomised trial to ALLTogether1 trial (which is Sponsored by Karolinska University Hospital and coordinated in the UK by the CR UK and UCL Cancer Trials Centre). This design optimises data collection and the efficacy of research; only the additional data required for CiproPAL will be collected onto an electronic database, removing duplicate data entry and outcome collection.

CiproPAL has been developed in close collaboration with the ALLTogether group, patient and parent representatives (funded through a Yorkshire and Humber RDS grant) and the Cancer Research UK and UCL Cancer Trials Centre, who will coordinate the study on behalf of the study Sponsor, UCL.

3. TRIAL DESIGN

This is a multi-centre, open label, randomised trial, to assess the efficacy of ciprofloxacin prophylaxis in reducing infections during the induction phase of the ALLTogether1 trial and to evaluate the impact of ciprofloxacin prophylaxis on antimicrobial resistance (AMR) (both invasive infections and colonising organisms).

Eligible patients who consent to take part in CiproPAL and who are already enrolled in ALLTogether1 will be randomised (1:1) to the interventional arm or control arm of the trial.

Patients randomised to the interventional arm will receive prophylactic ciprofloxacin (10mg/kg twice a day, enteral or intravenously) from randomisation to the end of induction. Specifically, prophylactic ciprofloxacin should commence as soon as possible after randomisation (preferably within the first 5-8 days of induction therapy, up to 14 days is acceptable) and continue until neutrophil recovery sufficient for the commencement of consolidation (ANC >$0.5x10^9$/L). See section 8.2 for further details.

Patients randomised to the control arm will receive no additional treatment during induction. Such patients should receive the standard of care, as per local policy.

Any febrile episodes should be treated according to local guidelines. For patients in the interventional arm (receiving prophylactic ciprofloxacin), ciprofloxacin prophylaxis should be stopped for the duration of any treatment with broad spectrum antibiotics, empirically or for a defined infection, and re-started afterwards. If antibiotic coverage is rationalised to treat a specific infection, for example teicoplanin for a Coagulase negative Staphylococcus central line infection, then ciprofloxacin should be restarted. If there are any uncertainties regarding restarting ciprofloxacin please contact UCL CTC who will enquire with the trial management group (TMG).

Patients will be followed up actively for 12 months. Colonisation patterns will be assessed from analysing stool samples or peri-rectal swab cultures. Samples will be obtained at baseline (following randomisation but prior to, or within 3 days of, commencing ciprofloxacin (interventional arm) or within 3 days (+/- 2 days) of randomisation (control arm)), between day 15-21 after commencing leukaemia induction treatment, within 2 weeks of completing induction, at the completion of intensive therapy (i.e. at the start of maintenance therapy which typically will be 6-7 months from randomisation), and at 12 months post randomisation into the CiproPAL trial. See the CiproPAL laboratory manual for processing guidelines for the samples.

Resistance will be monitored as part of the CiproPAL trial, addressing AMR monitoring of invasive infections, and during the randomised phase of CiproPAL, through AMR monitoring of colonising organisms. Invasive infection AMR monitoring will include sensitivity testing of all organisms isolated in confirmed bacteraemia or other sterile site infection.

3.1. Trial Objectives

1. To assess the efficacy of ciprofloxacin prophylaxis in reducing infections during the induction phase of the ALLTogether1 Trial.

2. To evaluate the impact of ciprofloxacin prophylaxis on antimicrobial resistance, both of invasive infections and colonising organisms.

3.2. Trial Endpoints

Primary:

- Bacteraemia or sterile-site bacterial infection during the induction phase of ALLTogether1.

Clinically significant infections will use Centres for Disease Control (CDC) definitions for blood stream infections ((BSI) (including Central Line Associated BSI (CLABSI)), and for other 'sterile site infections'.(19) Each clinically relevant infection recorded during the trial will be reviewed by two specialists who will be blinded to which arm the patient belongs to (11), using an algorithm based on the method in place in the PERFORM study (which is examining infections in children presenting to emergency departments). (Appendix 4, 22)

Secondary:

1. Febrile episodes, febrile neutropenia, severe infection (defined as the need for organ support or critical care intervention) and infection-related death.
    a. Fever is defined as temperature ≥38°C (as per CTCAE v5.0).
    b. Febrile neutropenia is defined as neutrophil count ≤0.5x10^9/L and either a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour.
2. Antibiotic exposure (20) relating to infections which result in an inpatient hospital stay: This will be reported as days on therapy per 100 patient days per antibiotic. Total exposure for IV antibiotics and IV+oral will be described. Separate analysis will be performed looking specifically at differences:
    a. Prophylactic antibiotics include ciprofloxacin (intervention), prophylaxis for Pneumocystis jirovecii infection (usually with co-trimoxazole on two days per week), and prophylaxis against urinary or respiratory infections.
    b. Empirical antibiotics are those given prior to the identification of a specific infection, and is usually defined within a centre's febrile neutropenia protocol.
    c. Treatment antibiotics are those targeted at a particular clinically or microbiologically defined infection.
3. Patterns of antimicrobial resistance and their changes over time in A) bacterial isolates from blood cultures or from other sterile sites, B) stool or peri-rectal swab isolates.
    a. Local sites to analyse, looking at standard resistance patterns, and report for each antibiotic class as resistant, intermediate or sensitive.
4. Secondary infections: *Clostridium difficile* infections (see current definitions) (23) and invasive fungal infections (following the 2020 EORTC definition).(28)
5. Specific quinolone adverse effects, including tendinitis and tendinopathy, visual disturbance, seizures, polyneuropathy and hepatic dysfunction which should be coded as per CTCAE v5.0.
6. Health economic analysis to assess the cost-effectiveness of ciprofloxacin prophylaxis versus no prophylaxis for patients receiving induction therapy for ALL.

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA).
- **‘**Adoption’ into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol trial 'site' refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority and the Medicines for Human Use Clinical Trials) Regulation (SI 2004/1031), and all amendments
- Data collection requirements, including adherence to eCRF submission timelines as per section 11.4 (Timelines for Data Entry)
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol section 144 (Trial Monitoring and Oversight)

4.1.1. Selection of Principal Investigator and other investigators at sites

Each site must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of a site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience of treating paediatric ALL. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI plans to take a leave of absence UCL CTC **must be informed promptly.** For absences greater than three months or where the PI is no longer able to perform his/her duties at the site UCL CTC may terminate recruitment at site. A new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

4.1.2. Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV with evidence of GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or two yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site Initiation and Activation

4.2.1. Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by teleconference with site. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

4.2.2. Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- A signed and dated copy of the PI's current CV (with documented up-to-date GCP training, or copy of GCP training certificate)
- Trial specific prescription & labels

In addition, the following agreement must be in place:

- a signed site agreement between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)

4.2.3. Site activation

Once the UCL CTC trial team has received all required documentation and the site has been initiated, notification of site activation will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion and return of eCRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- that the site has facilities to provide **24 hour medical advice** for trial patients

5. INFORMED CONSENT

For Patients aged 16 or over

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form. Sites must assess a patient's ability to understand verbal and written information in English and whether or not an independent interpreter/NHS approved translator would be required to ensure fully informed consent. If a patient requires an interpreter and none are available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient.

A minimum of twenty four (24) hours should be allowed for the patient to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the understands the trial and implications. A member of the research team at the hospital must then confirm with the patient in the following days that they are still willing to participate in the trial.

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient medical notes.

Site staff are responsible for:

- checking that the current approved version of the patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- following randomisation, adding the patients' trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file
- following randomisation, giving the patient a copy of their signed consent form, patient information sheet, patient diary* (where appropriate) and patient contact card

*A patient diary template will be supplied, and must be used for patients randomised to the intervention arm of the trial, unless there is prior agreement from UCL CTC to use alternative in-house records.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 155 (Withdrawal of Patients).

For Patients aged 15 or younger

The person with parental responsibility or legal guardianship of the child must be informed of all aspects of the trial using the parent/legal guardian information sheet and consent form. Site staff are responsible for assessing the capacity of the parent/legal guardian to give consent and for ensuring that consent is carried out in accordance with the standards listed above.

The child must also be informed about the trial to the extent compatible with their understanding. The same information must be provided to children of all ages, however the level of detail is age appropriate.

Information sheets are available for the following age groups:

- under 7 years old
- 7-12 years old
- 13-15 years old

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. If capable, the child may give assent by signing and personally dating the assent form, in addition to the parent or legal guardian signing the consent form. The discussion and consent process must be documented in the patient medical notes, and a copy of the assent form (where signed) should be given to the parent/legal guardian.

A child's refusal to participate in the trial must be respected.

If a child reaches their sixteenth birthday during the trial, they should be given the adult patient information sheet, and asked to sign the consent form if they are happy to continue on the trial. If they decline consent, they should be withdrawn from the trial. See section 15.2 (Discontinuation of Trial Treatment) for details.

6. SELECTION OF PATIENTS

6.1. Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record each patient screened for the trial (i.e. any ALLTogether1 patient registered at the site) and the reasons why they were not randomised in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2. Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to randomising the patient. Confirmation of eligibility must be documented in the patients' medical notes and on the randomisation eCRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Pre-randomisation Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1. Inclusion criteria

1) Paediatric patients (1-17 years inclusive) with de-novo Acute Lymphoblastic Leukaemia treated on ALLTogether1 in the UK as soon as possible after commencing induction, preferably in the first 5-8 days of therapy, up to 14 days is acceptable.
2) Written informed consent.

