From: George Woodall <Woodallg@api.org>
Sent: Friday, July 5, 2002 12:58 PM (GMT)
To: BenzConsort-TC@api.org
Cc: Lorraine Twerdok <Twerdokl@api.org>
Subject: FW: Progress Report
Attach: ProgRep6.02.DOC

Technical Committee,
Attached is Dr. Irons mid-year progress report. I have not had the opportunity to review or digest the information, but will plug the financials into the spreadsheet and the milestones into the Gannt chart when I get back in the office.
Hope you all had a great 4th.
George
George M. Woodall, Ph.D.
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Tel. (202) 682-8067
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-----Original Message-----
From: Richard.Irons@UCHSC.edu [mailto:Richard.Irons@UCHSC.edu]
Sent: Tuesday, July 02, 2002 7:06 AM
To: PatrickBeatty@chevrontexaco.com; George Woodall
Subject: Progress Report
Gentlemen,
Attached please find the progress report for the first half of 2002.
Best regards,
RDI <<ProgRep6.02.DOC>>

PROGRESS REPORT
JUNE 2002

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

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

A MULTICENTER INTERNATIONAL STUDY

Molecular Toxicology and Environmental Health Sciences Program
Dept. of Pharmaceutical Sciences, School of Pharmacy
Department of Pathology, School of Medicine
University of Colorado Health Sciences Center, Denver, CO.

–

School of Public Health, Hua Shan Hospital, Cancer Hospital,
Fudan University Medical Center, Shanghai, China

I Introduction

A Executive summary

1. Overall Status of the Budget

NOTE: this is the Semiannual Report of Progress as it Relates to the Budget set forth in our contract and is separate and distinct from the University of Colorado Health Sciences Report of Expenditures and Financial Statement, the Quarterly Report on Field Expenses and the Supplemental Summary Requested by API and the Technical Committee, each of which will be forwarded separately. Unless otherwise stated, actual budget numbers are "as of" May 30, 2002.

The overall status of the budget for this fiscal year is as follows: As of May 30, 2002 we have received $4,099,505 against a current approved budget of $4,870,330 exclusive of field expenses. We have expended $1,566,248 as of May 30. At the end of this fiscal year (August 31, 2002) we estimate total expenditures, both encumbered and projected, to be $3,061,859. This will leave a balance of $1,808,471 that includes $1,041,238 in sequestered funds originally earmarked for subject and clinical costs in Year 1.

We have been able to maintain an overall positive cash flow in the face of the budgetary shortfall described above that is due to several factors: salary and supply savings achieved as a result of delays in project funding and start-up, exercise of extended budgetary authority and cost shifting in multiple categories, successes in the negotiation of equipment and reagent contracts and deferral of the payment of incremental increases in EMBSI expenses as part of the revised budget. Because of the delay in project funding, many of the hires and non-capital equipment and reagent purchases scheduled for Fiscal Year 1 (FY1) are being expensed in the last half of the fiscal year. As a result, most of the expenditures estimated for the second half of FY1 are actually encumbered at this time. The progress and budgetary status of each project component will be discussed in subsequent chapters.

B FY2 Costs and Cash flow

1. Projected

Based on the original contract, we will receive $3,416,254 in FY2 against a currently approved budget of $3,284,446. We estimate actual expenses for FY2 to be $4,009,037. The projected differences here are primarily the result of expenses deferred from FY1 as a result of the delay in funding, and include charges against training, equipment, database and personnel. By the end of FY2 we estimate the cumulative deficit will be $592,783. In terms of cash flow (not balances) this is more than offset by the subject-related costs sequestered in FY1. It should be noted that the actual subject-related expenses encountered in FY2 and beyond will depend on the number of cases recruited to the studies: the more cases recruited, the less the balance we will

have on hand. Whether in fact we are able to maintain a positive cash flow in FY2 will depend on subject recruitment. However, it is also obvious that funds originally budgeted to cover subject-related costs that are expensed to cover cash shortfalls will necessarily have to be replaced, probably in early FY3.

