DFCI IRB – AMENDMENT SUBMISSION FORM

Use this form to request any change to an approved research protocol including changes to the protocol, consent form or other related documents. This includes revisions as a result of an Adverse Event, IND/IDE Safety Report, Deviation/Violation or a revised Investigator Brochure. This form is not to be used for responses to the IRB, SRC or PSRC.

Please note:

- Changes may not be initiated prior to IRB approval except as necessary to eliminate apparent immediate hazard to subjects [(45 CFR 46.103(b)(4)(iii) and 21 CFR 56.108(a)(4)]; Therefore, amendments *must* be approved by the IRB prior to implementation.
- This form may **NOT** be used for changes to study staff or the addition of new study sites. Such changes must be submitted on the **Research Team Update form**, **PI/Site PI Change form** or the **Request to Add New Site Form**.
- Submissions that are incomplete due to missing/inadequate documents, signatures or responses to the questions on this form may be returned to sender and will delay the review process.
- The **ENTIRE SUBMISSION MUST BE ELECTRONIC**. Each of the required revised documents MUST accompany the electronic submission.

DFCI Protocol Number: **06-172**	**Today's Date:** 10/9/07
Protocol Title: INTERNATIONAL COLLABORATIVE TREATMENT PROTOCOL FOR INFANTS UNDER ONE YEAR WITH ACUTE LYMPHOBLASTIC OR BIPHENOTYPIC LEUKEMIA	
Principal Investigator: Silverman, Lewis *First Name, Middle Initial, Last Name, Degree(s)*	**Sponsor/Source of Funding:**
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Study Contact for Questions about this submission: **Jane O'Brien**	Email: **jane_obrien@dfci.harvard.edu**
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Sponsor Amendment Number (if applicable): **01**	

1. DOSE ESCALATION STUDIES ONLY: N/A ☒
Does this amendment apply only to a change in cohort which is included in the current approved protocol and which does not change the risk/benefit ratio? Yes ☐ **No** ☐

2. What is the justification/rationale for this amendment? (Required) 1) The high risk (HR) criteria in Interfant-06 had been defined as follows:

1. MLL rearrangement AND
2. Age at diagnosis < 6 months (i.e. <183 days) AND
3. WBC > 300 x 10e9/L

The recent update of the Interfant-99 data showed that the outcome for infants with MLL rearrangement AND age < 6 months at diagnosis AND a poor prednisone response was equally poor as for HR patients defined above.

Based upon this the Interfant collaborative group has decided to change the risk group stratification criteria. The high risk criteria is now defined as:

1. MLL rearrangement AND
2. Age at diagnosis < 6 months (i.e. <183 days) AND
3. WBC > 300 x 10e9/L AND/OR a poor response to prednisone

2) A typo was corrected on page 24.

3. Does this involve consent form revisions? Yes ☒ No ☐

If YES, specify all additions/deletions (e.g. Page 4, replaced "30 subjects" with "40 subjects") 1) Induction consent: page 5 of 20 - #2 paragraph 2 the following sentence was added, "Infants whose leukemia does not respond well to treatment with a week of steroids during the Induction phase also have a higher chance of their leukemia coming back." In addition on that same page:
The statement: "and your leukemia responded well to steroids during the Induction phase." was added to the definition of Medium Risk. The statement: "and/or your leukemia did not have a good response to steroids during the Induction phase". - was added to the definition of High Risk.
2) Medium Risk Consent, paragraph 1, page 1: the statement, "and your leukemia responded well to treatment with steroids during the Induction phase." was added to the last sentence.
3) High Risk Consent, paragraph 1, page 1: the statement, " and/or your leukemia did not respond well to treatment with steroids during the Induction phase" was added to the last sentence.

Attach the following revised document(s):

☒ One copy of the revised document(s) with changes or additions underlined.
☐ For deletions, attach one hard copy of old pages with deletions crossed-out.
☐ One copy of the consent form (not underlined).

4. Does this involve protocol revisions? Yes ☒ No ☐ (New Version Name/Date: 11/July 17 2007**)**

If YES, specify all additions/deletions (e.g. Page 4, replaced "30 subjects" with "40 subjects") 1) Page 7, section 1.2.2 Prognostic factors in Interfant-99:

2nd paragraph, new 4th sentence, " An updated analysis in April 2007 showed that prednisone response also had independent prognostic value." was added.

A new 5th sentence was added to the 4th paragraph, "The updated analysis in April 2007 confirmed that MLL rearrangement and age < 6 months were the strongest predictors for poor outcome. Within the subgroup of patients who had MLL rearrangement and were < 6 months at diagnosis, a WBC ≥ 300 at diagnosis and a prednisone poor response were equally useful for further identification of patients with the worst prognosis (see table).".

A new 5th paragraph was added with a table:

" 5-yr EFS for patients who had MLL rearrangement and were < 6 months at diagnosis

Prednisone response	WBC	N	5-yr EFS (SE)
Poor	< 300	24	12.5% (10.2)
Good	≥ 300	30	19.0% (9.3)
Poor	≥ 300	42	20.6% (7.7)

Based on this, an amendment was agreed upon in April 2007 that infants with MLL rearranged ALL who are < 6 months at diagnosis, will be stratified as high risk in Interfant-06 if they have a WBC ≥ 300 AND/OR a prednisone poor response."