6.2.2. Exclusion criteria

1) Non-participants of the ALLTogether1 trial.
2) Patients with Down syndrome.
3) Patients with chronic active arthritis.
4) Patients with any other contraindication to fluoroquinolones.

6.3. Pregnancy and birth control

6.3.1. Risk of exposure to trial treatment during pregnancy

The risk of exposure to ciprofloxacin has been evaluated using the safety information available in the SPC.

Data available on pregnant women indicate no malformative or feto/neonatal toxicity risk, the animal studies show that a risk of damage to human articular cartilage can't be excluded.

The risk of teratotoxicity/fetotoxicity or genotoxicity for males is unknown, it would therefore be assumed to be high risk.

6.3.2. Pregnancy testing, contraceptive advice and breast feeding

All patients entering CiproPAL will already have been enrolled on the ALLTogether1 study, and have consented to comply with the pregnancy testing and contraception requirements dictated by the ALLTogether1 study protocol. Thus, patients will follow the ALLTogether1 study pregnancy testing and contraception requirements. Specifically, WOCBP must have a negative pregnancy test prior to starting treatment. They are excluded from entering the study if they are pregnant, breast feeding or not willing to comply with the contraception requirements.

As part of the ALLTogether1 study, WOCBP are required to use highly effective contraceptives and to have pregnancy testing monthly. WOCBP are expected to continue to take contraceptives for up to 6 months after their last administration of chemotherapy and undergo pregnancy testing for up to 30 days after the last administration of chemotherapy. Fertile men who are engaging with WOCBP are expected to continue to take contraceptive measures (condom) until 90 days after their last administration of chemotherapy.

The above timeframe covers the treatment period for this protocol. Please refer to the ALLTogether1 protocol for further details on pregnancy testing/contraceptive requirements.

7. RANDOMISATION PROCEDURES

7.1. Randomisation

Site staff responsible for patient randomisation must request access to the electronic case report forms (eCRFs) database by completing their contact details on the Database User Access Form; they must also be assigned this responsibility on the site staff delegation log. Access to the database will be provided by UCL CTC upon receipt of completed forms. Sites should contact UCL CTC if there are any difficulties in accessing the database.

Patient randomisation is via a data capture system hosted by UCL CTC, and this must be done prior to commencement of any trial treatment/interventions. Patients randomised to the interventional arm (prophylactic ciprofloxacin) should commence treatment as soon as possible after randomisation (preferably within the first 5-8 days of induction therapy, up to 14 days is acceptable) (see section 8.2 for further details).

Pre-randomisation evaluations should be carried out at sites as detailed in section 9.1 (Pre-randomisation Assessments). Patients will be allocated to a treatment arm using minimisation, stratified by intensity of chemotherapy (3 drug vs 4 drug induction), age (<10 years vs ≥10 years), antibiotic use at randomisation (patients given antibiotics at diagnosis for proven/suspected infection vs not), randomisation time point (≤7 days vs 8-14 days) and centre.

Following pre-randomisation assessments, confirmation of eligibility and consent of a patient at a site, the information from the assessments must be entered by the Site onto the eCRF database. The trial number will be automatically allocated when a new patient is entered.

Once all information has been entered onto the database Sites should notify UCL CTC (contact details below). This information will be used to confirm patient eligibility. If further information is required, UCL CTC will contact the Site to discuss the patient and request further information to be entered into the database if needed.

Once eligibility has been confirmed, treatment allocation will be assigned for the patient.

UCL CTC will email confirmation of the patient's inclusion in the trial and treatment allocation, to the PI, main contact and pharmacy.

UCL CTC Telephone number for queries relating to Randomisation:	
CiproPAL coordinator telephone number:	020 7679 9860
Trial email address:	ctc.cipropal@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient diary if randomised to the interventional arm*. Patients should be asked to use this to record the date, time and details of ciprofloxacin taken. They must be reminded to bring this with them every time they visit the hospital
- A patient contact card. Site contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

*A patient diary template will be supplied, and must be used, unless there is prior agreement from UCL CTC to use alternative in-house records. If the patient is readmitted to hospital they should be encouraged to ask staff or carers to complete the diary entries for reconciliation purposes.

7.2. Initial Trial Drug Supply

Ciprofloxacin is to be supplied from Hospital Commercial Stock as detailed in the Summary of Drug Arrangements (SoDA) .

8. TRIAL TREATMENT

Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMP is:

- Ciprofloxacin (supplied from Hospital Commercial Stock)

Please also refer to SoDA for full arrangements for the trial.

8.1. Investigational Medicinal Products

IMP from hospital stock

Ciprofloxacin is licensed for use within paediatrics. Ciprofloxacin tablets, liquid and intravenous preparations will be provided from hospital commercial stock. Pharmacies must ensure adequate supplies for the trial.

Please refer to local policy and the relevant SPC for handling and storage conditions (as this is dependent on the brand and formulation type).

8.2. Treatment Summary

Patients will be randomised (1:1) to the interventional arm or control arm of the trial.

- Interventional arm: prophylactic ciprofloxacin (10mg/kg twice a day, enteral or intravenously, dose capped – see below in section 8.3) from randomisation to the end of induction. Specifically, Prophylactic ciprofloxacin should commence as soon as possible after randomisation (preferably within the first 5-8 days of therapy, up to 14 days is acceptable) and continue until neutrophil recovery sufficient for the commencement of consolidation (ANC $>0.5x10^9$/L). Note: if the patient is taking a broad spectrum antibiotic they should commence ciprofloxacin after the broad spectrum antibiotics are completed.
- Control arm: no additional treatment during induction. Such patients should receive the standard of care, as per local policy.

A variety of dosing regimens have been recommended for ciprofloxacin prophylaxis through it's evolution in practice; most recent UK paediatric guidelines suggest a dose of 10mg/kg twice a day. No comparative trials exist, nor do strong studies exploring the use of IV instead of enteral dosing.(24)

Any febrile episodes should be treated according to local guidelines. For patients in the interventional arm (receiving prophylactic ciprofloxacin), ciprofloxacin prophylaxis should be stopped for the duration of any treatment with broad spectrum antibiotics, empirically or for a defined infection, and re-started afterwards. If antibiotic coverage is rationalised to treat a specific infection, for example teicoplanin for a Coagulase negative staphylococcus central line infection, then ciprofloxacin should be restarted. If there are any uncertainties regarding restarting ciprofloxacin please contact UCL CTC who will enquire with the trial management group (TMG). We expect patients should be offered appropriate PJP prophylaxis.

8.3. Trial Treatment Details

Patients randomised to the interventional arm should commence prophylactic ciprofloxacin as soon as possible after randomisation (preferably within the first 5-8 days of therapy, but up to 14 days is acceptable).

Ciprofloxacin

Ciprofloxacin is an antibiotic belonging to the fluoroquinolone family. Ciprofloxacin (10mg/kg twice a day, enteral or intravenously) should be administered from randomisation to the end of induction.

Doses should be capped at 500mg per dose (enterally) or 400mg per dose (IV). Ciprofloxacin should be administered as per local policy; dose banding is permitted within the trial if it is the sites local policy for ciprofloxacin prophylaxis. Tablets can be halved to achieve the required dose. Doses should not be routinely altered during the treatment period if patient weight fluctuates, though if the patient loses more than 10% of their initial weight adjustment may be undertaken.

In case of renal impairment (GFR <60ml/min/1.73m^2) follow the SPC advice on dose reductions.

For further details on the administration please refer to the SPC, or local renal dosing protocols, for details.

Ciprofloxacin is a licensed preparation and is available in the following forms:

- Tablets 100mg, 250mg, 500mg and 750mg
- Oral suspension 250mg/5ml
- Solution for infusion 100mg/50ml, 200mg/100ml and 400mg/200ml

Administration

Ciprofloxacin should be given twice a day, ideally at regular intervals at a similar time each day. Ciprofloxacin can be administered intravenously or via enteral dosing.

Due to good bioavailability, the oral/enteral route is preferred. If there are concerns relating to absorption or the patient is nil by mouth, then ciprofloxacin can be given intravenously. Doses administered via either route are considered nearly equivalent, though the maximum dose varies between routes. Dairy products, mineral fortified drinks, indigestion remedies or medicines containing iron or zinc, should be avoided, ideally for two hours before and four hours after each oral dose.(25)

Ciprofloxacin liquid is very thick and has the potential to block NG tubes. Administration of the liquid via an enteral tube should be avoided, if possible. For administration down enteral tubes, tablets may be crushed and dispersed in a small volume of demineralised water (for example Cow and Gate ® sterilised water) and administered immediately. The enteral tube should then be flushed well. Ciprofloxacin interacts with enteral feeds, significantly reducing the absorption of the drug. It is recommended that feeds are stopped one hour before and restarted two hours after each ciprofloxacin dose.(26)

See section 8.8 for cautions.

Other elements of supportive care should be given at the discretion of the local investigator as per local practice.

Control arm

Patients randomised to the control arm should receive the standard of care, as per local policy.

8.4. Dose Modifications

See above for recommendations on the dosing of patients with renal impairment with ciprofloxacin.

Other dose reductions for Ciprofloxacin are not expected; please contact UCL CTC if you believe your patient has an exceptional clinical need for a different dose. This will be discussed with the TMG on a case by case basis.

8.5. Treatment Delays

If for any reason a patient randomised to receive ciprofloxacin (interventional arm) experiences a delay in beginning treatment, there is no cut off point for when the patient may commence treatment. Ciprofloxacin should be given as soon as possible after the end of the delay, and the actual dates of administration will be captured in the eCRF. Sites should contact UCL CTC in the event of delays to the beginning of a patient's treatment.

