To: Clegg, Patsy M SCC-DCS/22 <patsy.clegg@shell.com>
From: Colmer, Robert W SC-DCS/18 </O=SHELL/OU=SI/CN=RECIPIENTS/CN=GBRCO2>
Cc:
Bcc:
Received Date: 2006-09-25 17:31:15 GMT
Subject: RE: SHS Study

Thanks Patsy - I guess all the sponsors will sit down and share their positions and then will all need to come to a conclusion?

Rob

-----Original Message-----
From: Clegg, Patsy M SCC-DCS/22
Sent: 25 September 2006 12:50
To: Colmer, Robert W SC-DCS/18
Subject: RE: SHS Study

Within the next few weeks.

Patsy

-----Original Message-----
From: Colmer, Robert W SC-DCS/18
Sent: Monday, September 25, 2006 4:50 AM
To: Clegg, Patsy M SCC-DCS/22
Subject: SHS Study

Patsy

Any idea when we will know what the positions of all the sponsors are on how much to pay and take forward the study?

Rob

Rob Colmer

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To: BenzConsort-OC@listserve.api.org <BenzConsort-OC@listserve.api.org>; BenzConsort-TC@listserve.api.org <BenzConsort-TC@listserve.api.org>
From: Russell White <whiter@api.org>
Cc: Howard Feldman <Feldman@api.org>; John Wagner <Wagner@api.org>
Bcc:
Received Date: 2006-09-27 18:32:16 GMT
Subject: Shanghai Health Study Conference Call - Thursday, Sept 28. 4 PM EDT

YES, there will be a conference call of the OC and TC. A Sept. 2006 progress report and a conceptual overview of the JCML business plan from Dr. Irons are attached.

Date: Thursday, Sept. 28, 2006
Time: 4 - 5 PM EDT
Call-in number: 866-443-0059 (international 707-765-9147)
Pass code: 202 682 8344

Proposed Agenda
1) Establish quorum - Patsy
2) Establish note taker - Patsy
3) Antitrust - Mark
4) Discuss JCML business plan provided by Dr. Irons - Jennifer
5) Discuss Dr. Irons' September 2006 progress report - Jennifer
6) Discuss SHS budget - Russ
    - 2006 income
    - UCHSC second-half disbursement
    - invoice for 2007
    - contract with Steptoe & Johnson

> >

Picture (Metafile)

Attachments:

JCML Business plan Concept Overview.doc
Picture (Metafile)
SHS Com PR Sep2006 (Final).doc

EXTENDED PROGRESS REPORT

September 2006

Shanghai Health Study

Richard D. Irons

I. ANALYSIS OF DISEASE PROGRESSION FOR APLASTIC ANEMIA, MYELODYSPLASTIC SYNDROME, ACUTE MYELOGENOUS LEUKEMIA AND BENZENE POISONING IN SHANGHAI, CHINA

II. MOLECULAR EPIDEMIOLOGY OF BENZENE-EXPOSED WORKERS IN SHANGHAI, CHINA

III. EXPOSURE ASSESSMENT AND DATA ANALYSIS

I. JCML

A. Progress

1. Case Contact

In the 16-month period ending September 1, 2006, 1202 cases were diagnosed at JCML, bringing total case contact to date to 2,635 for which 2,456 clinical diagnoses have been reviewed.

The caseload at JCML continues to increase at a rate of approximately 20% per year (Figure 1). This represents all cases diagnosed by the laboratory including those in the WHO case definitions for AML and lymphoid neoplasms, as well as the expanded disease list that was suggested by the SRP and added in 2004. The graph also includes nutritional, infectious or reactive diseases as well as other conditions that are excluded from the study. In addition, we have diagnosed or supported case management of approximately 47 patients for humanitarian reasons, most of whom are children.

Cases either caused or complicated by nutritional deficiencies have continued to rise and now represent about 30% of patients originally triaged as AA, MDS, BID and in some cases, AML. Our experience suggests that nutritional deficiencies pose a significant complicating factor and potential confounder in the interpretation of epidemiology and clinical studies in China. The frequency of these also moderate previous case accrual rate predictions.