C Budgetary and contractual issues

1. UCHSC contract

At present we have committed to equipment and supply purchases and payment schedules to Chinese entities that reflect the budget approved by the Consortium in December 01/January 02. This is being achieved by modifications that reflect realized salary savings and cost shifting at the expense of personnel and operating budgets as discussed in this document. To date, API has not provided UCHSC with any letter of intent or contract addenda to reflect the modified budget changes. In the absence of this, UCHSC will consider the project in default the moment we encounter a negative cash balance. Therefore, under our current contractual arrangements we will not be able to bridge any negative cash balance even for a short period of time. Alternatively, if we are provided a contract modified to reflect the current budget, short term bridging is possible. It is impossible to accurately estimate the timing of these impacts in the absence of being able to predict actual subject accrual rates, but our best estimates suggest a crisis is possible in the latter half of FY2/first half of FY3. Independently, even given a positive cash balance during FY2 we will not be able to modify our payments to EMBSI to reflect their increased costs without a contract addendum.

2. Fudan API contract

It appears that API does not yet have a contract with Fudan University to support Case Control Study operation. As a consequence, Fudan has been charging all Project-related expenses, including Case Control Study expenses, against the UCHSC account. To date the impact has been minimal (i.e. we estimate approximately $14,000 of expenses that should be borne by the Case Control Study will be charged against UCHSC during FY1). In order to facilitate project development and for humanitarian reasons we will continue to support personnel assigned to the Case Control Study. However, this issue is becoming an ongoing management problem with almost daily requests to authorize expenditures that relate to Case Control Study activities. The additional costs for the management of this activity have not yet been built into our budget, and we estimate that these will escalate significantly in FY2. It is our understanding that this practice will continue unless or until API has finalized a contract and funded an account at Fudan University or decides to expense these funds through UCHSC.

II Equipment

A Status

At the time of this writing we have ordered in excess of 80% of the major equipment budgeted for this project. Overall, we have been successful in meeting our budgetary projections for major equipment despite unforeseen costs associated with import-export issues that are described below. This was achieved primarily through budgetary planning, negotiated savings with manufacturers and through cost-sharing with the Shanghai Tumor Hospital Pathology Department. We anticipate similar success with those items remaining to be purchased. Because we critically reviewed equipment needs as part of the preliminary budget revision process conducted subsequent to the SRP review in the Fall of 2001, there are no major equipment items remaining to be purchased that are "optional" or for which procural can reasonably be deferred without jeopardizing laboratory operation. As discussed below, we do not foresee equipment availability as a limiting factor for scheduling the start of laboratory operations.

B Issues

Equipment procurement for JCML has proven to be a complex and cumbersome undertaking. Because of obvious fiscal reasons, no purchasing of equipment could begin before the actual transfer of funds to UCHSC. Beyond the predictable activities of selection, single source justification, negotiation, purchasing and shipment, we have had to contend with delays in obtaining VAT tax and duty exemptions in China as well as difficulties in harmonizing US and Chinese shipping, import and export regulations. Following successful negotiation with manufacturers and the immediate availability of equipment, the time delays in arrival of major equipment at JCML has or is expected to range between 18 and 27 weeks.

