CHILDREN'S ONCOLOGY GROUP
The world's childhood cancer experts

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CHILDREN'S ONCOLOGY GROUP

ACCL0934

A Randomized Trial of Levofloxacin to Prevent Bacteremia in Children Being Treated for Acute Leukemia (AL) or Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

A Groupwide Phase III Study

STUDY CHAIR

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3501

AGENT	NSC#	IND#
Levofloxacin	Not applicable	Exempt

SEE SECTION 13 FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

Bacterial sepsis continues to be a leading cause of morbidity and toxic death in children receiving treatment for acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL) and for those undergoing hematopoietic stem cell transplant (HSCT). Data from adult studies suggest that antibiotic prophylaxis decreases the incidence of infection-related death in patients receiving intensive myelosuppressive therapy; however, antibiotic prophylaxis in pediatric patients is largely unstudied. This open-label, randomized, controlled trial will evaluate whether prophylactic therapy with levofloxacin will decrease the incidence of bacteremia in pediatric patients being treated with intensive chemotherapy for acute leukemia (AL) or for those undergoing HSCT. In addition, the study design will allow assessment of the potential risks of prophylactic therapy such as impact on host flora and quinolone-related musculoskeletal side effects. The ancillary study within this trial represents a unique opportunity to establish the relative risk for evolution of resistance and persistence of resistance among gastrointestinal colonizing organisms frequently associated with invasive bacterial infection. Such data are necessary to judge the balance between the risks and benefits of antibiotic prophylaxis and thus help determine whether prophylactic levofloxacin should be incorporated in clinical care of children and young adults who are at high risk of serious infections secondary to cancer therapy.

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EXPERIMENTAL DESIGN SCHEMA

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              Eligibility Screening for
             Patients Being Treated for AL
               or Undergoing HSCT
                        │
                        ▼
               ACCL0934 Enrollment
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| AML | Relapsed ALL | Randomization to Arm A or B | Autologous HSCT | Allogeneic HSCT |

| Arm A No Levofloxacin | Arm B Levofloxacin [1] | | Arm A No Levofloxacin | Arm B Levofloxacin [1] |

Baseline [2, 3]   Baseline [2, 3]

Infection Observation Period

Start [2, 3, 4]
Day 3 of each chemotherapy cycle (patients will be on study for 2 consecutive cycles)

End
ANC > 200/µL and rising post-nadir or Day 60 if ANC > 200/µL is not reached, following the second cycle of chemotherapy.

Infection Observation Period

Start [2, 3, 4]
Day -2 from stem cell infusion

End
ANC > 200/µL and rising post-nadir or Day 60 if ANC > 200/µL is not reached

End of Study Therapy

Musculoskeletal Monitoring [2] at 2 and 12 months after the Infection Observation Period

End of Study

[1] See Section 4.0 for study treatment details

[2] See Section 7.0 for study evaluation details

[3] See Section 7.0 for optional ancillary resistance study evaluation details

[4] For patients in Arm B, see Section 4.1 for details regarding starting and stopping of levofloxacin treatment

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Specific Hypothesis

Prophylactic therapy with levofloxacin will decrease the incidence of bacteremia during periods of neutropenia in pediatric patients being treated with intensive chemotherapy for AL or for those undergoing HSCT.

1.1 **Primary**

1.1.1

To determine if levofloxacin given prophylactically during periods of neutropenia to patients being treated with chemotherapy for AL or undergoing HSCT will decrease the incidence of bacteremia.

1.2 **Secondary**

1.2.1

To determine the effect of prophylactic levofloxacin on (a) resistance patterns of bacterial isolates from all sterile site cultures; and (b) the evolution of antimicrobial resistance from peri-rectal swab isolates of Enterobacteriaceae, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Streptococcus mitis*.

1.2.2

To determine the effect of levofloxacin prophylaxis on total number of days of antibiotic administration (prophylactic, empiric and treatment) in children undergoing therapy for AL and HSCT.

1.2.3

To determine whether levofloxacin prophylaxis reduces the incidence of (a) fever with neutropenia; (b) severe infection; and (c) death from bacterial infection.

1.2.4

To assess the safety of levofloxacin prophylaxis, with specific attention to musculoskeletal disorders including tendinopathy and tendon rupture.

1.2.5

To assess the impact of prophylactic levofloxacin on (a) the incidence of *Clostridium difficile* associated diarrhea (CDAD); and (b) the incidence of microbiologically documented invasive fungal infections (IFI).

2.0 BACKGROUND

2.1 **Risk of Bacterial Infection**

Bacterial sepsis continues to be a leading cause of morbidity and toxic death in children receiving intensive therapy for AML, relapsed ALL, and for those undergoing HSCT. The risk of invasive bacterial infection in children with AML has been described by multiple cooperative groups. In a study of treatment-related mortality (TRM) in 901 patients enrolled on the AML-BFM 93 and AML-BFM 98 trials, 63 (6.9%) of patients died of infection which represents 60% of the TRM.[1] Of the proven infections, the majority were bacterial and included Gram positive isolates (including viridans group *Streptococcus*), Gram negative isolates (with *P. aeruginosa* and *Klebsiella spp.* predominating) and polymicrobial infections. In a study of 492 children with AML enrolled on the Children's Cancer Group protocol 2961, 39-50% and 18-28% of patients developed Gram positive and Gram negative infections

respectively, during the 3 phases of therapy.[2] Of the 58 patients with infection-related deaths, a significant proportion was associated with bacterial infections, including 15.5% with viridans group S*treptococcus*.

The TRM for children undergoing chemotherapy for relapsed ALL is consistently significantly higher than for those undergoing treatment for de-novo disease.[6,7] Various chemotherapeutic regimens have been studied for Re-Induction in children with relapsed ALL. A recent COG study evaluated a 3-block platform of intensive chemotherapy for children with first marrow relapse. The rate of febrile neutropenia and clinically or microbiologically documented infections were 59.7%, 39.6% and 79.4% per block of therapy.[5] There were 5 toxic deaths in 124 patients (4%), all of which were associated with bacterial sepsis.[5] Studies evaluating variations of "4-drug Induction" have rates of suspected or proven infection of 50-100%.[8-10] Small studies of combination regimens including clofarabine report rates of febrile neutropenia of 85-100%.[11,12]

The incidence of bacteremia during the neutropenic period post-HSCT ranges from 21-34% and 21-58% for patients undergoing autologous and allogeneic transplant respectively, although some studies report no difference between the 2 groups.[13-16] In most studies, Gram positive bacteria are the predominant pathogen. Bloodstream infections are an independent predictor of mortality after HSCT.[17, 18]

2.2   Antibiotic Prophylaxis in Cancer Patients

The significance of the morbidity and mortality associated with bacterial infections in neutropenic oncology patients has led investigators to assess the efficacy of preventative therapies. Studies of the use of prophylactic antibiotics in neutropenic adult oncology patients conducted over the last 30 years have consistently shown efficacy in reducing the incidence of fever and microbiologically documented bacterial infections, but individually the studies have failed to show an effect on overall survival.[19] Two contemporary large prospective, double-blind, randomized, placebo-controlled studies of 2,325 adult oncology patients receiving myelosuppressive chemotherapy demonstrated that levofloxacin prophylaxis decreased the incidence of fever, probable infection and hospitalization.[20, 21]

A recent meta-analysis of 95 randomized, controlled trials of prophylaxis for afebrile neutropenic oncology patients showed a significantly decreased risk of death in patients receiving prophylaxis.[22] The benefit was most substantial in studies utilizing fluoroquinolone prophylaxis with significant reductions in all-cause mortality, infection-related mortality, fever, and clinically and microbiologically documented infections for those receiving prophylaxis. In an analysis of studies of adult patients with AL or those undergoing HSCT, the risk of death from any cause was decreased by 33% in those receiving quinolone prophylaxis.[23]

The Infectious Disease Society of America guidelines published in 2002 recommend against prophylaxis.[24] However, the National Comprehensive Cancer Network Guidelines from 2008 suggest consideration of fluoroquinolone prophylaxis in patients at intermediate- or high-risk of infection.[25] Survey studies of North American adult oncologists suggest that prophylaxis is widely used in adult cancer patients.[26]

The investigation of the use of prophylactic antibiotics in children with cancer has been much more limited. Early studies of trimethoprim-sulfamethoxazole, erythromycin and amoxicillin-clavulanate failed to show significant benefit and were hampered by poor patient accrual and difficulties with patient compliance.[27-29] A recent pilot study of ciprofloxacin prophylaxis for pediatric patients receiving Delayed Intensification therapy for ALL showed a significant reduction in hospitalization, intensive care admission and bacteremia compared to historical controls.[30] A retrospective study of pediatric patients with AML treated prophylactically with cefipime or a combination of vancomycin and oral ciprofloxacin or a cephalosporin described a significant decrease in morbidity from bacterial infections and overall length of hospital stay.[31] However, a recent survey of COG institutions found that the majority of centers do not use antibacterial prophylaxis in children with AML.[32]

2.3   **Levofloxacin Prophylaxis**

Levofloxacin is an attractive agent to consider for the evaluation of prophylaxis in pediatric oncology patients. Available as an injection, tablet and oral solution formulation, the drug has a spectrum of activity that includes clinically relevant Gram negative and positive pathogens. The pharmacokinetics of levofloxacin in the pediatric patient population and dosing recommendations have been previously described.[33] As outlined above, the contemporary studies of prophylaxis in adult neutropenic oncology patients have utilized levofloxacin.

Analysis of the Phase 1, 2 and 3 trials and post-marketing surveillance for the currently available fluoroquinolones show that as a group, the safety profile is similar to other antimicrobial classes.[34] The most common adverse effects are gastrointestinal (nausea and diarrhea) and those related to the central nervous system (headache and dizziness). There is a very rare but consistent association between the use of quinolone antibiotics and a risk of tendonitis and tendon rupture with an estimated frequency of 0.5-0.6 cases per 100,000 treatments, primarily involving the Achilles tendon.[34, 35] The most significant risk factors for this complication are age > 60 years as well as co-administration of corticosteroid drugs.

In contrast to the issue of tendinopathy, the use of fluoroquinolones in pediatrics has been limited by concerns for the potential risk of arthropathy.[36] In juvenile animals, exposure to fluoroquinolones has been associated with a risk of arthropathy expressed clinically as lameness and with characteristic histologic findings including blisters and erosions of articular cartilage. There is, however, a significant body of evidence supporting the effectiveness and safety of quinolone antibiotics, including levofloxacin, in the pediatric population.[37-41] Ciprofloxacin is licensed by the FDA for specific clinical situations in individuals < 18 years of age.[42] A recent report on the safety profile of levofloxacin in children, which included more than 2,500 subjects, found that the incidence of musculoskeletal disorders (primarily arthralgia) was significantly higher in levofloxacin-treated patients (3.4% versus 1.8%, p=0.025 at 1 year post-exposure). However, this estimate was based on reporting from non-blinded parents and thus may have been biased.[43] In addition, the quality of the musculoskeletal disorder in the levofloxacin-treated and comparator groups did not appear to be different. Given the rare occurrence of these side effects and questionable attribution to levofloxacin, the continued evaluation of levofloxacin prophylaxis in specific high-risk pediatric populations in controlled research settings is justifiable.

2.4   B**acterial Resistance Aims Background**

Potential benefits of any intervention must be measured simultaneously against possible negative consequences. One of the primary concerns with the use of antimicrobial prophylaxis is the possibility for the development of resistant pathogens placing the patient at risk for a future infection secondary to a resistant organism. Transition from non-colonization to colonization with a resistant organism in a single patient is possible through a number of avenues: antibiotic selection of previously undetectable but present resistant bacteria; patient-to-patient transmission of pathogens; or via the *de novo* development of resistance in previously susceptible bacteria.[44] Each of these mechanisms may be directly or indirectly enhanced in the setting of antibiotic exposure.

Concluding that antibiotic exposure can increase the rate of resistance among colonizing organisms is not confirmation that colonization by a resistant organism can result in infection. There have, however, been a number of well-performed studies in patients with AL and those receiving HSCT that illustrate that invasive infection is often linked to previously noted colonization by the same organism.[45-47] Schimpff et al, showed that of 43 bacteremia episodes in patients with AL, 39 of them were preceded by surveillance cultures from various locations yielding the same organism.[45] Tancrede et al, had similar results showing stool colonization preceded bacteremia with the same enterobacteraciae in 31/38 cases and 13/16 patients with *P. aeruginosa* bacteremia.[46] Wingard et al, performed a prospective observational study surveying for resistant organisms in the stool of 86 bone marrow transplant recipients. They found that 25% of patients colonized with a resistant organism went on to have an infection from the same organism while

only 6% of patients developed an infection from a resistant organism that was not previously identified by surveillance stool cultures.[47] Therefore, these data suggest that if there is an increase in the frequency of colonization with resistant organisms, then there will be a dependent increase in the frequency of invasive infections from the same organisms.