2. Follow-up

Patients initially diagnosed in the disease progression study are contacted at 6-month intervals and asked to return for follow-up evaluation. Recruitment of follow-up cases has been somewhat limited by a decrease in subject compliance after initial visit and treatment. Predictably, if treatment is successful, some subjects do not agree to follow-up examinations after initial diagnostic evaluation, and some are lost to follow-up. As of September, 2006, we have approximately 159 cases that have been subject to periodic 6-month follow-up examinations (~27%), ranging from 1 to 4 visits, and we have collected previous medical and intervening treatment histories for these cases. This is a relatively small number and the follow-up period is short. However, the rate of follow-up cases presenting is increasing with continued laboratory operation.

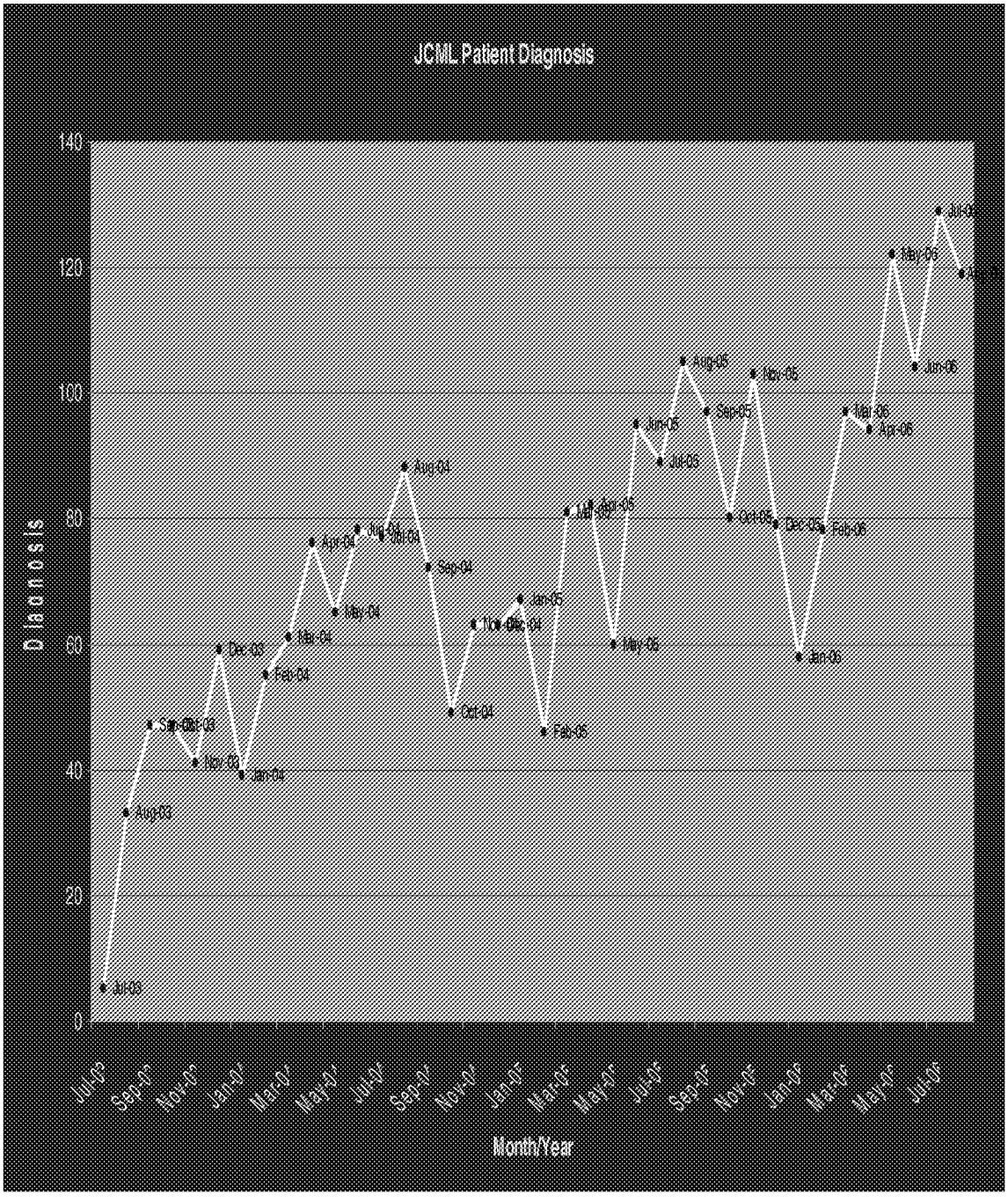

Figure 1. History of JCML Caseload by Month since the Beginning of Operations

C. Disease Progression (DP) Progress to Date

Results already published by JCML using state of the art diagnostic criteria have demonstrated for the first time that the frequency of individual subtypes of AML and NHL in Shanghai vary significantly from those reported in the West. The increased diagnostic precision of JCML provides greater resolution of disease entities than in previous studies. Identifying the underlying prevalence of these diseases is important to: 1) interpret risks specifically associated with exposure to benzene or other agents, 2) clarify disease-specific cellular and molecular mechanisms of leukemogenesis that are relevant to benzene, and 3) improve the biological basis for understanding the relative contribution of genetic, infectious and environmental influences in the development of these diseases in general. Additional publications are in press at the present time and will be communicated in due course according to study guidelines.

In the spring of 2006 we published the first definitive description of persistent bone marrow dysplasia occurring in workers with previous chronic exposure to benzene (Irons et al. *Leukemia Res.* (2006) 29: 1371.) Benzene-induced dysplasia (BID) is characterized by a constellation of abnormalities that strongly implicate inflammation and autoimmune-mediated bone marrow injury as playing important roles in the pathogenesis of persistent bone marrow injury following benzene exposure. A significant question raised by these findings is whether the pathogenesis of BID is directly related to the development of AML associated with benzene exposure.

