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July 21, 1999

Memorandum for the NCI Chernobyl Leukemia Working Group

Subject: Agenda, etc for Meeting in Rockville, 29 July, 1999

Enclosed you will find a suggested agenda for the meeting and some additional documents that will be helpful. In addition to Dr Finch's summary of the hematologic status of the work in Phase I that he has sent you separately, I am providing:

Two recent reports of site visits to the project

A brief note on the epidemiologic aspects of the work in Phase I

An exchange of correspondence between Dr Romanenko and Dr Masnyk regarding the work of the final six months

A letter I wrote to Dr Romanenko suggesting a schedule for reviewing the final report on Phase I and reaching consensus on Phase II

As you know, there will be a discussion of the leukemia project on 28 July, in connection with Dr Fraumeni's review of the entire Chernobyl research program. I believe the presentations and discussions at the two meetings will differ substantially and that we will have plenty to do on the 29th.

I should note, with respect to the agenda for the 29th, that I have put Dr Boice down for a review of what is known about any excess leukemia among the cleanup workers, but I could not reach him in Dublin and the entry does not have his agreement. Among all of us, however, he has been following the issue most closely.

  
G W Beebe, PhD, Chairman

CC Drs Ron and Masnyk  
Working Group Members

NCI CHERNOBYL LEUKEMIA WORKING GROUP

Agenda for Meeting on 29 July, 1999

Doubletree Hotel, Rockville, Maryland  
9:00AM - 4:30PM

Welcome and Introductions (Ron, Beebe)

Administrative History, 1995-1999 (Beebe, Masnyk)

Present Status of Work on Phase I

Hematology (Finch)

Dosimetry (Bouville)

Epidemiology (Howe, Beebe)

Evidence of Leukemia among Cleanup Workers (Boice)

WHO Case-Control Study of Leukemia among Cleanup Workers of the RF and BY (Tirmarche)

The Tasks before the Working Group

Review Work of Phase I

Plan and Schedule

Plan and Schedule Consensus with UA Working Group

Decision on Phase II

Modifications in 1995 Protocol

Prepare for Phase II

Making Changes in 1995 Protocol

Submittal for funding

Академія медичних наук  
України

Academy of Medical Sciences  
of Ukraine

НАУКОВИЙ ЦЕНТР  
РАДІАЦІЙНОЇ МЕДИЦИНИ



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May 5, 1999

To Ihor G. Masnyk, M.D.,  
Project Director  
National Cancer Institute,  
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USA  
Telephone 301-594-7659

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Cc: Gilbert W. Beebe, Ph.D  
Stuart C. Finch, Ph.D.  
Geoffrey Howe, Ph.D.  
Andrew Bouville, Ph.D.  
Olga Cvetkova, Ph.D.

Dear Dr. Masnyk:

We send you our proposals on the program of research for 6 months of Phase I extension. In this proposal the refinements made at the documents ("Summary on the tasks of the leukemia study", Dr.Beebe and Dr.Finch, May 12 1998, and subsequent) are taken into account as well as the results of discussion during last visit to Kiev. Also we tried to include suggestions of Dr.Beebe sent on April, 24, 1999.

Sincerely yours

A.Romanenko

## Investigation plan for 6 months period of extended Phase I

### **Task 4- Begin to assemble Cohort- 5.2.1.2 - months 19-21**

- 1) to continue representative cohort formation from the persons who had taken part at the clean-up works and were inhabitants of the 6 oblasts at the moment of registration at the Chernobyl registry

### **Task 6- Search for "Lost to follow-up"- 5.2.1.3- months 19-21**

- 1) to finish the search of 50 clean-up workers registered in the Dnepropetrovsk oblast, about which the information was absent in the Registry for 3 and more years.