The results from adult studies on the impact of fluoroquinolone prophylaxis in oncology patients on increased resistance among colonizing organisms and organisms causing documented infection have yielded conflicting results.[48-53] In the 2 contemporary, large, prospective adult trials of levofloxacin prophylaxis,[53,54] surveillance for development of resistant colonizing organisms was not performed. Neither study noted an overall increase in the rate of resistant organisms causing microbiologically documented infection; however, these studies were not powered to answer this specific question.

ACCL0934 provides an opportunity to define the risk of colonization and infection with resistant organisms in a high-risk sub-group of pediatric oncology patients in a prospective, randomized, controlled fashion. The antibiotic resistance aim is an optional ancillary study for patients enrolled on this protocol, but is anticipated to be of critical significance in providing data to allow clinicians to understand the possible benefits and risks of levofloxacin prophylaxis in this patient group.

In addition to evaluation for effects of prophylaxis on antimicrobial resistance, the study will also measure the impact of antibiotic prophylaxis on the incidence of CDAD and on the incidence of microbiologically documented IFI. In adult observational studies, prophylactic use of fluoroquinolones in patients with neutropenia was associated with an increase in CDAD; however, the incidence of CDAD was significantly greater in the setting of moxifloxacin as compared to levofloxacin.[55] Neither pediatric nor adult randomized trials have appropriately measured the risk of CDAD while on antibiotic prophylaxis during neutropenia. Although not as high as adult rates, the incidence of CDAD has increased among hospitalized pediatric patients in the past decade.[56]

Likewise, reasonable concern about an increase in IFIs exists in the setting of prophylactic antibiotics. A meta-analysis of 95 randomized controlled trials evaluating antibiotic prophylaxis in neutropenic patients did not identify an increase in the rate of IFIs.[22] Importantly, a retrospective study of pediatric AML patients given antibiotic prophylaxis did not result in increased fungal infection rates when compared to those patients not on prophylaxis.[31] While these data are reassuring, they do not specifically evaluate the impact that levofloxacin prophylaxis would have on invasive fungal rates. The 2 recent large, randomized, placebo-controlled trials in adult oncology patients utilized levofloxacin as the prophylactic antibiotic, but they did not document the rates of IFIs in either study arm.[20, 21]

2.5   **Summary**
Bacterial infections continue to be a leading cause of morbidity and toxic death in children receiving treatment for AML, relapsed ALL and for those undergoing HSCT. Data from adult studies suggest that antibiotic prophylaxis decreases the incidence of infection-related death in patients receiving intensive myelosuppressive therapy; however, antibiotic prophylaxis in pediatric patients is largely unstudied. This open-label, randomized, controlled trial will evaluate whether prophylactic therapy with levofloxacin will decrease the incidence of bacteremia in pediatric patients being treated with intensive chemotherapy for AL or for those undergoing HSCT. In addition, the study design will allow assessment of the potential risks of prophylactic therapy such as quinolone-related musculoskeletal side effects. The ancillary study within this trial represents a unique opportunity to establish the potential of increased risk of evolution of resistance and persistence of resistance among gastrointestinal colonizing organisms frequently associated with invasive bacterial infection. Such data are necessary to judge the balance between the risks and benefits of antibiotic prophylaxis and thus help determine whether prophylactic levofloxacin should be incorporated in clinical care of children and young adults at high risk for serious infections secondary to cancer therapy.

3.0   STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1   **Study Enrollment**

3.1.1   Patient Registration
Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only 1 BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.2   IRB Approval
Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU Webpage (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
Emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

3.1.3   Study Enrollment
Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG Website.

3.1.4   Timing
Patients must be enrolled before treatment (with protocol therapy) begins. The date protocol therapy is projected to start must be no later than *five (5)* calendar days after the date of study enrollment.

3.1.5   Inclusion of Women and Minorities
Both male and female children and adolescents of all races and ethnic groups are eligible for this study. To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.1.6   Randomization
Randomization will take place at the time a patient is enrolled on study via eRDES. Patients will be assigned to either levofloxacin treatment or no levofloxacin treatment. Randomization will be stratified by

diagnosis/therapy: 1) those with *de novo*, secondary or relapsed AML or acute leukemia of ambiguous lineage treated with standard AML therapy; 2) those with relapsed ALL; 3) those undergoing autologous HSCT; 4) those undergoing allogeneic HSCT.

3.2 Patient Eligibility Criteria
Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

INCLUSION CRITERIA
3.2.1 Age
Patient must be ≥ 6 months to ≤21 years of age at enrollment.

3.2.2 Diagnosis
Patient must fit 1 of the following 2 categories (a or b):

(a) **Chemotherapy patients**
Planned to receive at least 2 consecutive cycles (not required to be the first 2 cycles) of intensive chemotherapy for either:
1) *De novo*, relapsed or secondary AML, or acute leukemia of ambiguous lineage treated with standard AML therapy
2) Relapsed ALL.

For the purposes of this study, "intensive chemotherapy" is defined as regimens that are predicted by the local Investigator to cause neutropenia for > 7 days. Examples include, but are not limited to, treatment with "4-drug Induction" (anthracycline, vincristine, asparaginase, and steroid), high dose cytarabine, anthracycline/cytarabine, ifosfamide/etoposide, and clofarabine-containing regimens.

(b) **Stem cell transplantation patients**
Planned to receive at least 1 myeloablative autologous or allogeneic HSCT.

For the purposes of this study, myeloablative autologous and allogeneic HSCT are those in which the conditioning regimen is predicted by the local Investigator to cause neutropenia for > 7 days.

3.2.3 Organ Function
Adequate renal function defined as:
- Creatinine clearance or radioisotope GFR > 70 mL/min/1.73 m^2 OR
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL) Male/Female
6 months to < 1 year	0.5/ 0.5
1 to < 2 years	0.6/ 0.6
2 to < 6 years	0.8/ 0.8
6 to < 10 years	1/ 1
10 to < 13 years	1.2/ 1.2
13 to < 16 years	1.5/ 1.4
≥ 16 years	1.7/ 1.4

The threshold creatinine values above were derived from the Schwartz formula for estimating GFR (Schwartz et al, J Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.2.4   Performance Level
(See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Material for Protocols)
Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.

EXCLUSION CRITERIA

3.2.5   Patients previously enrolled on the trial are not eligible. Therefore, patients with AL who were on study during intensive chemotherapy are not eligible to be enrolled during the HSCT.

3.2.6   Patients with an allergy to quinolones.

3.2.7   Patients with chronic active arthritis.

3.2.8   Patients with a known pathologic prolongation of the QTc.

3.2.9   Females who are pregnant or breast feeding.

3.2.10   Patients being treated with antibacterial agents, other than any of the following:
        1. Cotrimoxazole or other agents including dapsone, atovaquone, and pentamidine administered for *Pneumocystitis jiroveci* (PCP) prophylaxis.
        2. Topical antibiotics
        3. Central venous catheter antibiotic lock therapy

        Note: prophylactic antifungal therapy is NOT an exclusion criterion.

3.2.11   Patients currently enrolled on the ACCL1034 study are not eligible until they have completed the 90 day observation period of that study.

Please see Section 4.1 for the concomitant therapy restrictions for patients while on study.

REGULATORY

3.2.11   All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.12   All institutional, FDA, and NCI requirements for human studies must be met.

4.0   TREATMENT PLAN

4.1   **Overview of Treatment plan**

> Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

In this study, patients will be randomized to no levofloxacin (Arm A) or levofloxacin (Arm B) at time of enrollment. Patients in Arm A receive no protocol treatment. Patients in Arm B receive levofloxacin as detailed below.

The required observations and adverse event reporting are identical in the two arms. See Section 7 for required observations and Section 11 for Adverse Event reporting.

4.1.1   Levofloxacin Treatment
Patients with AL

For children with AL and assigned to Arm B, prophylaxis will be administered during 2 consecutive cycles of chemotherapy; levofloxacin will start on Day 3 of systemic therapy for each of the 2 consecutive chemotherapy cycles.

Patients Undergoing HSCT

For children undergoing HSCT and assigned to Arm B, prophylaxis will be administered during 1 transplant procedure; levofloxacin will start on Day -2 from stem cell infusion.

For patients with AL and those undergoing HSCT, levofloxacin treatment will continue until one of the following is met, whichever occurs first:

1) ANC is > 200/µL and rising post-nadir OR
2) Day 60 (from Day 1 of each cycle of systemic chemotherapy or HSCT Day +60) if ANC > 200/µL is not reached OR
3) The day prior to the next cycle of chemotherapy OR
4) Patient meets criteria for removal from protocol therapy per Section 8.1.

For patients with AL receiving 2 courses of levofloxacin treatment, the first course of levofloxacin treatment will be discontinued when the patient meets the above criteria; unless the patient is off protocol, the second course of levofloxacin treatment will start on Day 3 of the next chemotherapy cycle. Patients who begin their second cycle of chemotherapy before the ANC > 200/µL and before Day 60 (for Cycle 1) should continue levofloxacin treatment until the ANC is > 200/µL and rising post nadir or they reach 60 days from Day 1 of the second cycle of chemotherapy.

For patients assigned to Arm B, **levofloxacin will be held any time that parenteral antibacterial therapy is initiated according to local supportive care standards** (for example, empiric antibiotics initiated for febrile neutropenia). For patients who have not met criteria for removal from protocol therapy, levofloxacin should be re-started when parenteral antibiotics have been discontinued (for example, following completion of a 14-day course of empiric therapy for febrile neutropenia), if the ANC is still < 200/µL, if Day 60 has not yet been reached and the next cycle of chemotherapy has not been initiated. For HSCT patients who develop fever between the time of enrollment and Day -2 of

conditioning (for example fevers associated with ATG therapy) who are started on empiric antibiotic therapy according to institutional standards, levofloxacin should be started once these empiric antibiotics are discontinued or on Day -2 of conditioning, whichever occurs later. Levofloxacin may be stopped and re-started multiple times according to when other parenteral antibiotics are administered.

Levofloxacin should be discontinued immediately for any patient with confirmed tendinopathy (tendonitis or tendon rupture).

Please note: For all patients on study (i.e., Arms A and B), decisions regarding the initiation and choice of empiric and treatment antimicrobial therapy should be made according to local supportive care standards.

For COG Supportive Care Guidelines see
https://members.childrensoncologygroup.org/prot/reference_materials.asp

4.1.2   Prophylactic Therapy
Antibacterial prophylaxis other than for PCP prophylaxis and levofloxacin for those on Arm B will not be permitted.

4.2   **Study Therapy**

Levofloxacin: PO* or IV
Age ≥ 6 months to < 5 years: administer 10 mg/kg twice daily for a total of 20 mg/kg per day
Maximum: 250 mg per dose; 500 mg per day

Age ≥ 5 years: administer 10 mg/kg once daily
Maximum: 750 mg per day

*The study medication will be given PO if tolerated. If PO is not tolerated, study medication will be given by IV with the same dose and schedule. The PO levofloxacin is preferably administered 1 hour before or 2 hours after a meal, but may be taken with food if better tolerated by the patient. Antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, multivitamin preparations with zinc, and didanosine oral solution should not be taken within 2 hours before or after PO levofloxacin administration.

For children/adolescents who choose to take tablets of levofloxacin, the dose should be rounded to the nearest multiple of 125 mg. Rounding 'down' is permitted as long as the delivered dose is ≥ 90% of the calculated dose. Otherwise, the dose should be rounded 'up' to the next multiple of 125 mg. For children using the oral solution, doses should be rounded to the nearest 25 mg.

If vomiting occurs within 30 minutes of taking the dose, the dose may be repeated once. If a dose is missed, it should be taken immediately and only if there are at least 12 hours until the next scheduled dose.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery maps (TDMs) for levofloxacin therapy are on the next 2 pages.