Several manuscripts concerning additional scientific findings have been generated, are in review, or have been accepted for publication and will be communicated in due course according to study protocol.

II. MOLECULAR EPIDEMIOLOGY (ME) Progress to Date

A. Molecular Epidemiology Phase 1

A total of 29 factories were evaluated for inclusion in the study and 21 were selected. This represents a somewhat larger number of facilities than we originally intended to use in Phase 1. However, finding facilities that meet study criteria with sufficient numbers of workers with accessible physical records has proven more difficult than anticipated. A total of 2,500 records were included in the Phase 1 database out of 2,800 examined. However, the number of these records with qualified exposure assessments is under investigation, and it is likely that the number of records with both qualified blood examination readings and reasonably accurate exposure assessments will be less than 1,000. Ongoing analysis of Phase 1 data has been severely impacted by the shortage of personnel.

B. Molecular Epidemiology Phase 2

During 2006 to date we have conducted analyses exposure assessment and evaluation of health effects in benzene workers has been conducted for 616 subjects, bringing the total to 831. Blood CBC and metabolite samples, samples for polymorphism analysis as well as before and after shift urinary samples have been obtained in conjunction with an average of 10 days of IH monitoring. Full sets of samples, including urine, have been collected for 490 subjects. Because of shortages in qualified personnel, analyses requiring immediate analysis are performed while samples that are stable are being stored for future analysis.

1. Metabolism Studies

Last year, because of repeated difficulties encountered in collaborating with other laboratories, JCML established and equipped an analytical laboratory unit at Fudan for IH and metabolism analyses. Analytical methodology for the analysis of benzene metabolites in blood and urine have been standardized and validated. Benzene metabolites in blood now have been measured in ME Phase 2 workers exposed to benzene over a wide range of area concentrations. Analysis of peripheral blood hematology, as well as some polymorphism analyses have also been performed. Our pace of subject sampling is resulting in a significant backlog of collected samples. However, this represents a unique opportunity to capture and preserve important and exceedingly rare data on benzene metabolism and exposure in humans. Prioritization of the ongoing work is based on the time-sensitive nature of parameters being measured, the stability of analytes in stored samples and the relative scientific importance of the information to be gained.