In January, 2002 we obtained approval from the Shanghai Bureau of Public Health for certifying equipment provided as a gift from UCHSC to Fudan University as exempt from VAT and import duties (which can amount to up to 100%). We have been uniformly successful in obtaining exempt status. However, this must be requested separately for every item on every invoice which must then be independently approved by Chinese authorities before the exemption is granted. To date, the time necessary to complete this process has varied between 11 and 16 weeks. Further, individual gift letters must be issued by the P.I. and accompanied by copies of the actual manufacturer's invoices. These typically have to be altered and invoices recalculated many times. To complicate matters, recent changes in US criminal law require manufacturers to ship equipment immediately upon invoicing. As a result, we have developed complex strategies to avoid having fragile equipment sit unprotected for weeks on the docks or in a warehouse in Shanghai. These usually involve contracting with holding companies in Hong Kong or bonded intermediaries in Shanghai. The alternative strategy, namely the transfer of funds to Fudan University and the purchasing of equipment directly by JCML, has proven to be too expensive, time consuming or simply impossible to arrange except for relatively minor equipment, such as some computers. These issues have been simplified when we have been able to single source equipment from foreign manufacturers governed by different export regulations. However, the savings in time has been partially offset by the requirement to individually negotiate terms of payment between UCHSC and foreign companies who do not employ similar business practices to US companies. In addition, despite the fact that we have obtained waivers on import duties

and VAT from China, Chinese customs has exacted unforeseen service charges that have exceeded $10,000 to date. These charges do not appear to be predictable based upon either the value or the size of the equipment. In order to offset these charges as best we can, we have cost shifted funds from our projected equipment budget to Fudan University in FY2.

These procedures have proven to be "workable." Nevertheless, they restrict our ability to procure equipment in an expeditious manner and have required that we invoke detailed and advanced planning for every aspect of anticipated laboratory operation. At present we cannot predict whether equipment availability will be a limiting factor for scheduling the start of laboratory operations.

C Supplier Contracts

1. Vysis/the Gene Company

JCML has reached a tentative agreement with the Gene Company, a sole exclusive sales agent for Vysis Inc. in China. Vysis is a US-based company that provides most of the FISH and genetic probes for molecular cytogenetics studies used in clinical laboratories and that will be used on study subjects. During next 5 years, the company will offer JCML a contractual price that is discounted 10% off the current US list price. Prior to this Gene Company has not discounted but has actually imposed a surcharge on list prices of reagents ordered in China. In order to meet our clinical obligations, the company is going to stock the FISH probes in Shanghai that will be commonly used in the JCML. This will significantly reduce the time for delivery which will be important for meeting clinical turn-around times. Furthermore, the company will be responsible for solving any technical problems related to the use of its products. The overall value of the contract is estimated to be approximately $300,000 over the course of the project.

D Equipment Budget Summary

1. Equipment Purchased or Encumbered

Vendor	Equipment	Budgeted	Negotiated Cost	Status	Encumbered
Abbott	Blood analyzer	$65,000	$65,518	At JMCL	$0
Beckman Coulter	Centrifuges	$34,750	$45,035	Shipping	$45,035
Beckman Coulter	Flow Cytometer	$162,500	$145,965	Ordered - waiting import approval	$145,965
Thermo Life	Incubators/laminar flow hoods/freezers/rate freezer/liquid nitrogen storage/alarm system	$195,957	$185,573	Ordered - waiting import approval	$185,573
Gene Company	Imaging system	$195,000	$195,000	At JMCL	$97,500
Ventana*	Discovery/Benchmark /Special stains - for slide preparation/staining	$205,000	$225,000	At JMCL	$0
Olympus	Microscopes	$65,000	$76,564	1 received; remainder Ordered - waiting import approval	$66,564
VWR Scientific	Slide stainer/Lyophilzer/ Refrigerator	$25,554	$33,510	Ordered - waiting import approval	$33,510
Rae Systems	Benzene Monitors	$20,000	$22,600	Ordered - waiting import approval	$22,600
*Cost sharing with Shanghai Tumor Hospital			($40,000)		
Total Equipment FY1:		**$968,761**	**$954,765**		**$596,747**