### **Task 10- Make physical dose estimates for 20 workers - 5.2.2.1- months 19-24**

- 1) To compare dose estimates obtained on calculations of the experts with EPR measurements in view of inaccuracies
- 2) Analysis of cases of discrepancies by the independent experts
- 3) Expertise of discrepancies with the help of the primary documents (enroute sheets etc.). The outcomes will be utilised for comparison of different dose estimations (task 19)

### **Task 13 Investigate tooth sampling - 5.2.2.1- months 19-24**

- 1) situation with teeth samples will be investigated to find the best approaches for tooth enamel availability from the persons of subcohort and leukemia/lymphoma patients

### **Task 14 Establish EPR dosimetry - 5.2.2.1- months 19-24**

- 1) To execute the final intercalibration stage of EPR-dosimetry assay with the usage of the modified equipment
- 2) To complete modification of EPR-spectrometer
  - To conduct integrated testing of EPR-technique after hooking up by the "Bruker" engineer of the unascertained equipment
  - Definition of basic parameters of a technique (sensitivity and time for reconstruction of one dose) at usage of the modified equipment)

### **Task 16 Do biological tests on bloods - 5.2.2.2- months 19-22**

- 1) 50 workers selected due to the adopted criteria have to be investigated by EPR, FISH and analytical dose reconstruction

### **Task 17 Validity of biological dosimetry - 5.2.2.2- months 19-24**

- 1) Blood samples from the leukemia and lymphoma patients will be investigated by G-banding
- 2) Blood samples will be collected for FISH -analysis in future if the possibility of reliable FISH-dosimetry will be shown in leukemia/lymphoma patients

### **Task 18 Accumulate tissues for Banks- 5.2.2.2- months 19-24**

- 1) To begin formation of archive of the medical files and biological samples from the liquidators living in 6 investigated oblasts and leukemia/lymphoma patients
- 2) To prolong teeth collection from the liquidators.

### **Task 19 Compare various dose estimates- 5.2.2.2- months 19-24**

- 1) To prepare formal methodology of the comparison of various dose estimates obtained independently by analytical dose dosimetry, FISH and EPR in 50 clean-up workers

- 2) To perform results analysis in pairs and for all three assays in the most available quantity of cases
- 3) SEAD assay testing support for clean-up workers
- 4) To compare SEAD with EPR and one of the subsequent assays (analytical dose reconstruction or official dose) in 50 clean-up workers and to select the most eligible assay for the Phase II.

**Task 23 Learn ascertainment, other diseases - 5.2.3.4- months 19-24**

- 1) Leukemia related pathology search will be continued in Hematology department of Dnepropetrovsk oblast
- 2) cases linkage will be performed with the registry.

**Task 27 Obtain and process pre-treatment blood and bone marrow - 5.2.4.2- months 19-24**

- 1) blood and bone marrow samples will be transferred from Dnepropetrovsk oblast.

**Task 28 Evaluate training and equipment needs ( for molecular biology), phase 2- 5.2.4- months 21-24**

- 1) with the experience of Phase I specific plans for Phase II have to be elaborated for equipment and training in USA and Ukraine

**Task 29 Explore high dose sample size- 5.2.4.2- months 19-21**

- 1) to explore is the high-dose sample size adequate for the Protocol scientific tasks fulfillment

**Task 32 Reevaluate organizational patterns for Phase 2 -5.2.7- months 19-24**

- 1) Cooperation partners and organizations will be determined and staff organization as well on the experience of Phase I and the estimated information needs.

**Task 33 Assemble advisory group, phase 2 -5.2.7- months 21-24**

- 1) Advisory mechanism will be clarified on the basis of needs of the Project.

**Task 34 Plan Protocol and Budget for Phase 2-5.3- months 19-24**

- 1) Revision of Protocol and Reports will be started to meet the Phase 2
- 2) personnel requirements, needed equipment and supplies list will be prepared and mutually discussed to plan the budget.

**Additional task 1- Select oblasts for Phase II - months 18-19**

**Additional task 2 - to begin the search of leukemia/lymphoma cases in clean-up workers of 6 oblasts selected for the study - months 19-24**

- 1) To find the informational sources about leukemia/lymphoma cases in clean-up workers in each of the 6 investigated oblasts
- 2) To elaborate the technology of cases search with the definition of most rational ways of information acquisition



20 May 1999

Academician Anatoly Ye. Romanenko  
Director, Research Center for Radiation Medicine  
53 Melnikova vul.  
254050, Kyiv, Ukraine

Dear Professor Romanenko:

Thank you for your letter of 5 May, 1999. I will summarize some of the reactions to your proposal for the 6 months extension from those of the staff that sent me comments. In general there is little to add or modify. We feel that most of the tasks are properly stated and acceptable. Your plan for the extension provides an excellent basis for completing Phase I and for the administrative reviews. The specific notes follow:

**Task 4, To Assemble the Cohort.** We do not feel that you are obligated to do more than determine the feasibility of creating the cohort by drawing subjects from each of the newly defined selection of oblasts.