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Prophylactic Therapy Delivery Map – AL Patients in Arm B Patients undergoing treatment for AL receive antibacterial prophylaxis during 2 consecutive cycles of chemotherapy.	_____ Patient name or initials _____ DOB

For each of 2 consecutive chemotherapy cycles, begin study treatment on Day 3 of systemic chemotherapy. Extensive details are in Section 4.0 (treatment overview). This Therapy Delivery Map is on **one** (1) page.   *Cycle: 1   2*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Levofloxacin	**PO*/IV** ***Given PO if tolerated; otherwise by IV.**	<u>Age</u> ≥ 6 months to < 5 years: 10 mg/kg twice daily ≥ 5 yrs: 10 mg/kg once daily	Daily beginning on Day 3 of systemic chemotherapy)^	^Continue until ANC is > 200/µL and rising post-nadir or Day 60 (from Day 1 of each cycle of systemic chemotherapy) if ANC > 200/µL is not reached or the day prior to the next cycle of chemotherapy. **Note age-based dosing** Maximum per day: 500 mg if < 5 years of age, 750 mg if ≥ 5 years See Section 4.2 for rounding of oral doses	a. History, physical, ht/wt, performance status b. CBC, Cr (at intervals according to good patient care) c. Optional peri-rectal swab or stool specimen (see Section 7.2) † Infection information during infection observation period (see Section 7.1.2) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht____cm   Wt____kg   BSA____m^2

Start Day Date (d/m/y)	Stop Day Date (d/m/y)	Age: ≥ 6 months to < 5 years LEVO^ ____mg ____mg	Age: ≥ 5 years LEVO^ ____mg	Studies †	Comments (Include any held doses, or dose modifications)
		**Enter calculated dose above and actual dose administered below**			
0-3				a, b, c	
3 (/ /)	_ (/ /)^	____mg ____mg	____mg		
__ (/ /)	_ (/ /)^	____mg ____mg	____mg		
__ (/ /)	_ (/ /)^	____mg ____mg	____mg		
__ (/ /)	_ (/ /)^	____mg ____mg	____mg		
	Continue until ANC is > 200/µL and rising post-nadir^; see Section 4.1 for details regarding starting and stopping of levofloxacin. Levofloxacin should be discontinued immediately for any patient with confirmed tendinopathy (tendinitis or tendon rupture) (see Section 4.1).				

On the TDM, indicate each start and stop dates of levofloxacin. The subject may start and stop levofloxacin multiple times prior to meeting the criteria for completion of levofloxacin. Levofloxacin should be held when parenteral antibiotics are administered for other indications such as for empiric or therapeutic management of infection.

See Section 5.0 for Dose Modifications for Toxicities and the COG Website posted materials for Supportive Care Guidelines

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Prophylactic Therapy Delivery Map – HSCT Patients in Arm B Patients undergoing HSCT receive antibacterial prophylaxis during 1 transplant procedure.	_____ Patient name or initials _____ DOB

Begin study treatment on Day -2 from stem cell infusion. Extensive details are in Section 4.0 (treatment overview).
This Therapy Delivery Map is on **one** (1) page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Levofloxacin	**PO*/IV** ***Given PO if tolerated; otherwise by IV.**	<u>Age</u> ≥ 6 months to < 5 years: 10 mg/kg twice daily ≥ 5 yrs: 10 mg/kg once daily	Daily beginning on Day -2^	^Continue until ANC is > 200/µL and rising post-nadir or HSCT Day +60 if ANC > 200/µL is not reached **Note age-based dosing** Maximum per day: 500 mg if < 5 years of age, 750 mg if ≥ 5 years See Section 4.2 for rounding of oral doses	a. History, physical, ht/wt, BSA, performance status b. CBC, Cr (at intervals according to good patient care) c. Optional peri-rectal swab or stool specimen (see Section 7.2) † Infection information during infection observation period (see Section 7.1.2) **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**

Ht_____cm   Wt_____kg   BSA_____m^2

Start Day Date (d/m/y)	Stop Day Date (d/m/y)	Age: ≥ 6 months to < 5 years LEVO^ _____mg _____mg	Age: ≥ 5 years LEVO^ _____mg	Studies †	Comments (Include any held doses, or dose modifications)
		Enter calculated dose above and actual dose administered below			
-3				a, b, c	
-2 # (__/__/__)	__(__/__/__)^	_____mg _____mg	_____mg		
__(__/__/__)	__(__/__/__)^	_____mg _____mg	_____mg		
__(__/__/__)	__(__/__/__)^	_____mg _____mg	_____mg		
__(__/__/__)	__(__/__/__)^	_____mg _____mg	_____mg		
	Continue until ANC is > 200/µL and rising post-nadir^; see Section 4.1 for details regarding starting and stopping of levofloxacin. Levofloxacin should be discontinued immediately for any patient with confirmed tendinopathy (tendinitis or tendon rupture) (see Section 4.1).				

#Stem cell infusion 2 days later on Day 0
On the TDM, indicate each start and stop dates of levofloxacin. The subject may start and stop levofloxacin multiple times prior to meeting the criteria for completion of levofloxacin.
Levofloxacin should be held when parenteral antibiotics are administered for other indications such as for empiric or therapeutic management of infection.
      See Section 5.0 for Dose Modifications for Toxicities and the COG Website posted materials for Supportive Care Guidelines

5.0   DOSE MODIFICATIONS FOR TOXICITIES

For any patient with signs or symptoms suggestive of a possible tendon rupture, levofloxacin will be discontinued immediately. See Section 7.1.3 for required musculoskeletal follow-up assessments.

The dose of levofloxacin should be modified for impaired renal function as follows:

Patient Age	CrCl (mL/min/1.73m^2)	Dose
6 months to 4.99 years	>50	10 mg/kg q12h
	20 - 50	5 mg/kg q12h
	CrCl <20	NONE
≥ 5 years	>50	10 mg/kg q24h
	20 - 50	5 mg/kg q24h
	CrCl <20	NONE

6.0   DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the commercial agent monographs manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group." This manual is provided under Standard Sections for Protocols at: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

> Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required & Optional Clinical, Laboratory and Disease Evaluations

Obtain prior to start of phase unless otherwise indicated.

STUDIES TO BE OBTAINED	Baseline [1]	Infection Observation Period	Late MSK Monitoring Period
History, Demographic & Clinical Information	X		
Ht, Wt	X		
Performance Status	X		
CBC, Creatinine [2]	X		
Musculoskeletal Assessment	X		X
Infection Information		X	
Sterile Site Culture [2]		X	
Optional Peri-Rectal Swab or Stool Specimen [3]	X	X	

[1] Baseline assessment will take place on Day 0-3 of the first cycle of chemotherapy on study for AL patients and between Day -5 and Day -3 from stem cell infusion for transplant patients.

[2] To be done at intervals according to good patient care.

[3] See Section 7.2, for collection details and Section 13.0 for shipping details.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care. See Section 11.4 for routine AE reporting guidelines.

7.1.1 History, Demographic and Clinical Information

Demographic and clinical information collected at baseline will include age, sex, performance status, Down syndrome, ethnicity, height, weight, and episodes of bacteremia in the month prior and receipt of antibacterial therapy (not PCP prophylaxis) within 7 days prior to enrollment. Other information collected will include type of malignancy, relapse status, and chemotherapy information. For HSCT recipients, information collected will include donor type, degree of match for allogeneic recipients, stem cell source, conditioning regimen and graft-versus-host disease (GVHD) prophylaxis.

7.1.2 Infection Observation Period and Infection Information

The observation period for infectious outcomes, including the primary endpoint will be the same for both arms irrespective of whether the child discontinues levofloxacin early for those allocated to that arm. Specifically for patients receiving chemotherapy, the infection observation period will begin Day 3 of each cycle of chemotherapy and will end when the ANC is > 200/µL and rising post nadir, or at Day 60 (from Day 1 of each cycle of systemic chemotherapy) if an ANC of > 200/µL has not been reached, or Day 1 of the next cycle of chemotherapy, whichever occurs first. For patients undergoing HSCT, the observation period will begin on Day -2 from stem cell infusion and end when the ANC is > 200/µL and

rising post nadir, or at HSCT Day +60 if an ANC > 200/µL has not been reached or the first day of subsequent cancer therapy, whichever occurs first.

7.1.2.1 *General Infection Information*
Data to be collected during the infection observation period will include incidence of fever with neutropenia, days of neutropenia, use of granulocyte-colony stimulating factor (G-CSF) and corticosteroid exposure (categorized as no exposure, ≤ 5 sequential days of or > 5 sequential days of corticosteroid treatment), incidence of signs or symptoms of tendinopathy (tendonitis or tendon rupture), incidence of fever, days until first fever, days of anti-fungal therapy given, hospitalization days, days of trial medication use, use of chlorhexidine baths (yes or no), use of prophylactic CVL locks (ethanol or antibiotic locks for bacteremia prophylaxis) (yes or no) and the name and start/stop dates for any oral and parenteral antibacterial therapy. Incidence of sepsis and severe bacterial and fungal microbiologically documented infections and clinically documented infections (CTCAE version 4, Grade 4 and Grade 5) will be recorded. For patients who die during the infection observation period and who have an autopsy performed, the report of the autopsy will be requested.

7.1.2.2 *Sterile Site Cultures*
Patients will have sterile site bacterial isolate data collected during the infection observation period. Sterile site cultures will be done as part of good patient care, for example blood cultures obtained in patients with new fevers. Decisions about what types of culture and when the cultures are drawn will be made according to local institutional practice.

Bacteria isolated from sterile site cultures will be processed at the microbiology labs at the local institutions caring for the patient. The final laboratory report for each bacterial isolate (including the bacteria name, date the culture was obtained, culture source, and antibacterial resistance profile) will be submitted via the document imaging system for central review. A panel of 4 committee members will centrally review all positive sterile site cultures and antibacterial resistance profiles. It is anticipated that the techniques for establishing an isolate's minimum inhibitory concentration (MIC) will vary between institutions. However, this variability should not have great impact on whether organisms are classified as resistant.

7.1.2.3 *Clostridium difficile Associated Diarrhea*
Data to be collected for CDAD will include positive *C. difficile* toxin assay results, date of the sample and if Grade 2 or higher (CTCAE version 4) diarrhea was present on the date of *C. difficile* positive toxin sampling.

7.1.2.4 *Invasive Fungal Infections*
Data to be collected for IFI will be limited to whether or not there was a culture or pathologically documented IFI and fungal name, and the source of the culture or pathology, if available, during the infection observation period.

7.1.3   Musculoskeletal Assessment
Evaluation for pre-defined musculoskeletal disorders will be collected at baseline and then in the late MSK monitoring period 2 and 12 months post-completion of the infection observation period (see Section 7.1.2 for definition). This evaluation will be done for all patients (i.e., Arms A and B). A window of +/- 2 weeks of the specific timepoint for the 2 and 12 month assessments is allowed to accommodate patient scheduling. The individual performing this evaluation will be assigned by the local institution and will be blinded to the patient's assigned study arm (whether or not they received levofloxacin). The individual performing the evaluation does not have to be a physician or an oncologist but must in the judgment of the institutional PI have the clinical skills to perform the assessment. Attribution of the

etiology of any musculoskeletal signs or symptoms will be made by the blinded assessor. The Musculoskeletal Data Form will be used for assessment at these timepoints (see Appendix I). The objective evaluation criteria for the musculoskeletal adverse events include:

     i.   Tendinopathy: inflammation or rupture of the tendon by physical exam or MRI
    ii.   Arthritis: inflammation of the joint evidenced by redness or swelling
   iii.   Arthralgia: complaint of pain in the joint (specifically the joint)
   iv.   Gait abnormality: limping or refusal to walk

It is anticipated that the etiologies for the musculoskeletal signs and symptoms for some patients may include steroid myopathy, vincristine neuropathy, avascular necrosis, fracture, tumor-related pain and filgrastim-related pain. If upon evaluation a patient is found to have evidence of new musculoskeletal toxicity that is not otherwise explained, it is suggested that the patient be referred to the appropriate specialist (e.g., pediatric rheumatologist or orthopedic surgeon) for further evaluation.

In addition to the baseline, 2 and 12 month assessments, monitoring for any patient with signs or symptoms suggestive of tendinopathy (tendonitis or tendon rupture) will be done. For any patient on Arm B with tendonitis or tendon rupture, levofloxacin will be discontinued immediately.

7.2   **Optional Study**
7.2.1   Study Design for Ancillary Study

As part of the ACCL0934 trial, an ancillary study will examine the association between receipt of prophylactic levofloxacin and colonization or infection with antimicrobial-resistant organisms. Stool or peri-rectal swabs will be collected for assessment of longitudinal changes in colonization including several clinically significant bacterial organisms (*E. coli, K. pneumoniae, P. aeruginosa,* and *S. mitis*) and evaluation for the presence of resistance for each of these organisms to levofloxacin and other commonly used antibiotics in pediatric oncology. In addition to screening for specific antibiotic resistance among the aforementioned organisms, screening for the presence of any carbapenem-resistant Enterobacteriaceae will also be performed on specimens collected at the end of each patient's reporting period (i.e. their second stool or perirectal swab).