2. Equipment Remaining to be Purchased in FY1

Items being processed as of June 1, 2002

Description	**Model**	**Unit Costs**	**No.**	**Budgeted**
Electrophoresis Power Supply		$2,500	2	$5,000
Electrophoresis set up		$3,000	1	$3,000
Thermal Cycler		$10,000	1	$10,000
Automated Harvest of coverslips (TECAN)	10-127	$29,500	1	$29,500
Cytogenetics Slide-maker	CDS-5 Drying Chamber	$12,000	1	$12,000
Deionizer Water System	UF-Plus	$15,000	1	$5,000
HIV/HBV/HCV Imx	IMx	$35,000	1	$20,000
HYBrite denatureation /Hybridization System for FISH	30-144020	$5,000	1	$5,000
Molecular biology Software	GeneTool (DNA sequence Analysis software) Mac compatible	$1,500	1	$1,500
		$116,000		$91,000

	Capital Equip.	
$86,500	Total	$71,500
	Non-capital	
$29,500	Equipment	$19,500

3. Non-capital equipment contracts negotiated.

a VWR Scientific

Vendor	Supplies/Noncapital equipment	Budgeted	Negotiated Cost	Status	Balance
VWR Scientific	Misc equipment (e.g. balances, pH meters, etc.	$114,240.42	$110,336.51	Ordered - waiting import approval	$110,336.51

III Laboratory

A Personnel

1. Recruitment and Staffing

We have been actively recruiting JCML laboratory personnel since September, 2001. Although, hiring was essentially limited to senior staff and consultants prior to formal commitment by the Consortium to study funding in January, 2002. Full time hires in the Fall of 2001 included: Ye Xibiao, MS, assistant director for administration; Wang Xiao qin, MD, PhD, associate director for clinical affairs; Jane Liu, MS, assistant to the Director (Dr. Irons). Part-time investigators and/or consultants retained in 2001 included: Professors Fu Hua; Lin Guowei, (Hematology); and Zhu Xiongzeng (Immunopathology-Tumor Hospital). Other consultants recruited during this period, but not added to the payroll in 2001 included: Professor Shi Da-ren, Chairmen, Department of Pathology, Shanghai Tumor Hospital (Fudan); Professor Ji Mei-rong, Department of Hematology, Huashan hospital (Fudan); and Professor Du Xin Xu, Department of Pathology (Shanghai Second Medical University). Together, professors Lin, Zhu, Ji, Xu and Irons will constitute the Expert Committee responsible for the differential diagnosis of hematopoietic and lymphoid diseases at JCML.

Additional personnel recruited to JCML during the first quarter of 2002 have included: a cytogeneticist/pathologist, three cytotechnology technologists, one sample collection technician and a laboratory assistant. In addition, Professor Liang Youxin, Chairman of the Department of Occupational Medicine (Fudan) and Chairman of the Chinese National Committee on Occupational Standards, was recruited as a part-time consultant to the Project. In addition, we have recruited Lv Ling, an occupational physician/hematologist at Huashan Hospital, who will serve as the Senior Occupational Physician for the ME study, beginning in July. During the second quarter of 2002, additional staff recruited include: Miao Luzhuang, as questionnaire QA/QC coordinator and Junming Dai an exposure assessment coordinator, both to be shared with the Case Control study. These individuals are also included in discussion of staffing in the Exposure Assessment Section. At the time of this writing we have also extended an offer for a full time Senior Hematology Technologist to start in July and are interviewing for an additional Hematology/Flow Cytometry technologist, laboratory assistant, and a driver, all scheduled to

hired beginning in the third quarter of 2002. In addition, we will recruit a temporary IT engineering consultant and a permanent database manager in the third quarter to complete installation of the study data system. Finally, two additional sample collection team members and two messenger/sample delivery team members will be recruited in the fourth quarter of 2002.

We anticipate that this level of manpower, together with temporary on-site support by UCHSC professional personnel, will be sufficient to begin JCML laboratory operations at the end of 2002. We anticipate scheduling additional professional staff recruitment pending review of laboratory caseload in the first half of 2003.