8.6. Management of Adverse Events

The treatment of adverse events related to ciprofloxacin (interventional arm) or standard of care treatment (control arm) should be managed as per standard local policy at the treating centre.

Please refer to the SPC for further details on the management of specific adverse events for ciprofloxacin. Discontinuing ciprofloxacin should be at the discretion of the local clinical team and the likely causative relation and the clinical situation.

If a patient experiences an AE of Special Interest between the start of treatment and the timelines specified in section 12.4, the site must inform UCL CTC immediately (see section 12 (Pharmacovigilance) for details on the reporting procedure).

8.7. Management of Overdoses, Medication Error / Investigational Treatment Error, Misuse, Abuse or Occupational Exposure

Overdose

Overdose is administration of a quantity of the IMP either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by the Sponsor upon review.

In the event of an overdose please refer to the SPC for guidance on the clinical management.

Overdoses should be reported on an incident report (see section 13.1). Any adverse events resulting from an overdose should be reported as an SAE (see section 12.2.2 for reporting procedures).

Medication error

A medication error is any unintentional error in prescribing, dispensing, or administration of an IMP while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

In the event of a medication error please refer to the SPC for guidance on the clinical management.

If the medication error is an overdose, refer to the section above. Otherwise medication errors should be reported on an incident report (see section 13.1). Any adverse events resulting from a medication error should be reported as an SAE (see section 12.2.2 for reporting procedures).

Misuse

Situations where the trial treatment is intentionally and inappropriately used in a way that is not in accordance with the protocol.

Any instances of intentional misuse should be reported on an incident report (see section 13.1). Any adverse events resulting from misuse should be reported as an SAE (see section 12.2.2 for reporting procedures).

Abuse

The persistent or sporadic, intentional, excessive use of an IMP, which is accompanied by harmful physical or psychological effects.

Any instances of abuse should be reported on an incident report (see section 13.1). Any adverse events resulting from abuse should be reported as an SAE (see section 12.2.2 for reporting procedures).

Occupational exposure

Exposure to an IMP as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.1).

8.8. Supportive Care

Any febrile episodes should be treated according to local guidelines. For patients in the interventional arm (receiving prophylactic ciprofloxacin), ciprofloxacin prophylaxis should be stopped for the duration of any treatment with broad spectrum antibiotics, empirically or for a defined infection, and re-started afterwards. If antibiotic coverage is rationalised to treat a specific infection, for example teicoplanin for a Coagulase negative staphylococcus central line infection, then ciprofloxacin should be restarted. If there are any uncertainties regarding restarting ciprofloxacin please contact UCL CTC who will enquire with the trial management group (TMG).

Supportive care should be administered as per standard local practice; in particular we expect all patients to be offered relevant PJP prophylaxis.

If patients in the control arm are given ciprofloxacin for any reason, they will not be considered to have “switched arms” and should not be withdrawn from the trial, but doses and reasons should be reported on the appropriate CRFs. This trial is comparing prophylactic ciprofloxacin to standard of care. In the control arm (standard of care) ciprofloxacin would only be given when clinically indicated. Therefore, we do expect that some patients in the control arm may still require treatment with the drug.

8.9. Cautions

QT prolongation: Ciprofloxacin can prolong the QT interval therefore administration with other drugs which may exacerbate this phenomenon is cautioned. If administration is unavoidable, consideration should be given to a baseline electrocardiogram (ECG) as per local standard practice. See appendix 3. Furthermore, it is recommended that the British National Formulary for Children (BNFc) interaction checker is to be used to confirm interaction information.

Steroids: The concomitant use of steroids with ciprofloxacin is cautioned due to the risk of hyper/hypoglycaemia. During the induction phase, blood sugar readings will be frequently measured therefore early identification of any problems will be possible. In patients where blood sugar control proves problematic, despite the normal measures including the use of insulins, consideration should be given to stopping the ciprofloxacin in consultation with the local diabetes/endocrinology team.

Patients with known G6PD deficiency should be cautioned as this may precipitate haemolysis, and patients should use sunscreen after ciprofloxacin use.

Risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH): ciprofloxacin can occasionally cause SIADH, which can also be caused by anti-leukaemic therapy. Consider discontinuation of ciprofloxacin in cases refractory to standard therapy.

Risk of seizures: Quinolones are known to reduce the seizure threshold and trigger seizures in patients with epilepsy. Ciprofloxacin should therefore be used with caution in patients with epilepsy, in patients with other seizure-prone conditions, and in patients taking additional medications that predispose to seizures. Leukaemic CNS disease and antileukaemic therapy, including intrathecal treatment, are not contraindications to ciprofloxacin use.

Peripheral neuropathy: Neuropathy is an expected side effect of vincristine therapy, but may also be related to ciprofloxacin use. If peripheral neuropathy is sufficient to reduce the dose or withhold vincristine, ciprofloxacin should be stopped and only restarted when 100% vincristine is reintroduced.

8.10. Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Ciprofloxacin is to be provided from hospital commercial stock. Pharmacies must ensure adequate supplies for the trial.

Please refer to local policy and the relevant SPC for handling and storage conditions. Further details can be provided in the summary of drug arrangements for the trial.

8.10.1. IMP accountability

The Pharmacy Lead must ensure that appropriate records for traceability of the IMP (Ciprofloxacin) are maintained. For this trial, it is not necessary to maintain full records of accountability, however simplified accountability including batch numbers and expiry dates should be kept by sites.

8.11. Clinical Management after Treatment Discontinuation

If a patient discontinues trial treatment early, they will remain on trial for follow up purposes unless they explicitly withdraw consent. Also refer to sections 9 (Assessments) and 155 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9. ASSESSMENTS

Please also see Schedule of Events table in Appendix 2.

9.1. Pre-randomisation Assessments

Patients must give written informed consent **before** any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- Medical history including demographics (including ethnicity, age and sex), start date of induction
- Baseline concomitant medication
- Weight
- Assessment of renal function (Creatinine Clearance calculated by Cockcroft-Gault)
- Baseline adverse event of special interest assessment

9.2. Pre-treatment Assessments

- Intervention arm - stool sample or peri-rectal swab culture to be obtained following randomisation, ideally prior to, but within 3 days of, commencing ciprofloxacin prophylaxis. *Optional procedure for the patient.*
- Control arm – stool sample or peri-rectal swab culture to be obtained within 3 days (+/- 2 days) of patient randomisation. (*optional procedure for the patient)*

  Health-related Quality of Life assessment (EQ-5D-Y questionnaire)

  Note: Where indicated, stool samples or peri-rectal swabs can be performed dependent on the patient's choice. This may be done whilst receiving an anaesthetic for another procedure, if the patient prefers.

  The stool samples (preferred) or peri-rectal swabs will be processed via the central laboratory. See the CiproPAL laboratory manual for processing guidelines for the samples.

  Of note, all patients (on the interventional arm or control arm) are to be asked for consent to obtain the stool samples or peri-rectal swabs to allow comparisons between the two groups.

9.3. Assessments during Treatment

The time points chosen for this trial have been selected to fit in with other key treatment time points in the ALLTogether1 study. Patients will be seen regularly during induction in line with the ALLTogether1 protocol. The following lists CiproPAL specific assessments to be performed during induction:

- From all consenting patients (irrespective of randomisation arm): Stool sample or peri-rectal swab culture to be obtained between day 15-21 of commencing leukaemia induction treatment* *(optional procedure for the patient)*
- Adverse event of special interest assessment (see section 12.4)

- Concomitant medication assessment (specifically recording antibiotic exposure)
- Infection information (specifically, incidences of bacteraemias/sterile site bacterial infections; details of bacterial isolates including sensitivity testing; incidence of *C. difficile* and invasive fungal infections; febrile episodes and febrile neutropenia; severe infection, infection-related deaths)
- Collection and review of patient diary (reconciliation purposes) if applicable
- Health-related Quality of Life assessment (EQ-5D-Y questionnaire) - to be obtained between day 15-21 of commencing leukaemia induction treatment

*** Note:** Where indicated, stool samples or peri-rectal swabs can be performed dependent on the patient's choice. This may be done whilst receiving an anaesthetic for another procedure, if the patient prefers.

The stool samples or peri-rectal swabs will be analysed via the central laboratory. See the CiproPAL laboratory manual for processing guidelines for the samples.

In the event of concerns regarding infection, further assessments should be performed as clinically appropriate as part of routine per patient care according to local practice. These may include, although are not limited to, blood cultures, sterile site cultures, biomarkers of infection, and other microbiological investigations as indicated. Sensitivity testing of all organisms isolated should be performed as per standard practice within each centre.

9.4. Assessments on Completion of Trial Treatment

Within 2 weeks of the completion of induction therapy on the ALLTogether1 trial (when neutrophil recovery is sufficient for the commencement of consolidation (ANC >0.5x10^9/L)) the following CiproPAL specific assessments are to be performed:

- From all consenting patients (irrespective of randomisation arm): Stool sample or peri-rectal swab culture to be obtained within 2 weeks of completing induction* *(optional procedure for the patient)*
- Adverse event of special interest assessment (see section 12.4)
- Concomitant medication assessment (specifically recording antibiotic exposure)
- Infection information (specifically, incidences of bacteraemias/sterile site bacterial infections; details of bacterial isolates including sensitivity testing; incidence of *C. difficile* and invasive fungal infections; febrile episodes and febrile neutropenia; severe infection, infection-related deaths)
- Collection and review of patient diary (reconciliation purposes) if applicable
- Health-related Quality of Life assessment (EQ-5D-Y questionnaire)

***Note:** Where indicated, stool samples or peri-rectal swabs can be performed dependent on the patient's choice. This may be done whilst receiving an anaesthetic for another procedure, if the patient prefers.