All patients enrolled on ACCL0934 will be offered the opportunity to participate in this ancillary resistance study. Colonization of resistant organisms will be determined by either peri-rectal or stool swabs. In comparison to stool specimens, peri-rectal swabs are 90% sensitive and 100% specific in identifying the presence of fluoroquinolone resistant *E. coli*.[57] Consequently, peri-rectal swabs will be the preferred method of resistance surveillance although an institution and/or patient may choose to use stool specimens as long as the method of collection is constant within an individual patient. If a stool specimen is chosen as the method of collection, but cannot be provided during a sampling period (for example, in the event of constipation), then a peri-rectal swab may be substituted.

Stool specimens or peri-rectal swabs will be obtained at baseline and then at the time of resolution of neutropenia for each of the study cycles (twice for those with AL and once for those undergoing HSCT). Sample collection will be obtained within 1 week of count recovery defined as an ANC $> 200/\mu L$ following the nadir. If a patient does not resolve their neutropenia, then the specimen should be obtained on Day 60 from the start of the infection observation period or within 2 days before the next chemotherapy cycle is initiated, whichever comes first. Figure 1 displays the planned specimen collection schema. Patients with AL will be followed for 2 cycles of chemotherapy resulting in 3 stool or peri-rectal specimens and those patients undergoing HSCT will be followed for 1 transplant procedure resulting in 2 stool or peri-rectal specimens.

Figure 1. Peri-rectal or stool specimen collection schema
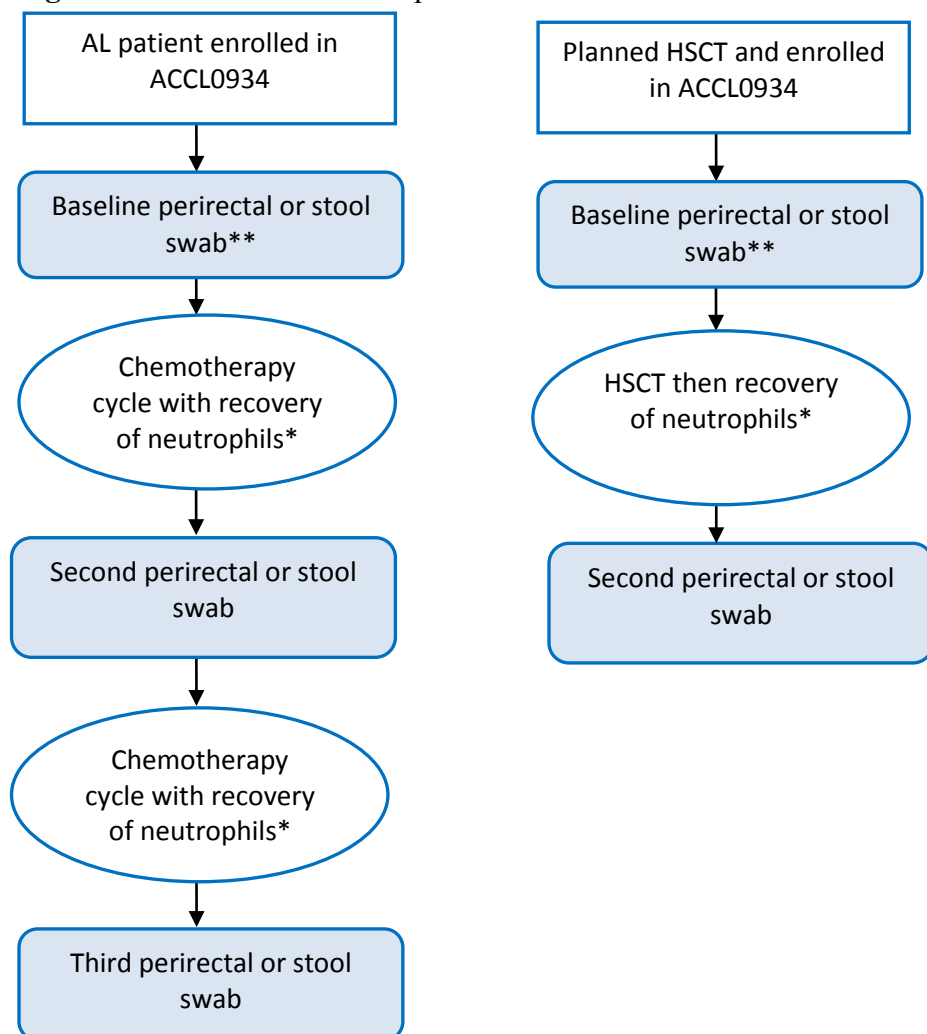
```
┌──────────────────────┐              ┌──────────────────────┐
│  AL patient enrolled │              │  Planned HSCT and    │
│   in ACCL0934        │              │  enrolled in ACCL0934│
└──────────┬───────────┘              └──────────┬───────────┘
           │                                     │
┌──────────▼───────────┐              ┌──────────▼───────────┐
│ Baseline perirectal  │              │ Baseline perirectal  │
│   or stool swab**    │              │   or stool swab**    │
└──────────┬───────────┘              └──────────┬───────────┘
           │                                     │
      ╱──────────╲                          ╱──────────╲
     ╱ Chemotherapy╲                       ╱ HSCT then   ╲
    │ cycle with    │                     │  recovery of  │
     ╲ recovery of ╱                       ╲ neutrophils* ╱
      ╲neutrophils*╱                        ╲──────┬─────╱
       ╲────┬────╱                                 │
           │                          ┌──────────▼───────────┐
┌──────────▼───────────┐              │ Second perirectal    │
│ Second perirectal    │              │   or stool swab      │
│   or stool swab      │              └──────────────────────┘
└──────────┬───────────┘
           │
      ╱──────────╲
     ╱ Chemotherapy╲
    │ cycle with    │
     ╲ recovery of ╱
      ╲neutrophils*╱
       ╲────┬────╱
           │
┌──────────▼───────────┐
│ Third perirectal     │
│   or stool swab      │
└──────────────────────┘
```

* Defined as ANC > 200/µL and rising post-nadir or Day 60 (from Day 1 of each cycle of systemic chemotherapy or HSCT Day +60) if an ANC > 200/µL has not been reached. For patients who begin their next cycle of chemotherapy before the ANC > 200/µL and before Day 60, the swab should be obtained prior to the first day of the next course of chemotherapy.

**Baseline swabs can be performed anytime between the date of enrollment and Day 3 of chemotherapy for leukemia patients or Day -2 for HSCT recipients.

7.3   Follow-up

See Section 7.1.3 for required musculoskeletal assessment follow-up.

8.0   CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1   Criteria for Removal from Protocol Therapy

a) Signs or symptoms suggestive of tendonitis or tendon rupture.
b) Refusal of further protocol therapy by patient/parent/guardian.

    c)   Completion of planned study treatment.
    d)   Physician determines it is in patient's best interest.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2   Off Study Criteria

    a)   Completion of study (12-month follow-up period evaluation).
    b)   Death.
    c)   Lost to follow-up.
    d)   Withdrawal of consent for any further data submission.

9.0   STATISTICAL CONSIDERATIONS

9.1   Statistical Design

This study is a randomized trial to investigate the effect of levofloxacin on preventing bacteremia in children being treated for AL or undergoing HSCT. Patients will be randomized between levofloxacin and no levofloxacin during 2 consecutive cycles of chemotherapy for AL or during 1 HSCT. Randomization will be stratified by 4 groups: 1) *de novo*, secondary or relapsed AML or acute leukemia of ambiguous lineage treated with standard AML therapy; 2) relapsed ALL; 3) autologous stem cell transplantation; 4) allogeneic stem cell transplantation. The study is designed to analyze AL and HSCT patients separately.

The primary aim is to determine the effect of levofloxacin on the incidence of bacteremia during the study timeframe of 2 cycles of chemotherapy or 1 transplant procedure among AL and HSCT subjects respectively. Besides assessing the safety of levofloxacin, especially on musculoskeletal disorders, other secondary aims are to determine the effect of levofloxacin on: total days of antibiotic administration, incidence of fever with neutropenia, incidence of severe infection, incidence of death from bacterial infection, incidence of CDAD, incidence of IFI, resistance patterns of bacterial isolates from sterile site cultures, evolution of antimicrobial resistance from stool or peri-rectal swab isolates of *E. coli, K. pneumoniae, P. aeruginosa* and S. *mitis* and presence of stool colonization by carbapenem-resistant Enterobacteriaceae.

9.2   Patient Accrual and Expected Duration of Trial

The study initially planned to enroll 532 eligible and evaluable children in total: 266 AL patients and 266 HSCT patients. Per Amendment #3, the sample size for HSCT patients is increased to 400. The study is designed to analyze AL and HSCT patient groups separately as it is important to know the effect of levofloxacin prophylaxis in each group. Taking into account up to 10% of enrolled patients being ineligible or inevaluable, the maximum study accrual per Amendment #3 is 740 patients: 296 AL patients and 444 HSCT patients.

COG enrollments on *de novo* and first relapse AML protocols have a combined estimate of 400 patients per year. Considering secondary and subsequent relapses, the number of AML patients potentially eligible for the study may go up to 450 per year. COG enrollments on first relapse ALL patients is at least 110 patients per year. Therefore, the AL patient pool should be at least 550 per year. As this study does not require concurrent enrollment to COG therapeutic protocols, the potential eligible AL patient pool should be even larger. As for HSCT patients, a recent COG randomized study ACCL0331 that investigated treatment of mucositis in HSCT patients enrolled about 110 HSCT patients per year. The

study initially projected to accrue 266 eligible and evaluable patients for each of AL and HSCT group in about 4 years. Amendment #3 increases the sample size for HSCT patients from 266 to 400. The recent accrual rate for HSCT patients on this study is slightly over 100 per year, which is higher than the previously projected 67 per year. Given the higher accrual rate, the accrual duration for HSCT patients will only be extended for approximately 6 months to achieve the increased sample size.

9.3   Statistical Analysis Methods

9.3.1   Endpoints

9.3.1.1 *Primary Endpoint*

The primary endpoint is occurrence of at least 1 episode of true bacteremia during the study timeframe of 2 cycles of chemotherapy or 1 transplant procedure among AL and HSCT subjects respectively. Similar to others,[49,50] positive cultures with common contaminants, namely coagulase negative *Staphylococcus*, *Corynebacterium* species, *Propionibacterium acnes*, *Bacillus* species, *Micrococcus* species, *Clostridium* species (except *C. septicum* and *C. perfringens*) and *Neisseria* species (except *N. gonorrhea* and *N. meningitides*), will require 2 positive blood cultures for the same organism within the same episode (irrespective of timing between the 2 or more cultures) or be associated with sepsis syndrome to be considered true bacteremia. We will use international consensus definitions for defining sepsis.[58-61] The observation period for infectious outcomes, including the primary endpoint will be the same for both arms irrespective of whether the child discontinues levofloxacin early for those allocated to that arm.

Specifically, the infection observation period will begin Day 3 of each cycle of chemotherapy and will end when the ANC is $> 200/\mu L$ and rising post nadir, or at Day 60 if an ANC of $> 200/\mu L$ has not been reached or Day 1 of the next cycle of chemotherapy, whichever occurs first. For patients undergoing HSCT, the observation period will begin on Day -2 from stem cell infusion and end when the ANC is $> 200/\mu L$ and rising post nadir, or at Day 60 if an ANC $> 200/\mu L$ has not been reached or the first day of subsequent cancer therapy, whichever occurs first.

Patients will be considered evaluable for the primary endpoint if data on bacteremia during the infection observation period are available, regardless of protocol treatment compliance.

9.3.1.2 *Secondary Endpoints*

Stool surveillance testing will investigate for the following resistance patterns among stool commensals at the start and end day of each treatment period: the susceptibility of *E. coli, K. pneumoniae,* and *P. aeruginosa* stool or peri-rectal swab isolates to cefepime, imipenem and levofloxacin; the susceptibility of *S. mitis* peri-rectal swab isolates to cefepime, levofloxacin and penicillin. Additionally, the presence of carbapenem-resistant Enterobacteriaceae will be screened from each enrolled patient's second collected stool or peri-rectal swab. The trajectory of the resistance patterns for the gastrointestinal isolates colonizing each patient will then be evaluated. Data regarding the resistance patterns of bacterial isolates from all sterile site cultures will be described. In interpreting antimicrobial sensitivity testing of both gastrointestinal organisms and organisms isolated from sterile sites, an intermediate result will be considered resistant for analytic purposes.