**Task 10, Make physical dose estimates for 20 workers.** We would propose to modify the text as follows:

“1) To compare dose estimates and uncertainties obtained when using the analytical dose reconstruction method and the EPR measurements.

2) To identify the discrepancies, if any, in the dose estimates obtained by the three experts involved in the analytical dose reconstruction method.

3) To analyze the reasons for discrepancies, if any, making use in particular of the available primary documents (en route sheets and others).

The results obtained in Task 10 will be utilized in the comparison of dose estimates obtained by various methods for 50 clean-up workers (Task 19).”

**Task 18, Accumulate Tissues for Banks.** In regard to subtask (2), we want to be sure we develop an actual archive for teeth and tooth material or develop a satisfactory plan for Phase II.

**Task 23, Learn Ascertainment of Other Diseases.** Even though as stated, the task for the next 6 months seems fine, we do need to decide whether the ascertainment of the “other” hematologic disease is a feasible undertaking for Phase II. This might need to be discussed later this year.

**Task 27, Obtain and process pre-treatment blood and bone marrow.** We feel that the protocol asks that the material be actually processed, not just transferred. Is this correct?

**Task 33, Assemble advisory group.** Our two working groups ( or at least those still left ~~working with us~~) that were responsible for the protocol formulation will have to meet and make recommendations for continuing into Phase II. Once the Phase II is implemented, a Bi-National Advisory Group will have to be convened replacing the old working groups.

In addition to the tasks listed by you, we feel a couple of them have inadvertently been omitted. Namely,

**Task 7, Identify High-Dose Sample.** If we are serious about the possibility of molecular biologic work in Phase II, we really need to do more than we have in the identification of high dose cases.

**Task 31, Determine Training Needs.** We will need some additional training, especially in data management but in hematology and molecular biology as well.

All other tasks seem entirely appropriate.

I have already started the process of extending financial support for the six months and I have been just informed that our agreement with the Department of State for the money transfer has been signed. It will take 3-4 weeks before you will be able to draw on it for the six month extension period. Also, this agreement includes the funds for Dr. Chumak's analytical work. Finally, Columbia has forwarded an order to Bruker for the visit of one of their engineers; they should be able to act by the time you get this letter.

In addition to the above matter, I would like to turn now to other current issues. As agreed earlier, we are planning a visit to your Center during 21-23 June. Most of us will arrive the preceding Sunday and work with the leukemia staff during these days. But there are individual variations. At this time the following schedule is planned:

Drs. Howe, Burch and Zablotska will arrive 15 June to do some preliminary work, preceding the plenary session, with Dr. Gudzenko on the analysis of the leukemia cases that she has access to (this was discussed several times in the past), to discuss future collaboration with Dr. Fedorenko from Ukrainian Cancer Registry and consider development of record linkage system. The new Columbia staff member, Dr. Zablotska is completing a Ph.D. program in epidemiology at Columbia University under Dr. Howe's direction. She has an M.D. degree from Belarus and residency experience from Ukraine. We feel that it would be a very good experience for her to see how actual epidemiologic study is carried out. She will act as an assistant to Dr. Burch and we look forward to her involvement in our work in the future.

Most of the team: Drs. Beebe, Luckyanov, Finch, McFee, Reiss and myself will arrive on Sunday, 20 June by the usual flight from Frankfurt (Lufthansa).

Dr. Bouville will arrive on Monday, 21 June at 15:10 (Flight Ukraine International 102

from Amsterdam. Because of other commitments on the West Coast he will not be able to arrive in Kyiv earlier than 21 June.

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Dr. Tirmarche and possibly Dr. Hubert will arrive on the 22 June and may stay one day beyond the official visit schedule. Unfortunately, they are already committed on Monday, 21 June so they will be late.

During 14-15 July there is a dosimetry/epidemiology meeting planned of the International Dosimetry Group in Slavutych. At this meeting preliminary results of the inter-comparison studies of various dosimetry methods applicable to clean-up workers will be discussed. From our side Drs. Bouville, Luckyanov and Howe will participate. This meeting is organized by Sergei Illychev of the Chernobyl Nuclear Power Plant. Dr. Chumak participated in the previous meetings of this Group and I expect that he will be allowed to participate in this meeting as well.