The stool samples or peri-rectal swabs will be analysed via the central laboratory. See the CiproPAL laboratory manual for processing guidelines for the samples.

In the event of concerns regarding infection, further assessments should be performed as clinically appropriate as part of routine per patient care according to local practice. These may include, although are not limited to, blood cultures, sterile site cultures, biomarkers of infection, and other microbiological investigations as indicated. Sensitivity testing of all organisms isolated should be performed as per standard practice within each centre.

9.5. Assessments During Follow Up

Follow-up assessments should proceed as per the ALLTogether1 trial. The following lists CiproPAL specific assessments to be performed during follow-up:

- From all consenting patients (irrespective of randomisation arm): Stool sample or peri-rectal swab culture to be obtained at the completion of intensive therapy (at start of maintenance therapy) – typically 6-7 months from randomisation* and 12 months (+/- 1 month) post randomisation into the CiproPAL trial* *(optional procedure for the patient)*
- Adverse event of special interest assessment (to be provided at the frequency and as outlined in section 12.4)
- Infection information, including antibiotic exposure, (specifically, incidences of bacteraemias/sterile site bacterial infections; details of bacterial isolates sensitivity testing; incidence of *C. difficile* and invasive fungal infections; febrile episodes and febrile neutropenia; severe infection, infection-related deaths) – to be provided after every episode until the end of the ALLTogether1 leukaemia treatment
- Health-related Quality of Life assessment (EQ-5D-Y questionnaire) – to be completed at the completion of intensive therapy (at start of maintenance therapy) –typically 6-7 months from randomisation and 12 months (+/- 1 month) post randomisation into the CiproPAL trial.

  ***Note:** Where indicated, stool samples or peri-rectal swabs can be performed dependent on the patient's choice. This may be done whilst receiving an anaesthetic for another procedure, if the patient prefers.

  The stool samples or peri-rectal swabs will be analysed via the central laboratory. See the CiproPAL laboratory manual for processing guidelines for the samples.

In the event of concerns regarding infection, further assessments should be performed as clinically appropriate as part of routine per patient care according to local practice. These may include, although are not limited to, blood cultures, sterile site cultures, biomarkers of infection, and other microbiological investigations as indicated. Sensitivity testing of all organisms isolated should be performed as per standard practice within each centre.

Additional variables required for statistical analysis (e.g. leukaemia information, time of event outcome data etc) which are collected as per the ALLtogether1 protocol will be obtained from the Sponsor of ALLTogether 1 via a data sharing agreement.

Interruptions to Trial Treatment

- If a patient does not start trial treatment due to any reason, see section 15.1 for further guidance.

- If a patient discontinues trial treatment due to any reason, see section 15.2 for further guidance.
- If a patient is discovered to have lymphoblastic lymphoma (LBL) post randomisation into CiproPAL, or becomes ineligible to continue on the ALLTogether1 study due to being positive for BCR-ABL1 fusion, see section 15.3 for further guidance.

10. CENTRAL LABORATORY

Stool samples or peri-rectal swab cultures will be obtained from consenting patients at the following timepoints and analysed at the central laboratory for the purposes of the secondary endpoint relating to looking at patterns of antimicrobial resistance and their changes over time:

Patterns of antimicrobial resistance and their changes over time in

- Baseline (following randomisation but prior to, or within 3 days of, commencing ciprofloxacin (interventional arm) or within 3 days (+/- 2 days) of randomisation (control arm))
- Between day 15-21 after commencing leukaemia induction treatment
- Within 2 weeks of completing induction
- At the completion of intensive therapy (i.e. at the start of maintenance therapy which typically will be 6-7 months from randomisation)
- At 12 months post randomisation into the CiproPAL trial.

See the CiproPAL laboratory manual for processing guidelines for the samples.

Providing the samples to the central laboratory is optional for the patient and patients or and/or parents/guardians will consent for sample donation as part of the main trial consent form.

Sites must keep a record of all samples sent to central laboratory. See the Laboratory Manual for more details of how to track samples.

The stool samples or peri-rectal swabs may be done whilst receiving an anaesthetic for another procedure, if the patient prefers. At each timepoint,1x stool sample or peri-rectal swab will be collected and sent ambient on the day of collection using Royal Mail Safeboxes to the central laboratory. Samples will be processed and stored at the central laboratory.

Analyses will include but not be restricted to surveillance of standard resistance patterns, in particular the evolution of antimicrobial resistance against fluoroquinolones and the emergence of multi-drug resistant strains, including Extended Spectrum Beta Lactamase (ESBL) and Carbapenemase Producing Enterobacteriaceae (CPE).

After completing trial related analyses, subject to patient and/or parent/guardian consent, leftover material will be stored for use in future ethically approved research if funding for storage can be secured, or will otherwise be destroyed.

The patient retains the right to have their samples destroyed at any time by contacting the principal investigator at the site at which they were registered for the study. The site principal investigator will then be responsible for contacting the sponsor to arrange for this to occur.

11. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using an electronic case report form (eCRF) created and maintained by UCL CTC. As this study is an add-on study to ALLTogether1 only CiproPAL specific variables will be collected on the UCL CTC database in order to minimize data entry duplication by sites.

Data must be accurately transcribed on to trial eCRFs and must be verifiable from source data at site. Examples of source documents are hospital records, which include patient's medical notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending, to maintain confidentiality. Refer to section 14 Trial Monitoring and Oversight for further details of centralised monitoring of source documentation.

11.1. Entering data into the eCRF

The eCRF must be completed by site staff who have been appropriately trained, are listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will be issued with their own unique login details for the eCRF by UCL CTC, and a list of current users at each site will be maintained by UCL CTC. Site staff must never share their login details with other staff as the eCRF audit trail will record all entries/changes made by each user. The PI is responsible for the accuracy of all data reported in the eCRF.

The use of abbreviations and acronyms must be avoided.

11.2. Corrections to eCRF Forms

Where necessary, corrections can be made by site staff to data on the eCRF, as long as the eCRF has not been locked/frozen by UCL CTC. The eCRF audit trail will record the original data, the change made, the user making the change and the date and time. Site staff should contact UCL CTC if changes need to be made to a locked/frozen eCRF.

11.3. Missing Data

To avoid the need for unnecessary data queries, fields should not be left blank on the eCRF. If data is unavailable, please refer to the 'eCRF Completion Guidance' for information on how to indicate that data is "Not Done", Not Applicable", "Not Available" or "Not Known" (only use if every effort has been made to obtain the data).

11.4. Timelines for Data Entry

The relevant eCRF forms must be completed as soon as possible after a patient's visit and within 7 days of the patient being seen. The exceptions to this relate to the following:

- Follow-up CRFs: To be completed and returned within 4 weeks of the patient being seen

- Death CRF: To be completed within the timelines specified in section 12.5 of becoming aware of the death
- SAE & pregnancy reports: within 24 hours of becoming aware (see section 12 for details)

Sites who persistently do not enter data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and this may trigger a monitoring visit. See section 14.2 (‘Triggered’ On-Site/Remote Monitoring) for details.

11.5. Data Queries

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning. The data can be corrected immediately, or where this is not possible, the warning can be saved and the data amended at a later stage.

Further data review will be carried out at UCL CTC and queries raised where necessary. Further guidance on the process for handling data queries can be found in the ‘eCRF Completion Guidance’.

12. PHARMACOVIGILANCE

12.1. Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with an IMP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP, whether or not related to that IMP. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. A causal relationship between an IMP and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See section 12.2.2 for SAE reporting procedures.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information.

i.e. an adverse event that meets all the following criteria:

- **Serious** – meets one or more of the serious criteria, listed under the definition of SAE above
- **Related** – assessed by the local PI or designee, or Sponsor as causally related to one or more elements of the trial treatment

- **Unexpected** – the event is not consistent with the applicable reference safety information

See section 12.3 for reporting procedures for these events.

Adverse Event of Special Interest (AESI)

An AE that is of scientific and medical concern to the Trial Management Group for which rapid communication is required. The AESI may not meet the standard criteria for seriousness and it may occur outside the standard AE reporting timeframes for the trial. The AEs of special interest for this trial are listed in section 12.4. See section 12.4 for reporting procedures for these events.

Urgent Event

An AE that is protocol-related and requires completion of a trial specific Case Report Form.

Urgent events for this trial are listed in section 12.5 of the protocol and need to be assessed for whether they meet the definition of an SAE or not.

See section 12.5 for reporting procedures for these events.

Overdose, IMP or Medication error, Abuse, Misuse or Occupational exposure

Refer to section 8.7 for details on reporting of these events.

12.2. Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 should be used. This is available online at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Severity grade

Severity grade of each adverse event must be determined by using CTCAE v5.0.

Causality

The relationship between the treatment and an adverse event will be assessed.

For AEs (including SAEs) the local PI or designee will assess whether the event is causally related to each IMP.

For SAEs a review will also be carried out by the Sponsor's delegate.

Causal relationship to each IMP must be determined as follows:

- Related (reasonable possibility) to an IMP
- Not related (no reasonable possibility) to an IMP

UCL CTC will consider events evaluated as related to be adverse reactions.