A secondary endpoint will be the duration of parenteral antibiotic administration during the study timeframe of 2 cycles of chemotherapy or 1 transplant procedure. Each day of parenteral administration will be collected irrespective of the indication or type of antibiotic given and the observation timeframe will be the same as that described for the primary endpoint. Other secondary endpoints include the incidence of febrile neutropenia, severe infection and death from bacterial infection. Severe bloodstream bacterial, fungal, and clinically documented infections and death from bacterial infection will consist of episodes of infection that are graded as CTCAE version 4 Grades 4 or 5 respectively. Secondary

endpoints on musculoskeletal adverse events and particularly tendinopathy (tendonitis and tendon rupture) will be collected. CDAD will be defined as a positive *C. difficile* toxin assay result and diarrhea, CTCAE version 4, Grade 2 and higher. Microbiologically-proven IFIs will be recorded.

9.3.2   Power Considerations
The primary outcome is the incidence of bacteremia during the study period. Analysis will be performed separately for AL patients and HSCT patients. For children with AL or HSCT, a child will have experienced the primary endpoint once he/she experiences at least 1 episode of true bacteremia during the study period. If we assume that the risk of at least 1 episode of bacteremia in either patient cohort in the control arm (no levofloxacin) is 30% and a clinically significant reduction in bacteremia is 15% (relative risk reduction of 50%), about 133 children in each arm will provide about 84% power in detecting the treatment effect on the incidence of bacteremia (30% in control without levofloxacin vs. 15% in treatment with levofloxacin). The test considered is a 2-sided Chi-square test with alpha level of 0.05. Therefore, in the original version of the protocol we proposed to enroll 532 eligible and evaluable children in total: 266 AL patients and 266 HSCT patients. Based on interim data released by DSMC in fall 2013, the recently observed rate of bacteremia in HSCT control arm is 22-25%. Given such observed rate of bacteremia being closer to 20% rather than 30% for HSCT control arm, to ensure adequate power for studying the effect of levofloxacin, in Amendment #3 we increased the planned sample size of HSCT patients to 400 eligible and evaluable patients (200 per arm), which will provide 80% power for detecting a 10% difference in bacteremia rate (20% in control arm vs. 10% in treatment arm) for HSCT patients. For AL patients, the sample size remains 266 patients. This sample size gives 84% power for a 15% reduction in bacteremia rate when the bacteremia rate for AL control arm is 30% (30% vs. 15%); the power is at least 80% for a 17.5% reduction in bacteremia rate when the bacteremia rate for AL control arm is 40-60% (control vs. treatment being 40% vs. 22.5%, or 50% vs. 32.5%, or 60% vs. 42.5%).

For the secondary endpoint on total number of days of antibiotic administration, considering a 2-sample t-test, with about 133 AL patients per arm we will have 90% power to detect a difference of 0.4 SD between the 2 arms in the mean of the number of days of parenteral antibiotic administration at 2-sided alpha of 0.05; with about 200 HSCT patients per arm we will have 85% power to detect a difference of 0.3 SD between the 2 arms in the mean number of days of parenteral antibiotic administration. For the secondary endpoints on the incidence of febrile neutropenia, severe infection, and death from bacteremia, the observed incidence rate will be compared between the 2 randomized arms. The power of such secondary analyses depends on the baseline incidence and the difference in incidence between the 2 arms. For these secondary analyses, if, for example, we consider possible baseline incidence values of 40%, 30%, 20%, 15%, 10%, or 5% in the control arm, in AL group (about 133 patients per arm) we will have a power of 95%, 84%, 63%, 49%, 34%, or 19%, respectively, to detect a levofloxacin treatment effect if levofloxacin leads to a relative reduction of 50% in the corresponding baseline incidence rate (i.e., rate with levofloxacin of 20%, 15%, 10%, 7.5%, 5%, or 2.5% respectively); for HSCT group (about 200 patients per arm), the corresponding power for a 50% relative reduction in these baseline incidence rates will be 99%, 95%, 80%, 66%, 48%, and 26% respectively. The test considered is a Chi-square test with 2-sided alpha of 0.05. It can be seen that the power for detecting a treatment difference in these secondary analyses might be limited if the baseline incidence is rare.

9.3.3   Analysis Plans
All primary analyses will be performed separately for AL and HSCT patients, and all primary analyses involving treatment effect will be intent-to-treat (ITT).

The primary outcome is the incidence of bacteremia during the study period. Within either patient cohort, we will compare the incidence of the bacteremia between the 2 randomized arms using the Chi-square test. If within either patient group the data suggest a possible difference in baseline incidence between the

2 randomization strata, we will consider Cochran-Mantel-Haenszel test to examine the association between the incidence of bacteremia and the study treatment with adjustment for the randomization strata; Breslow-Day test for homogeneity in odds ratio across the strata will also be considered. Logistic regression models will be performed to evaluate the treatment effect on the incidence of bacteremia adjusting for stratification and other baseline patient characteristics. Logistic regression models combining AL and HSCT patients will also be performed to evaluate the effect of levofloxacin on bacteremia in the two patient groups, and a test for interaction between treatment and patient group will be performed to examine if treatment effect differs between the two patient groups.

For the secondary endpoints, the total number of days of parenteral antibiotic administration will be compared between the 2 arms using 2-sample t-test. Wilcoxon rank sum test will also be considered. We will also use linear regression models to estimate any treatment difference in total days of parenteral antibiotic administration and adjust for randomization stratification and potentially other patient or treatment characteristics. The incidence of febrile neutropenia, severe infection from bacteremia, fatal infections from bacteremia and musculoskeletal adverse events will be compared between the 2 randomized arms similarly as the analyses on bacteremia. For the analysis on the incidence of tendon rupture, we will also consider separating levofloxacin patients into those with/without concurrent steroid use and comparing them separately to control patients, or adjusting for concurrent steroid use as covariate in logistic regression models. The incidence of CDAD and proven or probable IFIs will also be compared between the 2 study arms in a similar manner. A patient with multiple documented episodes of CDAD or proven or probable IFI will only be counted once when calculating the binary incidence rates. For these secondary endpoints, appropriate regression models that combine AL and HSCT patients will be performed to evaluate the treatment effect with levofloxacin in the two patient groups; test for interaction between treatment and patient group will be performed to examine if the effect of levofloxacin on these secondary endpoints differs between the two patient groups.

Factors that can potentially confound the true association of the randomized exposure (levofloxacin) with the primary and two of the secondary outcome measures (1.2.1 and 1.2.2) will be compared across the two randomization arms to assure a balanced distribution. These include the use of antibiotic or ethanol as dwells or locks in central venous catheters (CVC) to reduce CVC infections and the use of chlorhexidine gluconate baths to reduce CVC infections. Analyses adjusting for these factors will be exploratory in nature.

9.3.4   Interim Monitoring

Interim efficacy monitoring on the incidence of bacteremia will be performed twice when data is available for approximately one-third and two-thirds of patients (separately for AL patients and HSCT patients). Monitoring boundary will be based on Lan-Demet's method with spending function αt^2. Futility analyses based on conditional power will also be performed at the same time separately for each patient group. The probability of establishing efficacy of levofloxacin given the currently observed data will be calculated. In calculating the conditional power, the outcome for future patients will be assumed to follow the alternative hypothesis. If the conditional power falls below 10%, it will be considered evidence that it is unlikely to establish efficacy of levofloxacin in the particular patient group at the end of the study. The data will be referred to the COG Data Safety and Monitoring Committee (DSMC) for consideration of early termination for the particular patient group. Accrual will not be suspended for these interim monitoring and analyses. The incidence of musculoskeletal disorder will be monitored between the 2 arms by descriptive statistics and Fisher's exact test at each interim DSMC report, which occurs approximately every 6 months during the first 2 years and annually thereafter. For tendon rupture, as concurrent steroid use is considered a risk factor, the analysis will also be considered separately for levofloxacin patients with/without concurrent steroid use or with adjustment for steroid use. A previous report on > 2,500 patients found a small increase in the musculoskeletal disorder incidence (3.4% versus

1.8%) in levofloxacin treated patients; however our study is not powered to detect a difference of this magnitude. Therefore, the monitoring on incidence of musculoskeletal disorder will be informal and mainly for safety reassurance. Such safety monitoring will always be done at marginal alpha level of 0.05 and not adjusted for the multiple comparisons. If any such safety comparison suggests a significantly higher incidence of musculoskeletal disorder for levofloxacin, the study committee will carry out a review of the observed disorders; the results and any committee recommendation will be reported to the DSMC. The DSMC may also have its own assessment and recommendation about musculoskeletal event safety given the observed data.

9.4   Gender and Minority Accrual Estimates

Per Amendment #3, the study targets to enroll 666 eligible and evaluable patients (266 AL patients and 400 HSCT patients), with a maximum enrollment of 740 patients. The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	73	97	170
Not Hispanic or Latino	240	330	570
Ethnic Category: Total of all subjects	313	427	*740
Racial Category			
American Indian or Alaskan Native	2	1	3
Asian	12	13	25
Black or African American	44	45	89
Native Hawaiian or other Pacific Islander	0	5	5
White	255	363	618
Racial Category: Total of all subjects	313	427	*740

* These totals must agree

This distribution was derived from AAML0531, AALL01P2, POG-9411, ASCT0431 and ACCL0331. The first 3 studies were used to generate an estimated distribution for AL patients; the last 2 studies were used to generate an estimated distribution for HSCT patients. The overall distribution was estimated based on a 1:1 mixture of the estimated AL and HSCT distributions.

9.5   Resistance Surveillance Statistical Considerations

9.5.1   Ancillary Study Aims

9.5.1.1 *Primary Aim*
To determine whether prophylactic levofloxacin versus no levofloxacin is associated with an increased risk for the development of gastrointestinal colonization with certain antimicrobial resistant organisms. The following resistance scenarios will be analyzed first as a group and then 1-by-1:

1a. Levofloxacin resistance among *E. coli, K. pneumoniae, P. aeruginosa* and *S mitis*
1b. Cefepime resistance among *E. coli, K. pneumoniae, P. aeruginosa* and *S mitis*
1c. Imipenem resistance among *E. coli, K. pneumoniae,* and *P. aeruginosa*
1d. Penicillin resistance among *S mitis*

The above aim identifies 12 bacteria-antibiotic combinations for organisms to be identified from the gastrointestinal tract. The primary hypothesis for this primary aim is that the use of levofloxacin prophylaxis will result in a greater increase from baseline in the number of resistant combinations among these gastrointestinal organisms as compared to patients not receiving levofloxacin prophylaxis. In a sub-analysis, the change in frequency of resistance from baseline for each of the 12 bacteria-antibiotic combinations will be compared between patients in the 2 study arms.

9.5.1.2 *Secondary Aim*

The secondary aim is to determine whether prophylactic levofloxacin versus no levofloxacin is associated with an increased risk for the development of bacteremia or sterile site infection from either Gram positive or Gram negative resistant organisms. The following resistance scenarios will be considered independently:

1a. Levofloxacin resistant Gram positive and Gram negative organisms
1b. Cefepime resistant Gram positive and Gram negative organisms
1c. Imipenem resistant Gram positive and Gram negative organisms
1d. Penicillin resistance for *S mitis* only

The secondary hypotheses for these secondary aims are that the use of levofloxacin prophylaxis is associated with an increased risk of infection with levofloxacin resistant Gram positive as well as Gram negative organisms. Additionally, exposure to levofloxacin prophylaxis results in an increased risk of infection with both Gram positive and Gram negative organisms resistant to cefepime and imipenem. Lastly, levofloxacin prophylaxis is associated with an increased risk of penicillin resistant *S mitis*.

9.5.1.3 *Tertiary Aim*

The tertiary aim is to describe the frequency of stool colonization with a carbapenem-resistant Enterobacteriaceae in patients that have received prophylactic levofloxacin versus those that did not.

As this aim only plans to describe the frequency of carbapenem resistant Enterobacteriaceae there is no formal hypothesis.

9.5.2   Statistical Design for Ancillary Study

Factors that can potentially impact the analysis of the primary aim of the ancillary study include total days and class (carbapenem, cephalosporins, etc) of antibiotic exposure (other than the study drug). These will be compared across the two study arms and accounted for in all analyses related to the resistance aims. The adjusted analyses will be exploratory in nature.