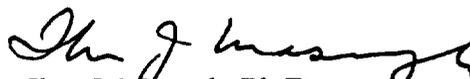
The next trip planned by us to your Center is scheduled for 15-17 September to begin discussing preparation of the final report for Phase I. At present the group will include: Drs. Bouville, Luckyanov, Beebe, Howe, Finch, and possibly myself. The dates for this meeting may be changed if they are not convenient to you or to your staff.

The final visit for this year is planned for 6-8 December for discussion on the completion of the report for Phase I. The team will consist of: Drs. Bouville, Luckyanov, Beebe, Voilleque, Finch, Howe, McFee, Reiss and myself. This date may be "soft" and with time we will be able to confirm it.

Your quarterly report (36 pages) arrived last week. I wonder why it did not contain the projections for the personal commitment for the next quarter and an invoice for the work performed. Is this being sent only to STCU? With the new requirements placed on our program, we would like to receive such statements. Could you send me a copy, please?

It is a long-winded answer to your last letter, but I hope that I have covered all burning issues at this time. Looking forward to seeing you again in June, I am

Sincerely yours,

  
Ihor J. Masnyk, Ph.D.  
Project Director

July 17, 1999

### Note on Epidemiologic Tasks of Phase I

Without going into detail with respect to the individual tasks undertaken by the epidemiologic group, and pending receipt of the final report on Phase I, it would appear that the questions we asked in 1995 will have been answered by the time Phase I is complete. We'll have a reasonable understanding of the Chernobyl Registry and assurance that the cohort we envisioned can be created according to study specifications. Losses to follow-up at the level of the raion polyclinics will have been estimated, and we'll have information on the willingness of representative cleanup workers to provide Chernobyl exposure information at interview and to give blood. We probably can not expect to have an adequate "high-dose" ( $> 0.5$  Gy) sample of subjects for molecular biologic or pathogenesis studies. We will know how best to arrange for full ascertainment of leukemias and lymphomas in any cohort we might establish, but the outlook for the ascertainment of other hematologic diseases will be less favorable. I expect that we can approach with confidence the ascertainment of leukemia in the retrospective period although its use will be subject to the usual restraints on the use of retrospective case material and the associated dosimetric information will be less satisfactory than for prospective cases. We will not be able to enter upon Phase II in the expectation of observing a large excess of leukemia in our cohort. Doubt will be cast on the likelihood that a Phase II study can produce useful information on the effect of dose-fractionation on the risk of leukemia, or on the time-response function for radiogenic leukemia. In short, it appears now that the feasibility of Phase II will have been demonstrated, but that some of its scientific objectives will appear less achievable.

G W Beebe

July 20, 1999

Trip Report: Leukemia Project, UA Cleanup Workers  
20-26 June, 1999

G-W Beebe, PhD

**Introduction:** This was a major site visit by an extensive NCI-IPSN team to review accomplishments and preparations for the completion of the work of the final 6 months of funding (July-December, '99). At issue were the completion of the final report on Phase I tasks, and scheduling its review by the originating working groups, the decision about Phase II, and any modification of the 1995 research protocol for Phase II.

The NCI delegation was led by Dr Masnyk, director of the NCI Chernobyl Projects, accompanied by Dr Bouville, Dr Luckyanov, and myself, and by consultants made available for the project through the support services contract with Columbia University: Drs Burch, Howe, McFee, Reiss, and Zablotska (Ukrainian physician studying epidemiology with Dr Howe). The IPSN delegation consisted of Dr Hubert and Margot Tirmarche. A representative of the Department of Energy, Mr Fountos, accompanied the NCI delegation.

**Six-Month Extension:** In his letter of 5 May Dr Romanenko had outlined plans for the final 6 months. Their discussion clarified the actual requirements for completing Phase I and led to a better understanding of the schedule for preparing and reviewing the final report on Phase I and for developing a position on Phase II.