III. EXPOSURE AND DATA ANALYSIS

A. Introduction

Based on our experiences in evaluating the Municipal Database for use in benzene exposure assessment, we realized that more robust alternatives for validation of information would be necessary than we originally anticipated. Therefore, in November 2005 we reported that we intended to utilize and validate data from diverse sources in constructing our exposure matrix. These include: sector, individual factory, historical, IPHS Municipal database, literature, current factory inspections, detailed IH analyses conducted as part of the ME study, as well as simulations. We are utilizing work patterns identified in hospital-based accrued subject work histories, the results of ongoing exposure analyses in support of DP and ME, as well as our independent validation of the municipal database and case-case disease comparisons in DP in order to identify data gaps and prioritize EA initiatives. An IH working group, including study personnel and SRP members, is meeting in September to review EA initiatives and develop plans for the construction of the study exposure matrix.

B. Exposure Assessment

Questionnaire administration and validation has been performed on approximately 6000 subjects (diagnosed patients and controls) in the hospital setting. In addition over 3000 secondary questionnaires have been taken. Data collection is reviewed immediately and followed up by telephone resulting in a first time validation rate of about 92%. The error rate determined from data entry validation continues to be about 2%. Preliminary benzene exposure assessment has been completed for most of these subjects with an estimated 7% being classified as benzene exposed or potentially benzene exposed. This process involves ongoing industry and job coding, qualitative assessment of cases/controls for exposure to benzene or other substances, obtaining historical exposure information from the IPHS database and/or direct follow-up site investigations. Over the past year the EA team visited 50 factory sites and collected personal, area and bulk samples. Major occupations represented in this group include: shoe making, rubber products manufacturing, printing, paint making and painting, home renovation and general repair and maintenance activities.

C. IPHS Municipal Database Review

An extensive collaboration between the Fudan/JCML team and the Shanghai IPHS was carried out in order to survey the accuracy and reliability of the IPHS Municipal benzene database and consequently the reliance that we should place on it in constructing the final exposure matrix. This collaboration involved a comprehensive analysis of original factory sampling and analytical reports from a single IPHS district, Yang Pu, which was then compared with the original IPHS database.

D. Historical analyses/Literature Review

Over the last 6 months our review of the Chinese literature has focused on the paint industry which represents the most frequently encountered occupational exposure to benzene in our subjects. In general, the paint industry is also very complex with a potentially large number of variables including different products, materials and application conditions, work histories, etc. The focus has been to understand the history of manufacturing and application with respect to the types of paints used, their composition, solvent content, changes in technology and application methods. To date this review includes 161 papers published in the Chinese literature. In addition the EA team has visited selected facilities for the purpose of systematic evaluation of current work processes and the occupational environment, as well as obtaining a picture of the historical use of benzene for individual job/tasks, frequency/duration, changes related to composition and process changes over time.

E. Exposure Simulation

We have identified several activities for which additional characterization of factors, such as material composition, application method, use rate, ventilation and other physical conditions, will significantly impact the accuracy of predictive mathematical models to support the EA matrix. These have been prioritized for simulation, the current list for which includes:

1. Interior painting with solvent-based paint in the construction and renovation trades.
2. Part washing (degreasing) in small shop situations with gasoline
3. Printing press cleaning and inking operations using hydrocarbon solvents
4. Benzene rubber glue applications

1. Interior Painting Simulations

Interior painting exposure simulations were completed in three rooms, with three coats of two different solvent-based paint formulations. Both personal and area exposure measurements, as well as room ventilation rates, air velocity, temperature, humidity, paint quantity applied, and surface area covered were among the parameters evaluated in the simulations. The formulations chosen for the simulation currently contain some benzene as well as older formulations that had traditionally had high benzene content, but the available blends use xylene and toluene instead of benzene. The exposure models resulting from these simulations will be used to account for the physical-chemical property differences between benzene and toluene or xylene.