9.5.2.1 *Preliminary Descriptive Analysis*

The initial analysis will involve describing the distribution of data. Specific demographic data will be characterized as described in the parent trial. We will additionally, characterize both groups (levofloxacin prophylaxis and no prophylaxis) by frequency of resistance to each antibiotic of interest for each of the gastrointestinal colonizing organisms, by frequency of resistance to each antibiotic of interest for both Gram positive and Gram negative infecting organisms, and by the amount of concomitant broad spectrum antibiotic utilization in addition to prophylactic levofloxacin (reported by class of antibiotics as an index of days of antibiotics per hospitalization days).

9.5.2.2 *Comparative Analysis for the Primary Aim*

The proposed study essentially represents a parallel safety study of the use of prophylactic levofloxacin in the setting of fever and neutropenia. As such it seeks to estimate the impact of such prophylaxis on the

evolution of resistance among gastrointestinal colonizing organisms (primary aim) and infecting organisms (secondary aim) as an important safety issue.

As an initial simple test of association of levofloxacin prophylaxis and the development of gastrointestinal resistance between the two study arms, we shall compute the change in the number of resistant combinations identified for a patient after the intervention or standard care as compared to their baseline count. The potential range for the difference from post intervention to baseline is from -12 to 12. The mean change in resistance combinations will be compared between the two study arms using the student's t-test. In the event that this change is not normally distributed a non-parametric approach will be performed utilizing the Mann-Whitney U test. The comparison in the change in resistance combinations will be done at the completion of the first course of prophylaxis or standard of care for all patients in the study. For children with AL, prophylaxis or standard care will continue through a second period of neutropenia. Therefore, the change in resistance combinations after this second period of neutropenia will be compared to baseline for AL patients only, again using the student's t-test.

9.5.2.3 *Secondary Analysis for the Primary Aim*
Although the parent study (on effectiveness of levofloxacin prophylaxis) will utilize standard principles of intent-to-treat analysis, those principles may be at odds with the goal of estimating the negative effects (resistance) of prophylaxis. Drop-out from the parent study might reduce power but be uninformative and unrelated to the eventual parent study outcome (incidence of bacteremia). In contrast, drop-out in this ancillary study might be acutely informative by being related to the emergence of an adverse event such as the development of infection due to resistant organism. Second, although randomization at baseline should balance all differences between the treatment groups by measured and unmeasured confounders, extra precautions are needed to guard against the potential bias of baseline covariates with chance imbalance from finite sample sizes. Additionally, there may be nonrandom assignment to additional antibiotics, and those post-randomization exposures might also bias results if they are not properly controlled. Finally, there is no guarantee that the subjects who enter the study will not carry resistant organisms at the time of initial enrollment. The presence of future carriage of resistant organisms by an individual is likely related to the presence of or absence of colonization at or prior to initiation of antimicrobial prophylaxis.

To address these issues, we propose a multivariate mixed-effects analysis that accounts for drop-out, variation in baseline covariates, and variation in post-randomization exposures (e.g. additional antimicrobials). A multivariate mixed-effects model has the versatility to be expanded to account for confounding from drop-out, covariate inequities from finite sample size, and administration of other antibiotics in addition to the prophylactic antimicrobials. For this model the multivariate outcome will be the 12 dichotomous outcomes (0 for no resistance and 1 for resistance) for each of the bacteria-antibiotic combinations. The model will account for the lack of independence of outcomes for each subject within a given measurement time, as well as the correlation of repeated measures over time. This multivariate mixed-effect model will attempt to assess the true causal effect of prophylactic levofloxacin on the risk of overall resistance among colonizing organisms.

9.5.2.4 *Comparative Analyses for the Secondary Aim*
Unlike the outcome for the primary aim which will be obtained at fixed timepoints, the outcomes for this secondary aim (positive sterile site culture with a resistant organism) will be present at varying times from study enrollment. Therefore, we propose a Cox proportional hazards regression model that will be adapted to address issues of concomitant nonrandomized treatment (time-dependent confounding),[27] and informative drop-out. Each outcome (presence or absence of resistance for the specified group of infecting organisms and antibiotic) will be evaluated in separate models.

9.5.2.5 *Descriptive Analysis for the Tertiary Aim*
This final aim focuses on describing the frequency of stool colonization with any carbapenem-resistant Enterobacteriaceae in patients after receiving or not receiving levofloxacin prophylaxis. The frequency of colonization with these resistant bacteria among children with leukemia is currently unknown. While it is likely that the frequency of carbapenem-resistant commensals will be too small to allow for formal statistical comparison between the two study treatment arms, the collected stool or peri-rectal specimens represent an ideal opportunity to define the epidemiology of these highly resistance organisms in this patient population after differing antibiotic exposures.

9.5.3   Estimated Sample Size and Event Rates

9.5.3.1 *Available Sample size*
A total of 666 eligible and evaluable study subjects will be enrolled in the parent study, 333 per treatment arm over the study period. Since this ancillary study does not include additional study visits and consists of obtaining stool or peri-rectal swabs for bacterial culture, a relatively easy and non-invasive procedure, we anticipate that at least 80% of subjects in the parent trial will also participate in this ancillary resistance study resulting in an effective sample size of 532 patients (266 in each study arm) for the primary aim of this ancillary study. For the secondary aim of this study the data for sterile site cultures are expected to be available for all 666 parent trial enrollees (333 in each study arm).

9.5.3.2 *Event Rates for Power Calculations*
Contemporary data are limited on the frequency at which colonizing organisms can be isolated from stool or peri-rectal swabs for each of the organisms of interest. It has been shown in a small study of adult patients with AL, that 31% of patients had *P. aeruginosa* identified on at least 1 stool specimen.[28] However, the goal of this ancillary study is to determine whether the presence of organisms retaining resistance to certain antibiotics are increased above baseline in patients receiving levofloxacin prophylaxis compared to those not receiving prophylaxis. Thus for each swab result, a dichotomous interpretation of each bacteria-antibiotic combination (presence versus absence of the resistant organism) is most appropriate. Interpreting swab results in this way will make the results of all swab specimens informative in the final analysis.

The evolution of resistance for each organism-antibiotic combination of interest is not known, and thus the anticipated mean change in resistance counts from baseline to post-exposure cannot be reasonably estimated for either treatment arm. Instead, we evaluated the power to detect various differences in the mean change of resistance counts between the 2 study groups. Assuming that each study arm will yield 266 (assuming 80% of parent trial patients enroll in this ancillary study) evaluable specimens at baseline and post prophylaxis or standard of care timepoints, then this study will have 97% power to detect a difference between the two study group mean resistance counts as small as 1.0. This power calculation also assumes a substantial standard deviation in the mean of the difference in resistance counts of 3.0. Thus, there is power to detect even a small change in the mean difference of resistance between the two study arms.

Only those patients with AL will have a stool or peri-rectal specimen obtained after a second course of levofloxacin prophylaxis or standard of care. It is estimated that 40% of the study enrollees will have AL (133 per arm). Again assuming that 80% consent to this ancillary study this will result in approximately 106 AL patients in each study arm contributing a stool or peri-rectal swab after a second course of prophylaxis or after standard of care. Maintaining all other parameters noted above, this scenario would still yield a power of 0.86 to detect a difference of 1.25 in the mean resistance counts between the two study arms. Power calculations were done using Stata v11.1 (Stata Corp, College Station TX, 2009).

For the secondary aims of this sub-study, we anticipate that all positive sterile site cultures from all evaluable neutropenic episodes in the parent trial will be available for analysis. Based on the frequency of Gram negative bacteremia events per neutropenic episodes that were resistant to levofloxacin in the adult levofloxacin prophylaxis trial (1% of neutropenic episodes on placebo versus 3% of neutropenic episodes on levofloxacin), it is anticipated that our study size will be insufficiently powered to analyze this outcome as a primary event.[21] Assuming n=466 neutropenic episodes per treatment arm (333 patients per treatment arm with 40% having AL and 2 neutropenic periods and 60% undergoing HSCT with 1 neutropenic episode) and assuming the above noted event rate for each arm (1% versus 3%), there would be 0.49 power to detect a statistically significant difference. Even if the event rate for resistance is as high as 8.7% (as was seen for Gram positive organisms in the adult trial), the power for this study would only exceed 0.80 if the event rate of resistance in the treatment arm was almost doubled to 15%. Power calculations were done using PASS 2008 (NCSS, Kaysville, UT, 2008).

Although the anticipated increase (2 percentage points) in sterile site cultures positive for resistant bacteria may be considered modest, such an increase may be clinically relevant if levofloxacin prophylaxis ultimately becomes standard of care for larger numbers of patients. Because this secondary aim is limited by the likely low event rate, evaluation of differences in resistance among colonizing organisms must be used as the primary endpoint. Based on the background discussion above, when patients are infected it is often the result of organisms to which they are colonized. Therefore, it is reasonable to suggest that if there is a significant increase in the resistance among colonizing organisms, then this could translate into a clinically important increase in infections from resistant organisms with worse clinical outcomes.[66,67]

10.0   EVALUATION CRITERIA

10.1   Common Terminology Criteria for Adverse Events (CTCAE)
This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the NCI Website at: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf).
Additionally, toxicities are to be reported on the appropriate case report forms.

11.0   ADVERSE EVENT REPORTING REQUIREMENTS

11.1   Purpose
Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2   Determination of Reporting Requirements
Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- *the current known toxicities for each commercial agent as provided in the <u>Drug Information for Commercial Agents Used by the Children's Oncology Group</u> posted on the COG Website; or*
- *the drug package insert.*

Secondary Malignancy
A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:
- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

11.3 **Reporting of Adverse Events for <u>Commercial</u> Agents - CTEP-AERS abbreviated pathway**
Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.4   Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 4 and higher non-hematologic Adverse Events.

Note: During the infection observation period only (see definition Section 7.1.2), fever, febrile neutropenia and sepsis (of any grade) are captured as study endpoints and therefore should be excluded from routine AE reporting.

12.0   RECORDS AND REPORTING

See the Case Report Forms posted on the COG Website with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1   CDUS
This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.0   SPECIAL STUDIES SPECIMEN REQUIREMENTS
In order to allow central review of the stool and peri-rectal swab specimens, samples will be collected at each participating institution, and processed and shipped in transport media to the Microbiology Laboratory of Michael D. Green, MD, MPH at the Infectious Diseases Research Laboratory (IDRL) of the Children's Hospital of Pittsburgh.

13.1 Samples Collection and Shipping Procedures

13.1.1 <u>Collection</u>
Collect perirectal, rectal or direct stool swab using any Dacron-tipped bacterial culture system (kits will not be provided). Stool or peri-rectal specimens will be obtained either by inoculation of a sterile dacron-tipped swab into stool in a diaper, or by placing a swab moistened with sterile saline into the peri-rectal area where it will be held in this position for 5 seconds. Ideally the surface of the swab should appear "dirty" after specimen collection. Once the specimen is collected the swab should be inserted into the swab's accompanying culture media sleeve. All specimens should be refrigerated immediately upon collection.

13.1.2 <u>Specimen Labeling</u>
Label each specimen with the following information:
- D.O.C. = date of specimen collected
- Source = Type of specimen (stool or peri-rectal swab)
- COG ID = Patient's COG ID number
- Institution = Name of institution
- Initials = Initials of person collecting specimen

13.1.3 <u>Specimen Shipping</u>
Place the swab in a plastic biohazard bag with 1-2 industrial strength paper towels. Place the biohazard bag into a shipping box with 1-2 cool packs. For smaller boxes (7"x6"x6"), 1 cool pack is sufficient. IF shipping from sites outside of North America please use dry ice instead of cool packs. When dry ice is used for shipping, a Styrofoam barrier needs to be placed between the specimens and the dry ice. Complete and include an ACCL0934 Microbial Resistance Transmittal Form with each shipment (see Specimen Shipping Forms on the protocol website). Ship specimen using either the FedEx (Account #: 318196451) or UPS (Account#: 486TDT). When using UPS you may need to know that the account number is affiliated with Brian Fisher, Children's Hospital of Philadelphia, 19104. Ship specimen to the following address:

> Infectious Diseases Research Laboratory
> Attention: Karen Barbadora M.T.
> Children's Hospital of Pittsburgh of UPMC
> Rangos Research Center of University of Pittsburgh
> 530 45th Street, 9th floor RM9170
> Pittsburgh, PA 15201
> Phone: (412) 692-9398

Please contact Karen Barbadora, MT, by phone (412-692-9398) or email: karen.barbadora@chp.edu to inform her of each shipment.

The email subject heading should read: "COG Swab Shipment". In the email provide the patient's COG ID, shipment tracking number and date of specimen collection.

13.1.4 <u>Special Instructions</u>
- If shipping on Monday, Tuesday or Wednesday please chose second day air shipping option. For example if shipping on Monday the package needs to arrive by Wednesday.
- If shipping on Thursday please chose standard overnight to arrive by Friday.