2. Training of JCML staff

a UCHSC

Formal training of JCML staff at UCHSC was inaugurated in February, 2002 with Wang Xiaoqin who studied bone marrow culture and diagnostic clinical cytogenetic techniques, became oriented in US clinical laboratory QA/QC procedures and rotated through clinical oncology, learning the hematology bone marrow aspiration and biopsy procedures to be used in this project. She completed her rotations and returned to Shanghai in April, 2002. One of her roles as associate director for clinical activities will involve training clinical coordinators at each of the participating referral and central district hospitals in the standardized procedures to be used for triage, bone marrow aspiration and biopsy techniques. Clinical orientation exercises will be scheduled in the Fall in order to minimize the time between training and study start-up.

Four Shanghai JCML laboratory staff are currently training in clinical cytogenetics at the Colorado Genetics Laboratory (CGL) at UCHSC. The goal of the training is to prepare them with appropriate knowledge and skills in clinical cytogenetics and to conduct chromosome analyses on the samples obtained from recruited study subjects in the project. These individuals are training in sample processing, fluorescence in situ hybridization (FISH) and competitive genomic hybridization (CGH), banded chromosome analysis and clinical cytogenetics, respectively. Because each of these trainees essentially requires full-time "one-on-one" supervision by a senior technologist or faculty member, this represents an unprecedented level of training activity for even a large genetics laboratory such as CGL (most genetics laboratories involved in training accommodate one or at most two trainees at a time). However, delays in project start-up have forced this strategy in order to provide competent staffing for JCML as close to laboratory start-up as possible.

Yao Li-Hong is training in sample preparation and is focused on chromosome analyses of samples such as bone marrow aspirates, bone marrow core biopsies, lymph nodes, solid tumors, and peripheral blood that will be encountered in our studies. The procedures include initial sample preservation and transportation, cell culture, metaphase harvest, slide-preparations for cytogenetics analysis, and chromosome banding techniques. She will be familiar with QC/QA procedures, reagent and solution preparations, image analysis for chromosome aberrations, and clerical supporting procedures. This person is expected to return to the JCML laboratory in

October before the laboratory starts receiving samples from study subjects. She will also learn to prepare and preserve samples to the stage required for shipment to UCSHC for further analyses, if needed.

Chen Hui will also train at UCHSC until October, training extensively in fluorescence *in situ* hybridization (FISH) techniques including sample preparations for interphase and metaphase studies, FISH probe preparations, and fluorescence microscopy analyses. She will also learn multiplex-FISH (M-FISH) and comparative genomic hybridization (CGH) analysis procedures.

Both Sun Hengjuan, the cytogenetics technologist, as well as Chen Yan, the clinical cytogeneticist, are expected to train at UCHSC for 12 months, returning to Shanghai in May of 2003. The training for Sun Hengjuan will be primarily focused on chromosome morphology analyses. She will receive solid training on chromosome pattern recognition, characterization of clone and subclone aberrations, and cytogenetics nomenclature. She will also be trained on different procedures for sample preparations. In the later stage of her training, she will be involved in analyzing samples collected from the study subjects. After her return, she will be the primary person to conduct chromosome morphology analysis in the JCML. Chen Yan is an anatomic pathologist with an MS in genetics that was recruited from Guandong and is training to become a clinical cancer cytogeneticist. She will gain experience in all aspects of clinical cytogenetics laboratory operations with the focus on cytogenetic interpretation, implementation of QA/QC policies, and management of daily cytogenetic laboratory operation. In addition to cancer cytogenetics, she will also become familiar with other subdisciplines of cytogenetics, which will prepare her to deal with wide range of cytogenetics issues that are expected to be encountered among study subjects. After her return to the JCML, she is expected to begin to assume a supervisory role in the cytogenetics operation in Shanghai and serve as an interface between clinicians and the clinical cytogenetics section at JCML