2. Degreasing Simulations

Degreasing exposure simulations were conducted with "banana water" and gasoline as the test solvents. Banana water traditionally contained benzene, and the industrial solvent gasoline also contained benzene.

F. Database Translation and Query

All questionnaire data and information concerning work histories, occupations, tasks and factory descriptions is collected and entered into the database in Chinese. Therefore, in order to analyze all of this information we are translating these datasets into English. This has proven to be a very daunting undertaking because of sheer size of the database, as well as the highly technical nature of the material to be translated: requiring knowledge of chemistry and industrial practices as well as language. Because of the lack of qualified personnel at the School of Public Health to perform this task, we have independently contracted with linguistics experts at Jiao Tong University to undertake these translations. Several sections have now been translated and are of uniformly high quality. However, the time necessary to translate this material is significant. It is estimated that there remain approximately 6-12 person.months of translation.

Simultaneously, an ongoing intensive effort is being devoted to fine tuning and vetting QA/QC and data migration issues that have to be resolved before the final framework for study

case analysis can be implemented. Because of the size and sophistication of the database, this represents a significant logistics issue which is being worked by the combined UCHSC, EMBSI and JCML teams.

A Business Plan for JCML

Concept Overview

September, 2006

Richard D. Irons

I. Introduction

A. History of JCML

The Sino-US Joint Clinical and Molecular Laboratory (JCML) is a clinical and molecular research facility that that uses state-of-the-art medical technology to support the diagnosis and management of patients presenting with hematopoietic and lymphoid diseases at hospitals in Shanghai. Since JCML began operation in August, 2003, the number of participating hospitals has grown from 17 to 31. During this period JCML has provided integrated laboratory diagnoses for over 3000 patients at no charge to them and has provided advanced training for fellows and graduate students in clinical and molecular research. JCML publications on acute myeloid leukemia, myelodysplastic syndrome, aggressive NK cell leukemia, benzene induced dysplasia and lymphoid diseases have been published in international journals and presented at professional and scientific meetings in China, the United States and Europe. To date, develoment and operation of JCML has been funded in its entirety by the Benzene Health Research Consortium.

JCML provides standardized sample and biopsy collection and diagnosis for patients in Shanghai with hematopoietic and lymphoid diseases. In order to do this, JCML integrates advanced techniques in histopathology and morphology, immunochemistry, flow cytometry, cytogenetics, pharmacogenomics, analytical chemistry and molecular biology in the diagnosis of hematopoietic and lymphoid neoplasms according to the WHO classification. All patient medical history, clinical laboratory and molecular data is integrated into a web-based data management system that supports clinical laboratory management and report generation as well as protocol-driven research.

JCML has also conducted clinical and molecular studies on health effects of exposure to benzene, the etiology and pathogenesis of hematopoietic and lymphoid diseases and established a tissue bank that is linked to the clinical and molecular data collected on these cases. JCML is staffed by personnel from UCDHSC, Univ. of Cincinnati as well as Chinese personnel, many of whom received advanced clinical and

laboratory training in the US as part of this program. The clinical operations and research activities of JCML conform to US Office of Human Research Protection (OHRP) standards, have been approved by the Colorado Multiple Institutional Review Board, the Fudan Institutional Review Board, the Shanghai Public Health Bureau and the Chinese Ministry of Health.

A unique resource is the JCML tissue bank which contains cryopreserved cells, DNA, RNA and tissue samples from patients obtained under informed consent. These samples are linked with individual diagnosis and molecular data by means of a computerized tracking system that facilitates management and access for clinical and molecular studies while preserving individual subject confidentiality. Together, JCML and the tissue bank represent an unprecedented resource for studying the pathogenesis and etiology of disease and clinical studies to predict individual response and follow up to treatment.