- For specimens collected on Friday, Saturday or Sunday please refrigerate the sample and wait until Monday to ship.
- Please do not ship on a holiday or the day before a holiday.
- If you need to store your specimens please store in a refrigerator at 5 to 10°C.
- For any inquiries contact Dr Brian Fisher at fisherbria@email.chop.edu or Karen Barbadora at karen.barbadora@chp.edu .

13.2   Sample Processing

Upon receipt, each swab will be streaked onto the first quadrant of Colistin Naladixic Acid (CNA) agar (screening for *S. mitis*) and then on to MacConkey agar (screening for the 3 Gram negative rods of interest) and incubated in ambient air at 37ºC for a minimum of 24 hours. Plates with no growth at 24 hours will be re-incubated for an additional 24 hours. When present, *E. coli, K. pneumoniae, P. aeruginosa* and *S. mitis* will be identified from the MacConkey agar or CNA agar plate using standard analytical profile index testing strips (specifically API E20 test kits). *S. mitis* was chosen as the representative species for all viridans group streptococci as it is the most frequently isolated species.

Sensitivity, intermediate and resistant status will be established for each Gram negative isolate to cefepime, imipenem, and levofloxacin and for each *S. mitis* isolate to cefepime, levofloxacin, and penicillin by E-test in accordance with guidelines from the Clinical Laboratories Standards Institute.[68] Table 1 displays the breakpoints to be used to determine sensitivity, intermediate and resistant status for each organism by each antibiotic.

Table 1. Interpretations of MIC's (µg/mL) to establish sensitive (S), intermediate (I), and resistance (R) status for each antibiotic by colonizing organism.

Antibiotic Agent	*Streptococcus mitis*	*Escherichia coli*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
Levofloxacin	S: ≤ 2 I: 4 R: ≥ 8	S: ≤ 2 I: 4 R: ≥ 8	S: ≤ 2 I: 4 R: ≥ 8	S: ≤ 2 I: 4 R: ≥ 8
Cefepime	S: ≤ 1 I: 2 R: ≥ 4	S: ≤ 8 I: 16 R: ≥ 32	S: ≤ 8 I: 16 R: ≥ 32	S: ≤ 8 I: 16 R: ≥ 32
Imipenem	N/A	S: ≤ 1 I: 2 R: ≥ 4	S: ≤ 1 I: 2 R: ≥ 4	S: ≤ 1 I: 2 R: ≥ 4
Penicillin	S: ≤ 0.12 I: 0.25-2 R: ≥ 4	N/A	N/A	N/A

For each enrolled research subject, the second stool or perirectal swab will also be utilized to perform additional screening for the presence of carbapenem-resistant Enterobacteriaceae. These second swab specimens will be streaked on to Oxoid Brilliance Carbapenem-resistant Enterobacteriaceae agar (Oxoid Limited, United Kingdom). This media selects against growth of Gram positive bacteria and selects for growth of Gram negative bacteria with decreased susceptibility to carbapenems. The carbapenem-resistant Enterobacteriaceae plates will be incubated in ambient air at 37ºC for a minimum of 24 hours. Carbapenem-resistant Enterobacteriaceae plates with no growth at 24 hours will be re-incubated for an additional 24 hours. Colonies that grow are presumed to be Gram negative bacteria and will undergo subsequent formal identification (using API E20 test kits) and susceptibility testing against meropenem, imipenem and ertapenem by E-test in accordance with guidelines from the Clinical Laboratories Standards Institute to determine presence or absence of carbapenem resistance.

APPENDIX I: MUSCULOSKELETAL DATA FORM

An assessor (assigned by the treating institution) who is blinded to patient treatment assignment will complete the musculoskeletal data form at baseline, and then 2 and 12 months following completion of the infection observation period. Baseline assessment should take place within 3 days of starting chemotherapy for AL patients and between Day -5 and Day -3 from stem cell infusion for transplant patients. The questions below are to be completed in reference to the day of assessment (not the period prior to the assessment). The completed form is to be submitted via eRDE.

COG ID Number: _____   Evaluation Date: _____

Study time point: ☐ Baseline
                   ☐ 2 months post infection observation period
                   ☐ 12 months post infection observation period

1. Does the patient currently have any of the following? *(please check all that apply)*
   ☐ Tendinopathy: inflammation or rupture of the tendon by physical exam or MRI
   ☐ Arthritis: inflammation of the joint evidenced by redness or swelling
   ☐ Arthralgia: complaint of pain in the joint (specifically the joint)
   ☐ Gait abnormality: limping or refusal to walk
   ☐ None of the above

If "none of the above" is checked then questionnaire is complete.
If any of the other boxes are checked, please continue to the questions below.

2. For patients with tendinopathy please describe the tendon involved:
   ☐ Achilles tendon
   ☐ other, specify: _____

3. For the patients with tendinopathy, does the patient have the following?
   ☐ Tendonitis: inflammation of the tendon
   ☐ Rupture of the tendon

4. For patients with arthritis and/or arthralgia, please describe the joint(s) involved:

	Right	Left
1. Temporomandibular joint (TMJ)	☐	☐
2. Acromio-clavicular	☐	☐
3. Sterno-clavicular	☐	☐
4. Shoulder	☐	☐
5. Elbow	☐	☐
6. Wrist	☐	☐
7. Metacarpophalangeal (MCP)	☐	☐
8. Interphalangeal (IP-1); thumb	☐	☐
9. Proximal interphalangeal (PIP)	☐	☐
10. Distal interphalangeal (DIP);	☐	☐
11. Hip	☐	☐
12. Knee	☐	☐
13. Ankle	☐	☐
14. Metatarsophalangeal (MTP)	☐	☐
15. Interphalangeal (IP)	☐	☐
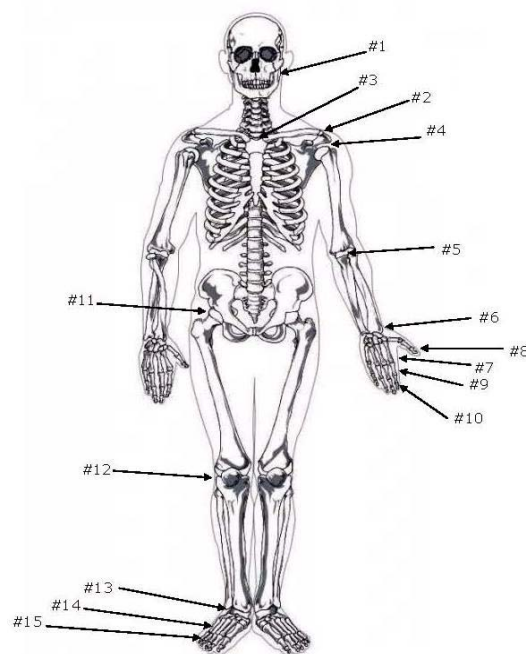
Musculoskeletal Data Form (continued)

5. For patients with **gait abnormality** please describe the joint involved, if any:

	Right	Left
1. ☐ Hip	☐	☐
2. ☐ Knee	☐	☐
3. ☐ Ankle	☐	☐
4. ☐ Metatarsophalangeal (MTP)	☐	☐
5. ☐ Interphalangeal (IP)	☐	☐

6. Clinical Diagnosis. Based on history, exam and other evaluations, the etiology of the current musculoskeletal symptoms is most likely secondary to:

☐ steroid myopathy
☐ vincristine neuropathy
☐ filgrastim related discomfort
☐ osteonecrosis (also referred to as avascular necrosis)
☐ fracture of bone
☐ bone or joint pain secondary to oncologic disease
☐ other , specify:_____
☐ the new musculoskeletal signs and symptoms are not consistent with any specific clinical diagnosis.

APPENDIX II: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY ACCL0934
(for children from 8 through 12 years of age)

A Randomized Trial of Levofloxacin to Prevent Bacteremia in Children Being Treated for Acute Leukemia (AL) or Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

1. We have been talking with you about an effect of intensive treatment for cancer or SCT called bacterial infection. Bacterial infection can occur in patients being treated with intensive chemotherapy for AL. Bacterial infection can also occur in patients being treated with a SCT.

2. We are asking you to take part in a research study because you will have an intensive treatment for cancer or a SCT. A research study is when doctors work together to try out new ways to help people who are sick. This study will find out if giving a medicine called levofloxacin will make it less likely that you get a bacterial infection. Levofloxacin is an antibiotic medication that may prevent bacterial infections. We don't know if it will prevent bacterial infections. That is why we are doing this study.

3. Sometimes good things can happen to people when they are in a research study. These good things are called 'benefits'. We hope that a benefit to you of being part of this study is helping us determine the best possible treatment to prevent bacterial infections for patients undergoing intensive treatment for cancer or a SCT, but we don't know for sure if there is any benefit of being part of this study.

4. Sometimes bad things can happen to people when they are in a research study. These bad things are called 'risks'. It is possible you could have side effects from the levofloxacin treatment. The use of levofloxacin in addition to the cancer treatment or SCT may cause more complications than just using the cancer treatment or SCT alone. Known side effects of levofloxacin include nausea, diarrhea, headaches, dizziness, and problems with your bones and/or muscles. Combining levofloxacin with cancer treatment or SCT may lead to these complications being more severe or new complications that have not been seen before.

5. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

6. There is also an optional part of this study that will find out if treatment to prevent bacterial infections makes antibacterial resistance more likely. For this sub-study, 2 or 3 stool or rectal swab samples will be collected from you. Your family can also choose to be part of this optional sub-study or not.

INFORMATION SHEET REGARDING RESEARCH STUDY ACCL0934
(for teens from 13 through 17 years of age)

A Randomized Trial of Levofloxacin to Prevent Bacteremia in Children Being Treated for Acute Leukemia (AL) or Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

1. We have been talking with you about an effect of intensive treatment for cancer or SCT called bacteremia. Bacteremia is a type of bacterial infection. Bacterial infection can occur in patients being treated with intensive chemotherapy for AL. Bacterial infection can also occur in patients being treated with SCT.

2. We are asking you to take part in a research study because you will have an intensive treatment for cancer or a SCT. A research study is when doctors work together to try out new ways to help people who are sick. This study will find out if giving a medicine called levofloxacin will decrease the occurrence of bacteremia. Levofloxacin is an antibiotic medication that may prevent bacterial infections. We don't know if it will prevent bacteremia. That is why we are doing this study.

3. Sometimes good things can happen to people when they are in a research study. These good things are called 'benefits'. We hope that a benefit to you of being part of this study is helping us determine the best possible treatment to prevent bacteremia for patients undergoing intensive treatment for cancer or SCT, but we don't know for sure if there is any benefit of being part of this study.

4. Sometimes bad things can happen to people when they are in a research study. These bad things are called 'risks'. It is possible you could have side effects from the levofloxacin treatment. The use of levofloxacin in addition to the cancer treatment or SCT may cause more complications than just using the cancer treatment or SCT alone. Known side effects of levofloxacin include nausea, diarrhea, headaches, dizziness, and musculoskeletal problems. Combining levofloxacin with cancer treatment or SCT may lead to these complications being more severe or new complications that have not been seen before.

5. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

6. There is also an optional part of this study that will find out if treatment to prevent bacterial infections makes antibacterial resistance more likely. For this sub-study, 2 or 3 stool or rectal swab samples will be collected from you. Your family can also choose to be part of this optional sub-study or not.

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SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

> This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

ACCL0934, A Randomized Trial of Levofloxacin to Prevent Bacteremia in Children Being Treated for Acute Leukemia (AL) or Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Why am I being invited to take part in this study?
You are being asked to take part in this research study because you will be receiving treatment for acute leukemia or a stem cell transplant.

When patients receive intensive cancer treatment or a stem cell transplant, bacterial infections can develop which can make you very sick.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for bacterial infection and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?
For patients receiving intensive cancer treatment or stem cell transplants, it is standard to treat bacterial infection when it develops with antibiotic medications. Antibiotics to prevent patients from getting a bacterial infection, also called antibiotic prophylaxis, are not normally given.

Why is this study being done?
This study looks at how well treatment with an antibiotic, called levofloxacin, can prevent bacterial infection from developing in children and young adults receiving intensive cancer treatment or a stem cell transplant. The levofloxacin treatment to prevent bacterial infection is experimental.

The overall goal of this study is to compare the effects, good and/or bad, of levofloxacin on people receiving intensive cancer treatment or stem cell transplant to find out if it is better than no preventive bacterial infection treatment.

What will happen on this study that is research?

The standard for treatment of bacterial infection has been to start antibiotics when a new infection is suspected or when an infection is proven (for example with a positive blood test). Standard treatment is Arm A of this study.