12.2.1. Reporting of Adverse Events (AEs)

Due to the extensive expected toxicity seen in this patient population, full reporting of adverse events according to standard guidelines would be of limited value when evaluating toxicity in this study. The volume could be prohibitive, and risk becoming less informative due to differences in interpretation and resources for reporting locally. For this reason, not, all AEs need to be reported on an ongoing basis, further detail of what is to be reported and how can be found below and, in the SAE, (12.2.2), AESI (12.4) and urgent event (12.5) sections.

All adverse events should be assessed for whether they meet the definition of a Serious Adverse Event (SAE) or Adverse Events of Special Interest (AESI), and therefore are reportable to UCL CTC using the trial specific SAE Report/AESI Report. Also see section 12.2.2 (Reporting of Serious Adverse Events (SAEs) and section 12.4 (Adverse Events of Special Interest)). Adverse events meeting the definition of an Urgent Event must be reported on an Urgent Event form (see section 12.5 Urgent Events).

Note: The reporting of SAEs for CiproPAL and ALLTogether1 are independent from one another. If an event meets the definition of a Serious Adverse Event (SAE), it should be reported on the specific SAE report for each trial as applicable to the trial.

12.2.2. Reporting of Serious Adverse Events (SAEs)

SAEs need to be reported to UCL-CTC that are either:

- Assessed as **unrelated** to Ciprofloxacin treatment and are Grade 4 and above,
- Assessed as (**reasonably possibly) related** to Ciprofloxacin treatment. Any Grade should be reported.

Control arm:

All SAEs grade 4 and above that occur between the signing of informed consent and 65 calendar days post randomisation into the trial must be reported by site in the SAE eCRF within **24 hours** of observing or learning of the event.

Investigational arm:

All SAEs that are grade 4 or above and assessed as unrelated to Ciprofloxacin treatment or are assessed as related (or reasonably possibly related) to Ciprofloxacin treatment and are of any grade that occur between the signing of informed consent and 30 calendar days post last IMP administration **(or after this date if the site investigator feels the event is related to an IMP)** must be reported by site in the SAE eCRF within **24 hours** of observing or learning of the event.

All sections of the SAE eCRF must be completed. If the event is **not being reported to UCL CTC within 24 hours**, the circumstances that led to this must be detailed in the SAE eCRF to avoid unnecessary queries.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE eCRF **unless considered to be related to the IMP**. However, the events must be recorded in the relevant sections of the trial eCRFs:

- SAEs grade 3 or below do not need to be reported as an SAE unless the event is assessed as related to ciprofloxacin (Note AESIs of all grades must be still reported using the SAE eCRF – see section 12.4 for list of events)
- events that occur more than **30 calendar days** post last IMP (investigational arm) or more than 65 calendar days post randomisation (control arm). Note: this does not include pregnancy related events (see section 12.7)
- disease progression (including disease-related deaths)

Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons does not qualify as an SAE.

SAEs must be entered into the SAE eCRF within 24 hours of the site becoming aware of the event

Email: ctc.ciproPAL@ucl.ac.uk for any queries

SAE Follow-Up Reports

UCL CTC will follow up all SAEs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to the delay must be detailed in the SAE Report to avoid unnecessary queries.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the approved RSI (the list of expected adverse events in section 4.8 of the SPC for Ciprofloxacin).

The CI, or their delegate (e.g. a clinical member of the TMG), will review the SAE and perform an evaluation of causality on behalf of the Sponsor. If UCL CTC has considered expectedness difficult to determine, the reviewer will be consulted for their opinion at this time.

12.3. SUSARs

If the event is evaluated as a SUSAR, i.e. an unexpected event that is related (reasonable possibility) to the investigational drug, UCL CTC will submit a report to the MHRA and the REC within 7 calendar days for initial reports of fatal/life threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events.

Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

Informing Sites of SUSARs

UCL CTC will inform all sites of any SUSARs that occur on the trial. Sites will receive a quarterly line listing which must be processed according to local requirements.

12.4. Adverse Events of Special Interest

The following adverse events of special interest must be collected between informed consent and the timeframes specified in the table below. They must be reported on the SAE eCRF and marked as an AESI in the database regardless of their seriousness within the timeframes specified in the table below. All sections on the SAE eCRF must be completed.

Adverse Event of Special Interest	**Timeframe for reporting**	**eCRF required**	**When to enter on eCRF**
Requirement of organ support or critical care intervention	From informed consent until end of leukaemia treatment	SAE eCRF	Within 24 hours of becoming aware of the event
QTc prolongation	From informed consent until 30 calendar days post last IMP administration (intervention arm) or day 65 post randomization (control arm)	SAE eCRF	Within 24 hours of becoming aware of the event
CNS toxicity (PRES, stroke-like syndrome, leukoencelopathy, seizures, coma, CNS bleeding)	From informed consent until 30 calendar days post last IMP administration (intervention arm) or day 65 post randomization (control arm)	SAE eCRF	Within 24 hours of becoming aware of the event
Invasive fungal infection	From informed consent until end of leukaemia treatment	SAE eCRF	Within 7 days of being aware of the result
C. difficile infection	From informed consent until end of leukaemia treatment	SAE eCRF	Within 7 days of being aware of the result
Tendinitis/tendon rupture *Defined as any tendinopathy diagnosed by an appropriate clinical expert (e.g. rheumatologist)*	From informed consent until end of leukaemia treatment	SAE eCRF	Within 7 days of being aware of the result

Allergic reaction (related to ciprofloxacin) **(Intervention arm only)**	From informed consent until 30 calendar days post last IMP administration	SAE eCRF	Within 7 days of being aware of the result

If an AESI of any grade, meets the definition of an SAE, this must be reported as an SAE, as well as an AESI, on the SAE eCRF, (in line with section 12.2.2) and will be processed by UCL CTC as usual

All AEs of special interest must be reported by site in the eCRF, within the timeframes as defined in the table above

12.5. Urgent Events

The following events must be collected and reported as urgent events **as per the timeframes defined in the table below**. They must be reported on the relevant Urgent Event Form in the eCRF. They will be processed at UCL CTC as CRFs. Sites must assess whether they meet the definition of an SAE (grade 4 or above and assessed as unrelated to Ciprofloxacin treatment or are assessed as related (or reasonably possibly related) to Ciprofloxacin treatment and are of any grade) and if applicable, report as per section 12.2.2.

Event	Description	eCRF required	Timeframe
Death	Death from any cause	Death Form	Interventional arm: If death occurs within 30 days after discontinuing prophylactic ciprofloxacin, report within 24 hours of awareness of the event.

			If death occurs at any point >30 days after discontinuing prophylactic ciprofloxacin (up until the end of trial declaration), report within 7 days of becoming aware of the event. Control arm: If death occurs in the control arm at any point prior to the end of trial being declared, report within 7 days of becoming aware of the event. *Note: disease related deaths are exempt from SAE reporting*
Syndrome of inappropriate antidiuretic hormone secretion (SIADH) *Defined as low sodium (<129mmol/L) in the presence of inappropriately concentrated urine which the investigator considers to be SIADH*	From informed consent until 30 calendar days post last IMP administration (intervention arm) or day 65 post randomization (control arm)	Urgent Event Form	To summarise data on eCRF at the point of treatment discontinuation. NB to assess whether an SAE report needs to be submitted in line with section 12.2.2
Hypoglycaemia leading to hospital admission			
Hyperglycaemia leading to hospital admission			
Peripheral neuropathy *Defined as any grade 2 or above as per CTCAE v5.0*			
Hepatic dysfunction *Defined as clinically significant disturbance in hepatic function, not merely transaminitis, for example deranged clotting or raised bilirubin of hepatic origin.*			

All Urgent Events must be reported by site in the eCRF, within the timeframes as defined in the table above

12.6. Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

The IDMC will review the following trial safety data:

- Disease-related events (exempt from SAE reporting as per section 12.2.2) according to treatment allocation to identify whether disease-related events appear to be enhanced by the IMP;
- Incidence of AESIs as outlined in section 12.4 of the protocol

The IDMC and TMG will review trial safety data to identify:

- A higher incidence of rare serious adverse reactions than is stated in the RSI for an IMP;
- Trial related events or incidents that may lead to changes to the trial documents.

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

12.7. Summary Table

The table below summarises each event and the required reporting procedure.

Event	Applicable eCRF name	Grade *(CTCAE v5.0)*	Reporting timeframe	Notes
SAEs	SAEs and AESIs	Grade 4 or above & unrelated to ciprofloxacin treatment	Within 24 hours of site becoming aware	Select “SAE” on eCRF.
SAEs	SAEs and AESIs	Related/ possibly related to ciprofloxacin treatment (All grades)	Within 24 hours of site becoming aware	Select “SAE” on eCRF.
SAEs	N/A	Grade 3 or below & unrelated to ciprofloxacin treatment	N/A	These events do not need to be reported.

AESIs	SAEs and AESIs	All grades	Within 24 hours of site becoming aware or within 7 days of result (table in section 12.4)	Select “AESI” on eCRF.
AESIs which meet the definition of an SAE	SAEs and AESIs	Grade 4 or above & unrelated to ciprofloxacin treatment, or related/ possibly related to ciprofloxacin treatment (All grades)	Within 24 hours of site becoming aware	Select both “SAE” and “AESI” on eCRF.
Urgent Events	Urgent Events	All grades	Once during the “within two weeks of completing induction” visit unless event is death (see table in section 12.5)	Deaths to be reported: Interventional arm: If death occurs within 30 days after discontinuing prophylactic ciprofloxacin, report within 24 hours of awareness of the event. If death occurs at any point >30 days after discontinuing prophylactic ciprofloxacin (up until the end of trial declaration), report within 7 days of becoming aware of the event. Control arm: If death occurs in the control arm at any point prior to the end of trial being declared, report within 7 days of becoming aware of the event.