Yang Jin, a chemist from the SMCDC is also training at UCHSC in analytical chemistry, GC-MS and LC-MSMS techniques in support of the pilot study on the analysis of benzene metabolites. He is expected to remain in Denver through September, returning to support exposure analysis for these studies. He is currently training on GC-MS instrumentation and repair, derivitization and solid phase extraction procedures for phenol, catechol and hydroquinone, as well as analytical standardization and QA/QC methods. In July and August he will apply these methods to blood and bone marrow samples, evaluating recovery and minimum detection limits for benzene metabolites in these tissues. He is scheduled to finalize his results in September, familiarize himself with LC-MSMS for the analysis of s-phenolmercapturic acid and return to Shanghai.

Lu Hongfen, a pathologist at the Shanghai Tumor Hospital, will visit Colorado and Arizona this summer in order to become familiar with our QA/QC procedures in histopathology and to train on automated Ventana immunopathology processing equipment jointly purchased by JCML and the Tumor Hospital and recently installed at the Tumor Hospital. Dr. Hongfen will supervise the processing of immunopathology and immunochemistry specimens as part of JCML. She is an Associate Professor who completed her pathology residency at UCLA.

b Shanghai

Additional training activities in support of JCML are projected for the last half of 2002 and forward. Agreements reached between Fudan University and UCHSC provide for continued cultural exchange and graduate training that will also support the research activities of the project. Dr. Irons has recently been appointed a Full Professor at Fudan University with the right to independently advise graduate and medical students. As a consequence of his faculty obligations at Fudan University, Dr. Irons has agreed to serve as PhD co-advisor for Ye Xibiao and PhD advisor for Lv Ling, two graduate students working full-time on the project. In addition, he has agreed to serve as mentor in clinical pathology subsequent to recruitment of a suitable candidate for the Senior Hematology Technologist position. Moreover, Dr. Irons, Dr. Bao and Dr. Wang will undertake together the training of clinical coordinators and additional JCML staff in Shanghai during the Summer and Fall of 2002.

These activities represent a significant reduction in the scope of the planned first year training operation. This is due partly from an effort to offset increased unit training costs associated with cytogenetics and partly to defer expenses originally scheduled for FY1 into FY 2.

B Infrastructure

1. Renovation

Renovation of JCML parent laboratory facilities is essentially complete with the exception of fume hoods, biosafety cabinets and large scale equipment that will be installed upon arrival. Significant laboratory features include: a self-contained HVAC system for climate control, emergency power generator with automatic power transfer capabilities, seamless epoxy resin flooring throughout and a multiple level alarmed security entry system that includes two separate electronic entry locks with computer-based access monitoring that are separated by a physical barrier lock. Laboratory instrumentation, physical data storage and tissue banks should be secure.

C Diagnostic Working Group

1. Organization

The organization of Chinese professional medical specialties was originally predicated on the British system in which strict separation of pathology and hematology disciplines has traditionally been maintained. This is in marked contrast to the US where laboratory examination and diagnosis of hematologic and lymphoid diseases has been fully integrated into subspecialties of pathology. A practical consequence of this in China today is that morphologic examination of bone marrow smears is normally performed by a hematologist, examination of bone marrow

biopsies is performed by a hemato-pathologist, and examination of lymphoid and tumor tissue is performed by an immunopathologist. The diagnostic criteria to be used in this study requires the full integration of all three approaches supported by laboratory molecular-, cytogenetic- and immunologic- analyses. Accordingly, we have developed a strategy for the differential diagnosis of all cases that will involve routine clinical-pathologic conferences of the Expert Committee consisting of professors Lin, Zhu, Ji, Xu and Irons. These conferences will be open to professional colleagues, fellows and students in hematology and pathology who may attend as observers.