2) Page 8, section 1.3.1 Stratification: read, " Stratification into 3 risk groups will be based upon the MLL status, age and WBC as argued above. The LR group will consist of all MLL germline cases, including MLL germline patients with a PPR. HR patients are MLL rearranged, < 6 mths and WBC ³ 300. MR patients are all others.", now reads, " Stratification into 3 risk groups will be based upon the MLL status, age and WBC/prednisone response as argued above. The LR group will consist of all MLL germline cases, including MLL germline patients with a PPR. HR patients are those who are MLL rearranged, AND < 6 mths AND have either a WBC ≥ 300 or a prednisone poor response.. MR patients are all others."

3) Page 24 under the section "First part", Read: PEG-Asparaginase: 2,500 U/m2 IV im on day 1, now reads: PEG-Asparaginase: 2,500 U/m2 IM on day 1

4) -Under Section 3.0 Eligibility Criteria and Definitions, the Definition section 3.2. A new 3.2.1 reads, Prednisone Response: Absolute Blast Count (WBC x %blasts) is measured on Day 8, and response is defined as follows:

a) Prednisone Good Response: Absolute Blast Count < 1000/mL

b) Prednisone Poor Response: Absolute Blast Count >= 1000/ mL"

-3.2.2 is now CNS-status and CNS involvement, 3.2.3 is now Testicular involvement, 3.2.4 is now Mediastinal mass.

5) Page 68, last paragraph, a new last sentence was added: "The DFCI ALL consortium sites should send these samples to Dana-Farber for processing in Dr. Scott Armstrong's laboratory at Children's Hospital in Boston, MA".

6) Page 70, The Instructions for Sampling and Shipment were edited to reflect that DFCI ALL consoritum participating sites should send samples directly to Dana-Farber instead of the lab in the Netherlands.

Attach the following revised document(s):.

☒ One copy of the revised pages(s) with changes underlined.
☐ For deletions, attach one hard copy of old pages with deletions crossed-out.
☐ One copy of the entire revised version of the protocol without changes underlined.
☐ One copy of the revised protocol (not underlined).

5. Does this involve revisions to other study documents (questionnaires, surveys, diaries)? Yes ☐ No ☒

If YES, specify all additions/deletions (e.g. Page 4, replaced "30 subjects" with "40 subjects") _____

Attach the following revised document(s):

☐ One copy of the revised pages(s) with changes underlined.
☐ For deletions, attach one hard copy of old pages with deletions crossed-out.
☐ One copy of the entire revised version without changes underlined.

6. Does this amendment add a front sheet or affect any information currently captured on the front sheet?
Yes ☐ **No** ☒
If YES, attach revised document. If an electronic copy does not exist, the study team is responsible for re-creating one, using the current DFCI IRB Protocol Front Sheet template posted on the OPRS website, which replicates what is currently on OncPro and incorporates the information being added/deleted through this amendment.
☐ One copy of revised front sheet with the changes underlined.
☐ One copy of the revised front sheet.

7. Will enrolled study subjects be informed of these changes? (Consider: Is it possible that the changes proposed would affect a subject's decision to continue participation?)
Yes ☐ If YES, how will this be accomplished? _____ **No** ☒ If NO, why not: The changes do not impact the treatment of currently enrolled subjects.

8. Does this amendment affect pharmacy orders including COE (chemotherapy order entry), drug preparation/administration, medication orders, treatment plan (including dose modifications)?
Yes ☐ **No** ☒
If YES, how: _____

9. Does this amendment either remove or modify an Alert Page currently posted on the Oncology Protocol System?
☐ Add or Modify. Specify changes and attach copy (or revised copy). _____
☐ Remove.
☒ N/A

10. Does this amendment modify the Eligibility Checklist?
☐ Yes
☒ No

11. Is this amendment being submitted as a result of an SAE, IND/IDE Safety Report or revised IDB?
☐ Yes – Include the SAE, IND/IDE Safety Report(s) and/or revised IDB for IRB Review.
☒ No

Assurance
The undersigned assures that the information provided in this application is complete and accurate, and that it is consistent with proposal(s) submitted to external funding agencies. The undersigned assures that modifications to the originally approved project will not take place without prior review and approval by the Institutional Review Board, and that all activities will be performed in accordance with state and federal regulations and DFHCC IRB policies and procedures.

Lewis Silverman, MD _____
Overall Principal Investigator (Signature/Name) **Date**

Jane O'Brien _____
Prepared By (Signature/Name) **Date**

FOR OPRS USE ONLY	Overall Status: _____ No. of subjects enrolled per QACT/OPRS: _____ Date: _____
IRB MEMBER REVIEW	☐ Minor modifications acceptable for expedited review (Changes are minor, administrative changes, and/or they do not make the protocol more complex or risky) EXPEDITED per 45 CFR 46.110(b) (2)/25 CFR 56.110(b) (2) _____ Brief Description: _____ *Signature of IRB Member/Date:* _____ ☐ Major modifications that require full IRB review (changes are substantial enough to warrant full committee review, make the study more complex or potentially increase risk or decrease potential benefit)