				Note: disease related deaths are exempt from SAE reporting
Urgent events which meet the definition of an SAE	SAEs and AESIs	Grade 4 and above	Within 24 hours of site becoming aware	Event to be reported on the Urgent Event eCRF at the point of treatment discontinuation.

12.8. Pregnancy

Reporting Period

For any pregnancy exposure to trial treatment, the site must submit a trial specific Pregnancy Report to UCL CTC using the Pregnancy eCRF **24 hours of learning of its occurrence**.

A pregnancy exposure to trial treatment includes:

- Pregnancy in a trial patient
- Pregnancy in a partner of a male trial patient
- Exposure to treatment in a partner of a male trial patient who was pregnant at the start of the trial

occurring between the start of treatment and the end of treatment with ciprofloxacin.

The site must request consent from the pregnant trial patient or pregnant female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial-specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of trial patients

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

Pregnancies must be entered into the Pregnancy eCRF within 24 hours of the site becoming aware of the event.

Email: ctc.ciproPAL@ucl.ac.uk for any queries

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up **at least monthly** for up to 6 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted to UCL CTC using the the Pregnancy eCRF within **24 hours** of

learning of the new information. In case of adverse outcome to the pregnancy reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC if the pregnancy outcome meets the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

12.9. Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

13. INCIDENT REPORTING AND SERIOUS BREACHES

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. When an incident report is requested by UCL CTC this should be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2. Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the Sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14. TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documents may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC or its representatives will conduct all monitoring in compliance with the participant consent, site policy and data protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required, based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

14.1. Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of the following documents by sites to UCL CTC for review: screening logs, accountability logs and staff delegation logs. Expectations for document submission will be explained during site initiation and UCL CTC or its representatives will send emails to sites requesting the documents when required.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency determined for the trial. Checklists detailing the current version/date of version-controlled documents will be provided by UCL CTC for this purpose.

14.2. ‘Triggered’ On-Site/Remote Monitoring

On-site/remote monitoring visits may be scheduled following UCL CTC review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

On-site Monitoring

Sites will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

UCL CTC defines remote monitoring as monitoring activities conducted at a location remote from the research site which replicate some on-site activities e.g. source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to participating sites (e.g. global pandemic) or conducted routinely.

Details of remote monitoring will be agreed with participating sites, conducted in accordance with site policy and documented in the monitoring plan.

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing remote monitoring.

Remote monitoring will be conducted by UCL CTC or its representatives via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties. Also refer to section 11 Data Management and Data Handling Guidelines for details of how source documentation may be submitted to UCL CTC.

Monitoring Follow up

Following on-site/remote monitoring, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.3. Escalation of monitoring issues

Where monitoring indicates that a patient may have been placed at risk e.g. evidence of an overdose having been administered, the matter will be raised urgently with site staff and escalated as appropriate.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches) for details.

14.4. Oversight Committees

14.4.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and CiproPAL trial staff from UCL CTC (see page 3). The TMG will be responsible for overseeing the trial. The group will meet regularly (approximately bi-annually) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Children's Cancer and Leukaemia Study Group and NIHR Children's Allergy, Infection and Immunity group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

TMG members will be required to sign a TMG charter which described the committee's responsibilities in relation to the trial and requires any potential conflicts of interest to be declared.

14.4.2. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

TSC members will be required to sign a TSC charter which describes the committee's responsibilities and requires any potential conflicts of interest to be declared.

14.4.3. Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held at least annually, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

IDMC members will be required to sign an IDMC charter which describes the committee's responsibilities and requires any potential conflicts of interest to be declared.

14.4.4. Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 122 (Pharmacovigilance).

15. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1. Patients who do not start Trial Treatment

If a patient does not start treatment the reasons for this must be recorded in the patient's medical notes and on the relevant eCRFs. Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision
- No longer eligible

If the patient was eligible at randomisation and does not explicitly withdraw consent for follow-up, they will remain on the trial for follow-up purposes and outcome data (see table below) will still be required. This, and data collected about the patient so far will be used in the trial analysis, where appropriate. Biological samples collected may still be used unless the patient explicitly withdraws consent to this.

What is the treatment plan?	**Induction data**	**Post induction data**
Remaining on ALLTogether but not CiproPAL	All data and samples	All data and samples
Removed from ALLTogether, but given a similar treatment i.e. patients found to have a BCR-ABL1 fusion or to be or lymphoblastic lymphoma (LBL) post registration/randomisation	All data and samples	None
Removed from ALLTogether and **not** given similar treatment i.e. other misdiagnoses or patients not fit for induction treatment.	None	None

If you are unsure of what data is required for a patient discontinuing trial treatment please contact UCL CTC.

15.2. Discontinuation of Trial Treatment

A patient may discontinue trial treatment if the treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's medical notes and on the relevant eCRFs. Reasons for discontinuing treatment may include:

- Patients testing positive for BCR-ABL1 fusion or discovered to have LBL post randomisation into the CiproPAL trial (see section 15.3 for further details)
- Unacceptable toxicity
- Intercurrent illness that prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition that justifies the discontinuation of trial treatment in the site investigator's opinion

- Non-compliance with the trial treatment and/or procedures
- Patients found to be ineligible for any other reason

In these cases, patients will remain on the trial for the purposes of follow-up and will be included in appropriate data analysis, unless they explicitly withdraw consent to this. With the exception of LBL patients or those with BCR-ABL1 fusion (which are detailed in section 15.3) follow up should be as per the table below.

If a patient expresses their wish to discontinue trial treatment, sites should explain the importance of remaining on trial follow-up, or of at least allowing routine follow-up data and data already collected to be used for trial purposes. If the patient gives a reason for their withdrawal, this should be recorded.

Type of discontinuation	Induction data	Post induction data
CiproPAL treatment only (i.e. patient continues with ALLTOGETHER-1)	• All data and samples • Completion of treatment form	All data and samples
CiproPAL treatment **and** ALLTOGETHER-1 (except BCR-ABL1 fusions and LBL diagnosis)	• All data and samples (up to discontinuation) • Completion of treatment form	SAE/AESI/urgent event reports only

If you are unsure of what data is required for a patient discontinuing trial treatment please contact UCL CTC.

15.3. Patients positive for BCR-ABL1 fusion or diagnosed with LBL

Patients who test positive for BCR-ABL1 fusion [t(9;22)(q34;q11.2), Philadelphia chromosome], or those discovered to have LBL, become ineligible to continue on the ALLTogether1 study. These patients may continue on CiproPAL and complete the trial treatment (prophylactic ciprofloxacin). This must be recorded in the patient's medical notes and on the relevant eCRFs.

These patients will be included in appropriate data analysis (data to be collected as per table below), unless they explicitly withdraw consent to this.

Type of discontinuation	Induction data	Post induction data
BCR-ABL1 fusion or LBL diagnosis	• All data and samples • Completion of treatment form	SAE/AESI/urgent event reports only

If you are unsure of what data is required for a patient discontinuing trial treatment please contact UCL CTC.

15.4. Withdrawal of Consent

If a patient withdraws consent for any aspect of the study, UCL CTC should be notified and the Change of Status/Withdrawal Form should be completed and submitted to UCL CTC.

15.4.1. Withdrawal of consent for follow up

If a patient withdraws consent for trial follow up, but is happy to continue with future data collection from hospital notes:

- They will remain on trial for follow up
- The patient will no longer have trial-specific visits and assessments. Follow up forms should be completed based on the routine visit nearest the due date for the follow up form
- The following eCRFs/data must be submitted at time of withdrawal:
    - Change of Status/Withdrawal Form
    - All CRFs up to and including the date of withdrawal of consent
- Thereafter, the site should report SAE/AESI/urgent events, end of induction infection form and follow up forms, including notifications of death.

15.4.2. Withdrawal of consent for data collection

If a patient **explicitly** states they do not wish to contribute further data to the trial their decision must be respected. The following eCRFs must be submitted at the time of withdrawal of consent:

- Change of Status/Withdrawal Form
- All data up to and including the date of withdrawal of consent

Thereafter, no further data should be submitted, with the exception of SAE reports as per section 12.2 (due to the regulatory requirement for oversight of IMP safety).

15.4.3. Withdrawal of consent for use of samples

If a patient withdraws consent for the use of their samples for future research, this should be reported on the Change of Status/Withdrawal form in the eCRF. Unless the patient has also withdrawn from trial treatment/follow up, management and data collection should continue as per protocol.

15.5. Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for the patient to be followed up via the patient's GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to another participating site, the registering site remains responsible for submission of eCRFs.

If a patient is lost to follow-up, every effort should be made to contact the patient's GP to obtain information on the patient's status.

At the time of loss to follow up, the following eCRFs should be submitted:

- Change of Status/Withdrawal Form
- All data due up to and including the date of loss to follow up

If contact is re-established with the patient, a change of Status form should be submitted and further follow up forms should be sent. A death form should also be submitted if the site becomes aware that the patient has died.

Prior to primary analysis and presentation/publication of the primary endpoint data, UCL CTC may ask sites to attempt to re-establish contact with patients who were lost to follow up and/or check hospital records for evidence of when the patient was last known to be alive and other relevant information.

16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be when the last patient has completed the follow-up for ALLTogether1 (this is estimated to be December 2031). At this point the 'declaration of end of trial' form will be submitted to the MHRA and Ethics Committee, as required, and sites notified.

UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3. Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.4.2 Trial Steering Committee (TSC) and 14.4.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4. Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the site agreement.