D Clinical Networking

1. Signatory Hospitals

To date JCML has signed 16 major referral and central district hospitals to participate in the study. In return, JCML will provide laboratory diagnostic support for clinical activities at these facilities related to the study mission. A list of signatory hospitals is provided:

Hua Shan Hospital
Zhongshan Hospital
Renji Hospital
Changzheng Hospital
Changhai Hospital
Huadong Hospital
Tongji Hospital
Xinhua Hospital
Shugan Hospital
First Municipal Hospital
Fifth Municipal Hospital
Sixth Municipal Hospital
Ninth Municipal Hospital
Railway Hospital
Changning Central District Hospital
Wampu Central District Hospital

Our clinical colleagues estimate that during the first year of operation, clinical agreements between JCML and these institutions will enable the laboratory to capture approximately 85% of the hematologic diseases of interest presenting at area hospitals. We also have been told to expect an increase in the proportion of these cases seen by JCML in successive years as our relationship to the Shanghai clinical community becomes more prominent.

2. Organization of Clinical Coordinators

Clinical coordinators have identified by the respective chairs of Hematology and Pathology at each of the participating hospitals. Under the auspices of the Shanghai Hematology and Pathology Societies, several meetings have held to orient coordinators to the purpose and

organization of the studies. Additional training in triage, control selection, informed consent, clinical and sampling procedures will begin in September and continue until the start of laboratory clinical operations and case accrual. The organization and training of clinical coordinators is the primary responsibility of Dr. Wang Xiaoqin. She will be assisted in these efforts by Dr.'s Irons and Bao.

E Satellite Laboratory Facilities

We have arranged for limited participation by two hospital laboratories in Shanghai to provide specific support services for our clinical activities. These include the histopathology/immunopathology laboratory at the Shanghai Tumor Hospital and the hematology laboratory at Huashan Hospital. Both hospitals are part of Fudan University. These laboratories, which are directed by Professors Zhou and Ji, respectively, will support processing of bone marrow smears and lymphoid/tumor tissue sections as part of the initial morphologic review by the Expert Diagnostic Committee. The QA/QC for procedures provided by these laboratories will meet CAP guidelines.

F Budget Analysis for Training

Training costs for FY1 are estimated to be $80,736 versus $162,813 budgeted, resulting in a projected positive balance of $82,097. This is mostly due to the delay in funding and to a lesser extent to the deferral of some training until FY2. The positive balance projected for the end of FY1 is offset by a projected negative balance of $56,658 projected for training in FY2.

IV Institute for Public Health Supervision and the Shanghai Municipal Centre for Disease Control and Prevention

A IPHS-Overall Progress

In anticipation of our study IPHS has been working since June of 2001 to convert their original database storage media format from 3.5 inch floppy discs to CD's. In February, 2002, as part of their contract with UCHSC, they purchased a Dell Dimension PC system to use as a platform for exposure database management for the project. This system also supports database migration to SAS, which will improve data queries in support of our studies. In February, using a test license copy, we successfully imported a test set of data from the current IPHS Foxpro database. There are three separate historical exposure databases, each with a different structure and coding system, that cover the periods, 1952-1989, 1990-1996 and 1996-present. A SAS software licensing agreement was signed in March between IPHS and the SAS Institute in Shanghai after protracted negotiation. The agreement is not optimal and lacks online support for SAS. Despite these issues, IPHS personnel have succeeded in transferring the first of the three databases. It is projected that the remaining two databases will be transferred and integrated into a single SAS-based structure by Fall, 2002. Additional details are provided in Section VI. In

addition to these acquisitions, IPHS has also purchased a smaller PC, printer, scanner, laptop computer and digital camera in order to facilitate on-site factory evaluations and data analysis and has renovated facilities to house and secure the computer system in a clean, secure and air conditioned environment.

Earlier this year IPHS convened a meeting of the directors and deputy directors of the 19 district offices that will play a major role in identification of facilities and I.H. exposure assessments that will support all three studies. A mechanism was established for assigning tasks as well as orienting and coordinating the personnel that will be required for this project. In addition, a team consisting of 4 central office personnel, together with three people from each of 7 major district offices (total=25), conducted a preliminary survey of approximately 20 industrial facilities, identifying 6-7 factories in which the fraction of workers exposed to benzene approached 80%.