This study involves medication to try to prevent bacterial infection called antibiotic prophylaxis. The use of the antibiotic prophylaxis medicine, called levofloxacin, is the experimental arm. It is Arm B of this study.

Summary of Study Treatments

In this study you will get 1 of 2 treatment plans. The 2 treatment plans are the same except that patients in Arm B will get antibiotic prophylaxis treatment with levofloxacin.

The 2 treatment plans are called Arm A and Arm B, as follows:
- **Arm A: No Levofloxacin**
- **Arm B: Levofloxacin**

Random Assignment

You will receive 1 of 2 different treatment plans. The treatment plan that you receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You will have an equal chance of being either on Arm A (no levofloxacin prophylaxis) or Arm B (levofloxacin prophylaxis). The randomization process is described in the COG Family Handbook for Children with Cancer.

Some subjects will be randomized to receive treatment on Arm A; others will be randomized to receive treatment on Arm B.

Diagram of Treatment

This chart shows the treatments on this study.

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                          ┌──────────────┐
                          │  Screening   │
                          └──────┬───────┘
                                 ▼
                          ┌──────────────┐
                          │Study Enrollment│
                          └──────┬───────┘
                                 ▼
                          ┌──────────────┐
                          │Randomization │
                          └──────┬───────┘
                    ┌────────────┴────────────┐
                    ▼                         ▼
           ┌─────────────────┐      ┌─────────────────┐
           │     Arm A       │      │     Arm B       │
           │ No Levofloxacin │      │  Levofloxacin   │
           └────────┬────────┘      └────────┬────────┘
                    └────────────┬───────────┘
                                 ▼
                    ┌────────────────────────┐
                    │Intensive Cancer Treatment or│
                    │  Stem Cell Transplant  │
                    │                        │
                    │Without levofloxacin if in Arm A│
                    │                        │
                    │ With levofloxacin if in Arm B │
                    └───────────┬────────────┘
                                ▼
                    ┌────────────────────────┐
                    │  1 year of follow-up   │
                    └───────────┬────────────┘
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                    ┌────────────────────────┐
                    │   Study Completion     │
                    └────────────────────────┘
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Patients with AL: Treatment during 2 cycles of intensive chemotherapy

Patients having stem cell transplant: Treatment during 1 stem cell transplant procedure

Patients will have study assessments just before starting treatment, during treatment, and at 2 months and 1 year following treatment.

Treatment that is Research

For patients assigned to Arm B, the antibiotic prophylaxis treatment with levofloxacin will be given from Day 3 of your chemotherapy cycle (for patients being treated with chemotherapy) or 2 days before you get your stem cells infused (for stem cell transplant patients).

The levofloxacin will be stopped once you have recovered your blood counts (your neutrophil count is higher than 200). The levofloxacin may be stopped and re-started later if your doctor decides that you need antibiotics for treatment of a new suspected or proven infection.

Treatment for patients who are on Arm A
No levofloxacin treatment.

Treatment for patients who are on Arm B
Various methods may be used to give the levofloxacin:

- **PO** - Given by tablet or liquid swallowed through the mouth.
- **IV** - Given using a needle or tubing inserted into a vein.

Drug	How the drug will be given	Days
Levofloxacin	PO* or IV	Daily starting on Day 3 of chemotherapy for patients with AL and Day -2 from stem cell infusion for patients having a stem cell transplant. Treatment will stop when neutrophil count is >200 or Day 60 if neutrophil count >200 is not reached.

* If tolerated, drug will be taken PO (by mouth), otherwise by IV

Study Tests
Subjects will have tests during the study that are part of standard care (for example physical exams and evaluation for infection).

In addition, as part of this study, your doctor will check your muscles and joints before and after treatment (at 2 and 12 months). These tests will help us learn more about levofloxacin and may help children who receive levofloxacin in the future. The information learned from the muscle and joint tests will not change the way you are treated. The muscle and joint tests will be done at times when you are seeing your doctor as part of your regular care.

Optional Research Study Tests
We would also like to do some tests called biologic studies. Some bacteria are able to survive treatment with antibiotics. This is called antibiotic resistance. We would like to look for bacteria that are resistant to antibiotics in your stool. These tests are important to help us learn more about levofloxacin and whether it increases antibiotic resistance in bacteria. This information may help children and young adults who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be given to you. You do not have to do these tests if you do not want to. You can still be in the study if you do not want to do these tests. At the end of this consent form, there is a place to record your decision about taking part in each test.

We would like to collect peri-rectal swabs (placing a sterile swab in your rectum for 5 seconds) or stool specimens (collecting a sample of your feces when you have a bowel movement) from you during the study. These methods of collecting a sample from you will not cause any pain. The samples would be collected from you 3 times if you are a patient getting chemotherapy for leukemia or 2 times if you are undergoing stem cell transplant.

For subjects receiving treatment for acute leukemia, a swab will be collected before the start of the first (or next) chemotherapy course, and then after each course of chemotherapy, when the blood counts are back to safe levels (for up to 2 courses).

For subjects receiving a stem cell transplant, a swab will be collected before the SCT treatment begins and then after the SCT, when blood counts are back to safe levels.

What side effects or risks can I expect from being in the study?

Risks of Study
The use of levofloxacin as antibiotic prophylaxis may cause more complications.

One of the possible side effects for children who receive levofloxacin involves the musculoskeletal system (the bones, muscles and joints in the body). Levofloxacin is a member of a family of medications called quinolones. Many years ago it was observed that young laboratory animals that were given quinolones developed problems with their joints. This was not seen in older animals. Because of this finding, the safety of levofloxacin in children has been carefully studied. More than 2500 children were involved in a study to look at possible effects of levofloxacin on the musculoskeletal system. In this study parents were asked to report if their children had any symptoms a year after talking levofloxacin. The children who received levofloxacin had a higher frequency of having complaints a year later (3.4% for those who had levofloxacin versus 1.8% for those who didn't) but the types of joint symptoms were very similar in the two groups and in general the symptoms were mild.

One of the other possible risks of taking levofloxacin is the development of bacterial resistance. Your body is colonized with bacteria. That means bacteria live in the intestine, the mouth and on the skin of everybody. Any time you take an antibiotic these bacteria that colonize your body can be affected. Bacteria exposed to an antibiotic sometimes become resistant which means they develop ways to avoid being affected by that antibiotic. Antibiotic resistance can be a problem. If one of the organisms colonizing your body becomes an organism that causes an infection and if this organism is resistant to the antibiotic then that antibiotic will be less effective at treating the infection. Taking levofloxacin may increase the chance of having bacteria that are colonizing your body, and potentially bacteria that cause an infection, of being less able to be effectively treated.

Possible Side Effects of Levofloxacin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Levofloxacin, more than 20 and up to 100 may have:
• **None**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Levofloxacin, from 4 to 20 may have:
• **Diarrhea, nausea** • **Dizziness** • **Headache** • **Difficulty sleeping** • **Change in the heart rhythm** • **Rash, increased risk of sunburn** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **A condition where the layer of tissue (retina) at the back of the eye separates from the layer of blood vessels that supply oxygen and nutrition to the eye** • **For patients who have a diagnosis of myasthenia gravis: worsening of symptoms which may include weakness or tiredness**

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Levofloxacin, from 4 to 20 may have:
• **Swelling, irritation, tearing, or damage of a tendon (a cord that attaches muscle to bone) which may cause pain near a joint and may limit movement**
• **Numbness and tingling of the arms and legs**
• **Increased risk of infection with bacteria that may be resistant to other antibiotics**

RARE, AND SERIOUS
In 100 people receiving Levofloxacin, 3 or fewer may have:
• **Heart stops beating**
• **Abnormal heartbeat which may cause fainting**
• **Severe skin rash with blisters and can involve inside of mouth and other parts of the body**
• **Abnormally low level of blood sugar which cause confusion, changes in vision, shaking, or sweating and may require treatment**
• **Infection, especially when white blood cell count is low**
• **Anemia which may cause tiredness, or may require transfusion**
• **Bruising, bleeding**
• **Blood clot which may cause bleeding, confusion**
• **Hepatitis**
• **Seizure**
• **Kidney damage which may cause swelling, may require dialysis**
• **Infection with a bacteria which may cause pain or cramping in the belly, bloody stool, and fever**

Many of these side effects happened in adult patients. We do not know if children will have the same side effects as adults. Levofloxacin has been prescribed to more than 20 million adult patients. Some of the serious side effects that have been reported occurred in very small numbers of individuals.

Talk to your doctor if you have specific questions about levofloxacin.

Some drugs, food, and supplements may interact with <u>levofloxacin</u>. Examples include:

Drugs that may interact with levofloxacin*
• **Antacids and salt replacement** 　　○ **Aluminum hydroxide, calcium carbonate (Tums), magnesium hydroxide**
• **Antibiotics** 　　○ **Azithromycin, clarithromycin, erythromycin**
• **Antidepressants and antipsychotics** 　　○ **Aripiprazole, citalopram, clozapine, desipramine, escitalopram, fluvoxamine, paliperidone, quetiapine, risperidone, sertraline, trazodone, ziprasidone**
• **Antifungals** 　　○ **Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole**
• **Anti-rejection medications such as cyclosporine or mycophenolate**
• **Antiretrovirals and antivirals such as didanosine, rilpivirine, saquinavir**
• **Heart medications**

> o **Amiodarone, dronedenarone, procainamide, quinapril, sotalol**
> - **Non-steroidal anti-inflammatory drugs, including aspirin**
> - **Salt and electrolyte replacement**
>   - o **Iron salts, magnesium salts, zinc salts**
> - **Some chemotherapy, steroids, and anti-nausea medications (be sure to talk to your doctor about this)**
> - **Many other drugs, including the following:**
>   - o **Artemether/lumefantine, droperidol, haloperidol, insulin, lanthanum, methadone, mifepristone, pentamidine, pimozide, probenecid, sevelamer, succinylcholine, sucralfate, sulfonylureas, varenicline, warfarin**

Food and supplements that may interact with levofloxacin**
- **Echinacea** - **St. John's Wort** - **Grapefruit, grapefruit juice, Seville oranges, star fruit** - **Multivitamins with minerals** - **Antacids such as aluminum hydroxide, calcium carbonate (Tums), magnesium hydroxide**

*Sometimes these drugs are used with levofloxacin on purpose. Discuss all drugs with your doctor.

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided. Talk to your doctor before starting any new medications or herbal supplements and before making a significant change in your diet.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

<u>Reproductive risks</u>
Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Are there benefits to taking part in the study?
We hope that this study will help you personally, but we do not know if it will.

We expect that the information learned from this study will benefit other patients in the future.

What other options are there?
Instead of being in this study, you have these options:

- **Current standard therapy at your hospital. For most patients it is standard to treat bacterial infection when it develops with antibiotic medications. Antibiotics to prevent patients from getting a bacterial infection, also called antibiotic prophylaxis, are not normally given. For some patients in some hospitals using prophylactic antibiotics may be considered the standard therapy.**

- **Taking part in another study.**

Please talk to your doctor about these and other options.

How many people will take part in the study?
The total number of people enrolled on this study is expected to be approximately 740.

How long is the study?
Subjects receiving a stem cell transplant may receive treatment on this study for up to 60 days. Subjects receiving treatment for acute leukemia may receive treatment on this study for up to 2 chemotherapy cycles lasting up to 60 days each. The time will depend on how long it takes for your neutrophil count to recover or until your doctor decides to treat you for a new suspected or proven infection. After treatment, you will have follow-up examinations and medical tests at 2 and 12 months after treatment.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:
- if he/she believes that it is in your best interest
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

What about privacy?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included in **Attachment #1**.

Organizations that may look at and/or copy your research records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other US and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**

- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for this study to pay for medical treatment and/or levofloxacin prophylaxis. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Website at http://www.cancer.gov/clinicaltrials/learningabout.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new products developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Deciding to stop participating will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all children on the study is completed, and not only when your child completes treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* IRB Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, stem cell transplants, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.childrensoncologygroup.org/familyhandbook

Visit the NCI's Website at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

A description of this clinical trial will be available on the internet at: http://www.Clinical Trials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies. There will be no additional cost to you or your insurance company related to the optional research test.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

#1   My stool/peri-rectal specimen may be sent to a COG laboratory and studied to see if antibiotic prophylaxis treatment is associated with bacterial resistance changes.

Yes_____   No_____   _____ / _____
                                        Initials   Date

Signature

I have been given a copy of all _____ pages of this form. The form includes one (1) attachment.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# _____   IRB Approved: _____

Attachment #1

Information About Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.