**Selection of the Six Oblasts:** Although an initial selection had been made in 1995 when the research protocol was prepared, the finding, in the recent diagnostic review, that records of the retrospective period were inadequate in 2 oblasts, necessitated their replacement with 2 other oblasts. Medical record reviews were being conducted; one replacement had been accepted and work on another was almost complete. We went back and forth over the criteria that the leukemia records of the cleanup workers should satisfy in order to qualify an oblast for inclusion, but without taking a formal position. My own suggestion was to frame criteria in terms of the proportion of the leukemia cases of the retrospective period with slides, tissue, and medical records for review, and to avoid the necessity for an actual study of the diagnostic materials. The selection of the substitute oblasts was a task being handled by the hematology and the epidemiology groups.

**Phase II.** Discussion quickly turned to Phase II, whether it would be recommended and what its content would be. Dr Bebesko wanted to be sure that lymphoma was retained. Dr Howe outlined the reasons why lymphoma might not be an acceptable cancer to study in Phase II. Others favored discussion of the pros and cons of a review of Phase II objectives and methods, but it was possible to limit the discussion largely to Phase I, its completion, the preparation of a

summary report, and scheduling the steps that would need to be taken in the final 6 months. Hope was expressed that Phase I could be brought to a quick conclusion so that the final report could be evaluated promptly and attention turned to deciding about Phase II, including any modifications of the 1995 protocol.

The *molecular studies* proposed in the 1995 protocol were also defended by Dr Bebeshko. The Phase I task of assembling the high-dose cohort for these studies was incomplete and doubt was expressed that a sample of sufficient size could be assembled. On the other hand, there was evidence that the Ministry of Internal Affairs would release its file on cleanup workers, and that file was believed to contain additional workers with relatively high doses. Also, the eligibility criteria for the high-dose sub-cohort were not those set for the main cohort. With only about 1,000 in hand it had thus far been difficult to obtain a cohort of 2,500 with doses of 0.5 or more GY, and there also was little evidence of the excess leukemia among the workers that would encourage the studies envisaged in the protocol.

**Work on Specific Tasks:** Pilot work on the *ascertainment of leukemia* indicated that the most reliable and inclusive source would be the hematology dispensaries at the oblast level. Diagnoses entered into the National Chernobyl Registry would be worth scanning for leukemia and a variety of related diagnoses, as was also true of the geographically incomplete Ukrainian Cancer Registry. At best, however, these sources could supplement in only a minor way the ascertainment based on the hematology dispensaries at the oblast level. I advocated that CLL not be neglected in collecting cases, as some of them might turn out to be other forms of leukemia and the absence of a dose relationship with CLL, in the presence of such relationships with other forms of leukemia, could be supportive.

The *diagnostic review* conducted in January seemed to me to require no supplementary work based on other, smaller, and less formal evaluations. There was, however, some opinion favoring an integration of all available data of this kind in Ukraine, although the protocol does not require it. I suggested that Dr Finch could be expected to provide a draft on this task for the final report and that it could be ready for review soon. Dr Klimenko was concerned that the records of the cleanup workers might differ from those of the general population that had been sampled for the diagnostic review.

The *dosimetry group*, with considerable assistance from outside groups interested in the problem, was close to performing its planned comparisons of dose estimates made by the several methods available, none of which could produce estimates for all the subcohort and all the cases of interest. The EPR appeared to have been accepted as the "gold standard" and the task would be to correlate the estimates of each of the other methods with the EPR estimates for the same subjects. The dosimetry group was waiting for the FISH results to be made available for about 50 subjects, and that work, initially delayed by equipment and supply problems, was now well under way with technical assistance from Dr McFee. It was planned that individual dose estimates would be accompanied by ranges of uncertainty. Dr Bouville thought the dosimetry group would complete its tasks by the end of September.

The *ascertainment of hematologic diseases other than leukemia and lymphoma* had been partially investigated and would have to be re-worked by the epidemiology group to satisfy the Phase I requirement.

The *epidemiologic field work in Dniepropetrovsk*, the test oblast, was essentially finished and had produced estimates of the frequency with which workers had not been seen in the polyclinics for several years, the ease of locating representative workers, their willingness to be interviewed, and their willingness to give blood. Two estimates were cited: 31 of 47 approached (67 %) could be interviewed, and 11 of 31 requested (35%) had given blood.

*Collecting, Processing, and Archiving Samples of Blood, Marrow, and Teeth:* These activities had been well organized but the bloods had not been processed as prescribed in protocol Appendix 3. A catalog system was needed for bloods; one was available for the tooth archive.