B. Mission and Scope of JCML

The rationale for transitioning JCML into an independent clinical and molecular laboratory is to enable it to continue to provide services to the local health care community in Shanghai and to offer the laboratory's research capabilities and resources to a broader set of national and international sponsors and stakeholders. This is also consistent with the current economic realities in China which require that JCML exploit a diverse set of revenue streams in order to support the delivery of state-of-the-art clinical diagnostic services to the Shanghai public.

The specific aims of the laboratory are as follows:

A. To provide standardized state-of-the-art hematologic laboratory diagnoses for adult and pediatric hematopoietic and lymphoid diseases and integrate morphology, immunohistochemistry, FISH, cytogenetics, and molecular and genetic analyses in support of its diagnostic activities.

B. To provide laboratory services in support of other clinical activities including: Genetic analysis and hematopathology support for bone marrow transplantation (BMT), constitutional and family genetic testing, infertility evalution, cytogenetic and FISH analyses of solid tumors etc.

C. To maintain an active developmental molecular pathology program in support of new clinical diagnostic procedures.

D. To conduct sponsored protocol-driven translational research in molecular pathology, medicine and epidemiology. These activities will 1) enable follow up studies of subjects identified and characterized in the SHS project and 2) support and exploit JCML resources, such as the JCML tissue bank.

E. To provide graduate, professional and technical training in hematopathology, clinical and molecular pathology, cytogenetics, toxicology and molecular epidemiology.

II. Business Plan

A. Rationale

Research and clinical activities in China have traditionally been conducted by independent organizations that do not share functions or resources in a meaningful way. Health care delivery and research are usually conducted by different institutions with separate backgrounds, cultures and management. The transition of JCML in to an independent laboratory requires the development of an organization and infrastructure that can bridge the academic and research functions of a Chinese university with the diagnostic and health care delivery functions of the Shanghai medical community.

B. Organization

In order to accomplish this, a joint venture corporation (JVC) will be formed to manage and integrate clinical and research functions of the laboratory. The principals will include the Fudan University Institutes of Biomedical Sciences, the newly established Shanghai Pathology company and a US corporation that will anchor JCML clinical laboratory and research management and attract international research investment and support.

The Institutes of Biomedical Sciences is an academic University-based research institute dedicated to excellence in research and training in the biomedical sciences. It has recently completed construction of a 13 story building on the Fudan University Medical Campus.

The Shanghai Pathology company was created last year to integrate and standardize pathology diagnostic services for the eight hospitals under the Fudan University umbrella and to make them available to a broader segment of the Shanghai and Chinese medical community.

The US corporation will be an independent entity, incorporated in the US, affiliated with the University of Colorado and registered in China that will serve as a Western interface for JCML, harmonizing Chinese and Western diagnostic and operating standards. This corporation will provide guidance and direction in meeting the regulatory and safety requirements for Western laboratory certification, facilitate research and grant management, provide scientific expertise and ensure operation according to Western-based business practices. In order to maintain scientific independence the

corporation will establish a Scientific Advisory Panel that will provide independent review of research results prior to publication.

C. Operation and Marketing Strategies

The JVC structure will optimize the opportunities for 1) obtaining funding to supplement clinical health care delivery and research in Shanghai and 2) utilizing the valuable clinical and molecular resources available for biomedical and health care research. In addition, this operating structure will encourage Chinese University and domestic investment/participation in the development of the laboratory. Based on the current resources and capabilities of the laboratory, areas for development and marketing include:

A. Molecular toxicology, pathology and epidemiology studies supported by ongoing clinical laboratory diagnoses and tissue banked samples. Because there are cultural and legal restrictions regarding selling DNA or tissues in China,, a unique strategy will be to market the conduct of sponsor-directed research utilizing JCML's tissue banked material with the stated goal of making the results public via publication in the peer-reviewed literature

B. Protocol-driven clinical/pharmaceutical research and study management

C. Consultation on Chinese health care regulatory issues, occupational health care monitoring and diagnostic standards in China.