17. STATISTICS

17.1. Sample Size Calculation

The primary endpoint for CiproPAL is the confirmed bacteraemia rate during induction treatment (from randomisation until the start of consolidation, discontinuing protocol anti-leukaemic therapy or death post induction).

Dana Faber group quoted a bacteraemia rate in induction of 24.7% in the pre-prophylaxis cohort. (11) The comparable UKALL 2003 trial found a proven infection rate of 15%. (18) Paediatric observational studies and adult trial data showed a reduction in bacteraemia of ~50%. Here we are assuming a more conservative, but still highly clinically meaningful, difference of 40%.

Assuming a 15% rate in the control arm, we aim to show that prophylaxis with Ciprofloxacin will reduce the rate to 9%. 1052 patients randomised 1:1 will give us 85% power to show this difference with a 5% 2-sided alpha.

The sample size was calculated using NQuery 8 (test of two proportions).

17.2. Statistical Analysis

17.2.1. Analysis of main endpoint

The rates of confirmed bacteraemia or sterile site bacterial infection during induction (from randomisation until the start of consolidation, discontinuing protocol anti-leukaemic therapy or death post induction) will be compared between the arms using a chi-squared test. The analysis will be intention to treat, however patients who are found to be not eligible post randomisation (except patients with a BCR-ABL1 fusion, or LBL i.e. those who continue CiproPAL treatment through induction) or die without an infection reported during induction (likely fewer than 5 cases) will be excluded.

17.2.2. Analysis of secondary endpoints and secondary analyses

Febrile episodes, febrile neutropenia, severe infection (defined as the need for organ support or critical care intervention) and infection-related death.

Rates of these events during the induction period (as described above) will be compared using Chi squared tests (or Fisher's exact test if more appropriate). This will be analysed as the proportion of patients with at least one event of each type, and as at least one of these events. We will also look at rates of these events post induction (by treatment phase) to see if there are any later effects.

Antibiotic exposure, including for prophylactic, empiric and treatment.

Antibiotic exposure (20): This will be reported as days on therapy per 100 patient days per antibiotic. Total exposure for IV antibiotics and IV+oral will be described. Separate analysis will be performed looking specifically at differences:

1. Prophylactic antibiotics include ciprofloxacin (intervention), prophylaxis for Pneumocystis jirovecii infection (usually with co-trimoxazole on two days per week), and prophylaxis against urinary or respiratory infections.
2. Empirical antibiotics are those given prior to the identification of a specific infection, and is usually defined within a centre's febrile neutropenia protocol.
3. Treatment antibiotics are those targeted at a particular clinically or microbiologically defined infection.

Total days and days of prophylaxis will not be directly compared between the arms i.e. no p-value will be generated, but days of empirical and treatment antibiotics will be compared using a T-test or, a Wilcoxon Mann-Whitney test (if non-normally distributed).

Patterns of antimicrobial resistance and their changes over time in A) bacterial isolates from blood cultures or from other sterile sites, B) stool or peri-rectal swab isolates

Sites will report resistance levels for each antibiotic class (as resistant, intermediate or sensitive) whenever possible, and these will be analysed with an ordinal logistic regression repeated measures model to see if there are differences between the treatment arms during the first year of treatment. We will also consider the time point of treatment i.e. time measured from the opening of CiproPAL so we can assess whether treating 50% of patients with prophylactic antibiotics has changed the resistance patterns in the patients recruited early, vs the patients recruited later in the study (~4.5 years from first randomisation until final swab).

Secondary infections: *Clostridium difficile* infections and invasive fungal infections

Rates of secondary infections during the induction period (as described above) will be compared using Chi squared tests (or Fisher's exact test if more appropriate). This will be analysed as the proportion of patients with at least one event of each type, and as at least one of these events. We will also look at rates of these events post induction (by treatment phase) to see if there are any later effects.

Specific quinolone adverse effects, including tendinitis and tendinopathy, visual disturbance, seizures, polyneuropathy and hepatic dysfunction

Rates of these events during the induction period (as described above) will be compared using Chi squared tests (or Fisher's exact test if more appropriate). This will be analysed as the proportion of patients with at least one event of each type, and as at least one of these events. Patients in the control arm will also be split by whether they were given quinolones before the onset of the event or not. We will also look at rates of these events post induction (by treatment phase) to see if there are any later effects.

Any patients with medically significant events thought to be related to quinolones will be presented in more detail i.e. severity, outcome, effect on later treatment etc.

Compliance to Ciprofloxacin and induction treatment

Numbers and proportions of patients completing Ciprofloxacin treatment during induction will be reported along with any reasons for early discontinuation.

Delivery of induction treatment including delays, reductions and omissions of induction drugs, and the time between induction and consolidation 1 will also be compared between the arms.

Outcomes post Induction

Rates of complete remission and MRD negativity at day 29, event free, overall survival and time to relapse rates (as defined within in the ALLtogether1 protocol) will also be compared.

17.2.3. Economic evaluation

We will undertake a model-based health economic analysis from the perspective of the National Health Service (NHS) and Personal Social Services (PSS). The model will adopt a lifetime horizon, with cost-effectiveness estimated in terms of the incremental cost per quality-adjusted life year (QALY) gained. Health outcomes and costs will be discounted at 3.5% per annum.

The model will use a hybrid approach comprised of an initial decision tree to reflect the incidence and health consequences of infections during the neutropenic period of induction, and a longer-term valuation of outcomes and costs for patients who survive beyond this initial treatment period. Estimates of treatment effects relating to the avoidance of infections and death during induction will be estimated directly using data collected within CiproPAL. Estimates of long-term outcomes will be derived from previous economic models in the first instance, with a later analysis to be conducted using data from ALLtogether1. This later analysis is likely to involve the development of a state-based model (cohort-level state transition model or partitioned survival model) with parametric survival models fitted to data from ALLTogether1.

We will use data on health-related quality of life collected using the EQ-5D-Y at baseline, between 15-21 days of commencing induction, within 2 weeks of completing induction, at the completion of intensive therapy (i.e. at the start of maintenance) and at 12 post randomisation, together with information on the duration of infections from CiproPAL, to estimate health utilities for patients with and without infection, including the disutility associated with chemotherapy. The EQ-5D-Y will be self-completed by children who are able to do so (age ≥8 years) or by parents as proxy for younger children who are unable to complete the questionnaire. The EQ-5D-Y will be valued using the adult 3-level tariff. Imputation may be required to handle missing data.

Resource use will include: costs of the ciprofloxacin prophylaxis; hospital-based IV ABs (by type), and hospital bed days (by type). Resource use associated with downstream treatments (e.g. front-line therapy and treatments for relapsed disease) will be based on the results of previous models in ALL in the first instance, with a later analysis anticipated based on the protocols used in ALLtogether1. Costs will be valued at current prices using routine reference cost sources and other literature.

Uncertainty will be assessed using deterministic and probabilistic methods. Deterministic analyses will include 1-way sensitivity analyses and scenario analysis to identify key drivers of cost-effectiveness. Probabilistic sensitivity analysis will be undertaken to

estimate the likelihood that ciprofloxacin prophylaxis is cost-effective relative to no prophylaxis. Value of information analysis will be undertaken to inform the prioritisation and design of future research.

17.3. Interim Analyses

There are no formal interim analyses but an independent data monitoring committee (IDMC) will review the unblinded data at least yearly and can recommend changes to the protocol and an end to recruitment based safety or efficacy.

18. ETHICAL AND REGULATORY CONSIDERATIONS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- Human Rights Act 1998
- Data Protection Act 2018, and General Data Protection Regulation (EU)2016/679 (GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority

Where applicable, UCL CTC and sites will work towards implementation of the EU Clinical trials Regulation EU/536/2014.

18.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London-Brent Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

18.2. Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

18.3. Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.4. Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

18.5. Patient Confidentiality & Data Protection

Patient identifiable data, including initials and date of birth will be collected by UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL

19. SPONSORSHIP AND INDEMNITY

19.1. Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2. Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20. FUNDING

National Institute for Health Research (NIHR) is supporting the central coordination of the trial through UCL CTC.

Research A and B costs will be reimbursed to sites as per the finance section of the site agreement.

21. PUBLICATION POLICY

The results of the CiproPAL trial will be presented at relevant conferences and published in a peer reviewed journal. The primary publication from the CiproPAL trial will be written by the TMG. Authors will include the CI, TMG members, representatives of UCL CTC including the trial coordinator and trial statistician, and PIs at sites that make a significant contribution to patient recruitment.

It is anticipated that three publications will arise from the CiproPAL trial – the first reporting the primary outcome (sterile site infection within the period of induction), the second of the data relating to colonising organisms and the third of the data relating to infecting organisms.

Abstracts and papers will be reviewed by Karolinska prior to submission in accordance with the requirements of the collaboration agreement.

The Clinicaltrials.gov number and/or ISRCTN of the trial and the funder reference number will be quoted in all publications. Reference to the funding should be in line with the Funder agreement, specifically the following should be included:

"This report is independent research funded by the National Institute for Health Research (NIHR Health Technology Assessment, NIHR130848 - CiproPAL (Ciprofloxacin Prophylaxis in Acute Leukaemia): A randomised trial to assess the use of ciprofloxacin prophylaxis to prevent bacterial infection in children treated on the induction phase of the ALLTogether1 treatment protocol). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care."

Furthermore, Karolinska's collaboration in CiproPAL should be acknowledged in any publication arising from the trial.

Sites may not publish any data pertaining to CiproPAL patients without prior written permission from the TMG.

Data generated from the CiproPAL trial will be the property of UCL as Trial Sponsor.