**Preparation on Report on Phase I:** Dr Romanenko said that Dr Pyatak would be the editor. I suggested that the report consist of an introduction, and in their sequence, the consolidated summary of each task, followed by a brief account of its investigation, amplified by such statements or appendices as seemed necessary to those who did the work. I promised to write Dr Padauk along the lines of our discussion. I also indicated that NCI staff and consultants were available to assist in the preparation or the review of draft material. I expressed surprise that only Dr Chumak had provided draft material for this meeting, as I had been told of an agreement in March that draft material should be available for this meeting on all the tasks. I repeated that NCI staff and consultants were available to assist in the preparation or the review of draft material. I urged that no new work, not explicitly called for in the research protocol, be added to any existing Task, and that only what was required according to the protocol be represented in these write-ups, with the exception of dosimetry where the work had gone beyond what had been foreseen in the research protocol.

As we discussed the preparation of the report on Phase I it became clear that each group finishing a task would naturally consider how its results might affect the Phase II plan in the protocol of 1995. I reminded the group that the 1995 protocol called for the evaluation of Phase I and the modification and re-budgeting of phase II. In fact, the schedule in the protocol ( para 5.2.9) provides for these activities to occupy the last several months of the projected 18-month period, now stretched to 24 months.

To stimulate discussion I suggested the following time-table:

July-September: Completion of outstanding tasks

Drafting task reports

Review of draft material

by 30 September Complete Draft Report

October Technical reviews of Phase I report by NCI, IPSN, and Radiation  
Medicine Center

- November      Formulation of protocol changes desired for Phase II  
Joint meeting in Washington of US and UA working groups that  
authored the 1995 protocol, together with IPSN representatives
- December      Decisions on protocol changes for Phase II  
A joint editorial group would make the necessary changes in  
the 1995 research protocol  
Submittal of revised Phase II research protocol to funding  
agencies by 31 December, 1999



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July 9, 1999

Dr Anatoly Ye Romanenko, Director  
Research Center for Radiation Medicine  
FAX 9-011-380-44-213-7202

Dear Dr Romanenko:

For me the visit was most worthwhile, especially since I had been unable to visit the Center for so many months. Dr Masnyk will undoubtedly write you more fully about the visit, but I want to make certain that we are in reasonable agreement as to the formalities for ending Phase I and making preparations for any Phase II. A number of meetings are required and the preparation of the report for Phase I needs to be available on time for the required reviews.

The schedule I outlined in our meeting on 23 June needs to be confirmed or modified as may be necessary. The extension, as I understand it, ends 31 December, 1999. My proposal was as follows:

Preparation of Report on Phase I	July-September
Final Report on Phase I due	30 September
Review by National Working Groups	October
Joint Review by both Groups	1-15 November
Modification of 1995 Phase II Protocol	December

Some of the implications of this schedule are:

- 1) draft material needs to be circulated in July-September as it is prepared; NCI should see this material for comment, task by task as the sections are prepared
- 2) a uniform format and editorial direction are needed now
- 3) if the report on Phase I can be completed before 30 September we can have more time to revise the Phase II protocol
- 4) the national groups meeting in October need to develop their positions regarding the desirability of Phase II in preparation for the bi-national meeting in November
- 5) the bi-national meeting would be held in Washington
- 6) you and I need to think about what we would do if one working group wants to proceed to Phase II but the other does not.
- 7) almost all the work required by the protocol has been completed and it is important that additional work, not required by the protocol, not be done.

Throughout the period of the preparation of the Phase I the authors should be thinking about the implications of their work for the revision of the original 1995 research protocol for Phase II. In 1995 we thought we knew what we would like to do, but were uncertain as to its feasibility. With the questions of feasibility answered by the work in Phase I there will surely be changes we'll want to make in the Phase II protocol. We don't want these suggested changes to appear in the Phase I report, but we should be prepared with them once we have decided to recommend that Phase II go forward and be funded.

I offered to write Dr Pyatak some suggestions about format, organization, etc and will do so immediately.

Please let me know if the above schedule seems practical from your standpoint or whether we need to make some changes.

Sincerely,

A handwritten signature in cursive script, appearing to read "Gilbert W Beebe".

Gilbert W Beebe, PhD

Cc. Drs Masnyk and Finch  
Dr Tsvetkova  
Dr Ron