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APPENDIX 1: ABBREVIATIONS

AB	Antibiotics
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
AMR	Antimicrobial Resistance
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
BNFc	British National Formulary for children
BSI	Blood Stream Infections
CDC	Centre for Disease Control
CDI	Clostridium difficile infection
CI	Chief Investigator
CLABSI	Central Line Associated BSI
CNS	Central Nervous System
COG	Children's Oncology Group
CPE	Carbapenemase Producing Enterobacteriaceae
CRF	Case Report Form
CT scan	Computerised Tomography scan
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CR UK	Cancer Research UK
CV	Curriculum Vitae
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESBL	Extended Spectrum Beta Lactamase
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation (EU)2016/679
GFR	Glomerular Filtration Rate
HRA	Health Research Authority
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRM	Infection-Related Mortality
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LBL	Lymphoblastic Lymphoma
MDI	Microbiologically Documented Infections
MHRA	Medicines and Healthcare products Regulatory Agency
MRD	Minimal Residual Disease
NCRI	National Cancer Research Institute
NG	Nasogastric
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health Research
PI	Principal Investigator
PPI	Patient and Public Involvement
PRES	Posterior reversible encephalopathy syndrome
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
RDS	Research Design Service
REC	Research Ethics Committee
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIADH	Syndrome of Inappropriate Antidiuretic Hormone secretion
SoDA	Summary of Drug Arrangement
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TRM	Treatment-Related Mortality
TSC	Trial Steering Committee
UCL	University College London
UCL CTC	CR UK and UCL Cancer Trials Centre
URL	Uniform Resource Locator (Web address)
WOCBP	Women of Child Bearing Potential

APPENDIX 2: QUICK REFERENCE GUIDE TO PATIENT VISITS

	Screening	Pre-treatment	Day 15-21 after commencing leukaemia induction treatment	Within 2 weeks of completing induction therapy[2]	At completion of intensive therapy (at start of maintenance therapy [6-7 months from randomisation])	At 12 months (+/- 1 month) post randomisation into CiproPAL	During long term follow-up
Informed consent	X						
Demographics (age, ethnicity and sex)	X						
Medical History	X						
Concomitant Medication	X (including start date of induction)		X (recording antibiotic exposure)				
Weight	X						
Assessment of renal function	X						
Adverse events of special interest, SAE reporting and urgent event reporting	X (see section 12.2, 12.4 and 12.5 for reporting timeframes)						
Stool sample or peri-rectal swab culture *(optional)*		X[3]	X	X	X	X	
EQ-5D-Y questionnaire		X	X	X	X	X	
Infection information[1]			X	X	X	X	X[5]

Collection of patient diary[4]			X	X			

[1] Infection information includes: incidences of bacteraemias/sterile site bacterial infections; details of bacterial isolates including sensitivity testing; incidence of *C. difficile* and invasive fungal infections; febrile episodes and febrile neutropenia; severe infection, infection-related deaths

[2] When neutrophil recovery is sufficient for the commencement of consolidation (ANC >0.5x10^9/L)

[3] *Optional procedure for the patient*. Intervention arm - stool sample or peri-rectal swab culture to be obtained following randomisation, ideally prior to, but within 3 days of, commencing ciprofloxacin prophylaxis. Control arm – stool sample or peri-rectal swab culture to be obtained within 3 days (+/- 2 days) of patient randomisation.

[4] Patient diaries are to be collected for reconciliation purposes if randomised to the interventional arm

[5] To be provided after every episode until the end of the ALLTogether1 leukaemia treatment

APPENDIX 3: QT PROLONGING MEDICATIONS

Antimicrobials

Erythromycin

Clarithromycin

Fluconazole

Antiemetics

Chlorpromazine

Ondansetron/Granisetron

Antidepressants

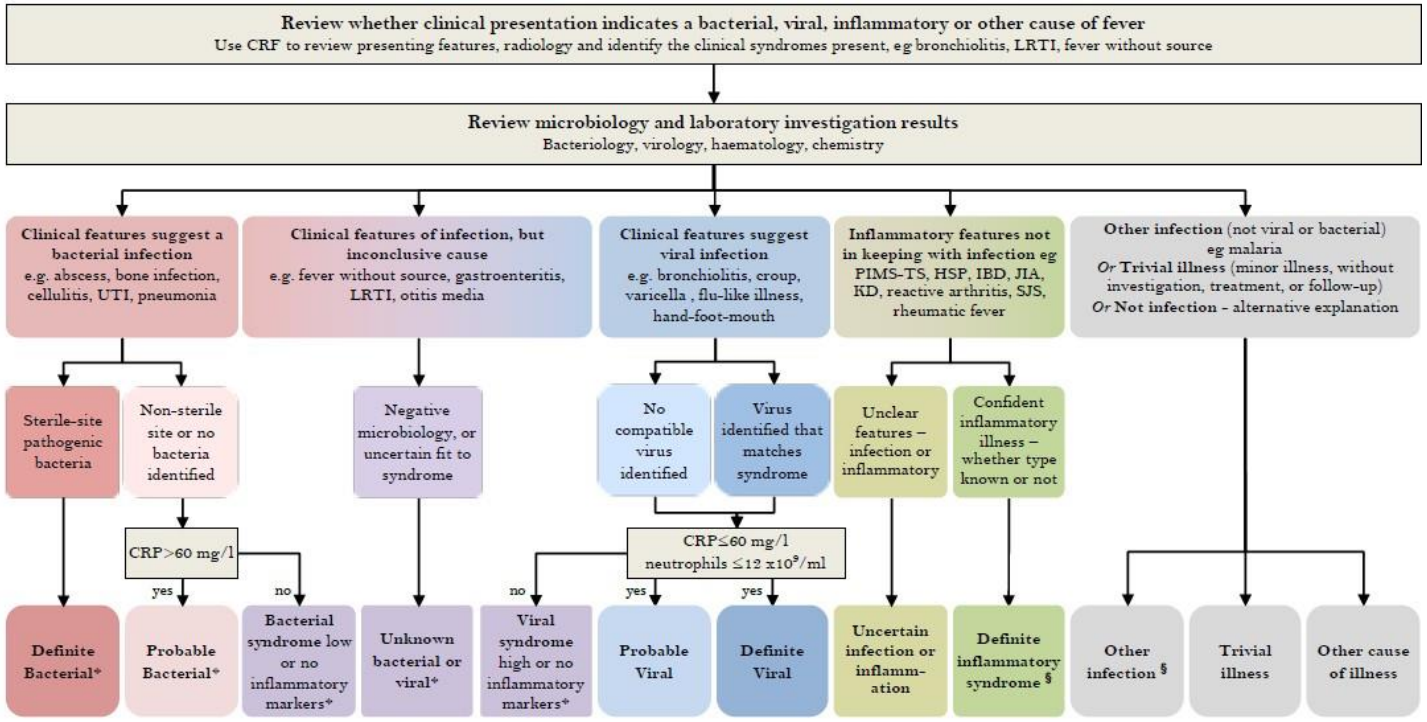
Citalopram/escitalopram

Amitriptyline

Others

Protein kinase inhibitors e.g. imatinib

APPENDIX 4: ALGORITHM FOR INFECTION PHENOTYPING



* Detection of virus does not exclude attribution of these infection phenotypes

§ Note that two phenotypes can be assigned to a patient if one is a non-viral/non-bacterial infection, or an inflammatory phenotype

APPENDIX 5: PROTOCOL VERSION HISTORY

Protocol:		**Amendments**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	22/09/2021	N/A	N/A	N/A – Initial version
2.0	20/04/2022	1	Front page	CTA number has been added.
			12.2.2 Reporting of Serious Adverse Events (SAEs)	Text in the red box on page 42 has been updated to reflect SAEs are reported by sites directly into the eCRF, and not via email.
3.0	19/01/2023	4	Multiple sections	Typos and formatting errors corrected throughout
			Protocol signatures	Names and job titles updated.

			Trial Management Group	Additional names added.
			1.1 Summary of trial design	Inclusion criteria changed to as soon as possible after commencing induction, preferably in the first 5-8 days of therapy, up to 14 days is acceptable. Wording changed throughout protocol to reflect this
			1.2 Trial schema	Updated to reflect inclusion criteria change
			7.1 Randomisation	Additional stratification added for randomisation time point (≤7 days vs 8-14 days)
			8.9.1 IMP accountability	Updated to remove the need for full

				records of accountability
			10 Central Laboratory	Collection timepoint for baseline samples in the interventional arm increased to 3 days. Protocol updates throughout to reflect this change.
			12 Pharmacovigilance	SAE exemptions lists updated to remove the need to collect every SAEs of grade 3 and below. Reporting procedures and eCRF collection clarified throughout section.
			Appendix 5 Summary of Event Reporting	Summary table of event reporting requirements added.

4.0	19/09/2023	5	Protocol signature	Names and job titles updated
			Trial Management Group	Additional names added.
			1.1 Summary of trial design	Clarification of secondary endpoint 2 added.
			3.2 Trial Endpoints	
			1.2 Trial Schema	Typo corrected to reflect randomisation can happen up to 14 days.
			8.5 Treatment Delays	Section added.
			12.2.2 Reporting of Serious Adverse Events (SAEs)	Clarification added that SAEs of any grade related to Ciprofloxacin require reporting.
			12.4 Adverse Events of Special Interest	Definitions clarified for events where appropriate.
			12.5 Urgent Events	
			12.8 Pregnancy	Changing reporting

				requirements from Email reporting to within the eCRF.