During the second and third quarters of 2002, IPHS personnel will participate in questionnaire development and piloting for the ME study, database conversion, and training of personnel for exposure assessment in support of all three studies. Preliminary identification of candidate facilities for use in Phase I of the ME study will begin as early as September in anticipation of a January start date.

B SMCDCP-Overall Progress

The SMCDC analytical laboratory successfully obtained Chinese National Laboratory Accreditation in accordance with ISO/IEC guideline 25 in January of 2002. This is an important first step toward the international validation of I.H. analyses to be conducted as part of this Project. SMCDCP has currently assigned two analytical chemists to this project, one of whom, Yang Jin, is currently training in GCMS and LCMSMS procedures at UCHSC. He is also participating in the development of solid phase extraction procedures for benzene metabolites that will be used in the pilot feasibility study of the analysis of human bone marrow being conducted at UCHSC during the last half of 2002. He is scheduled to return to Shanghai in September, 2002. Additional personnel committed to the project include: 2 additional laboratory support staff, 3 senior I.H. personnel experienced in field exposure analysis, an occupational physician and a driver. Similar to IPHS, SMCDCP has plans in effect to supplement these individuals with additional personnel when project requirements and field conditions warrant.
The SMDCDP Occupational Health Laboratory, under the direction of Xu Yi-sheng, is currently working with EMBSI to obtain external standardization of QA procedures for the recovery and analysis of benzene and related compounds in air, with external standardization of air sampling and personal monitoring procedures scheduled for August, 2002

C Budget analysis

Shanghai regulatory agencies collaborating in this project do not calculate costs on the basis of personnel time-effort. However, we have agreed to accelerate the payment schedule to IPHS in order to balance the relatively large organizational costs they are encountering early in the

project. This is balanced by comparably smaller payments later on in the project. For information purposes, this is being managed without any additional contractual changes between the Consortium, UCHSC or IPHS. Even so, the expenditure of funds has been extremely cost-effective: Based on our calculations, we have provided support for 4 FTE at IPHS since September, increasing support for an additional 5 FTE in the second quarter of 2002. At the end of May, 2002, payments to IPHS will provide support for 3.25 FTE years. Review of time-effort for IPHS activities described above includes: 2 man-years expended on database conversion, 2.5 man-years devoted to organizational meetings and factory evaluations and at least 0.25 man-years devoted to supervision of these activities. These statistics do not include paid training time of IPHS personnel on SAS software, the projected time-effort expended by IPHS senior staff in questionnaire development or additional efforts on database conversion that will continue in June.

SMDCDP will have been provided payments in support of slightly less than 5 FTE years by the end of June, 2002. In addition, funds totaling $7,000 have been provided to date for the stockpiling of supplies necessary to support exposure analyses. Subsequent to the signing of a contract with UCHSDC, the SMCDC purchased a Finnegan Quadrapole GC-MS instrument which will be used directly to support the analysis of benzene and metabolites. No capital funds are provided as part of SMCDC's agreement with UCHSC. Therefore, participation by SMCDCP in this Project is highly leveraged.

Estimated costs for IPHS in FY1 are $105,522 versus $100,985 budgeted, resulting in a negative balance of $4,537. Costs for IPHS in FY2 are projected to be $56,679 versus $55,130 originally budgeted. Estimated costs for SMCDCP for FY1 are $66,749 versus $69,058 budgeted for a positive balance of $2,309. Costs for SMCDCP for FY2 are projected to be $304,863 versus $296,093 budgeted for a negative balance of $8770. This last projection is entirely dependent on patient/subject accrual rate and should be viewed as a "soft" projection.

V Exposure Assessment Status for Case Control, Disease Progression and Molecular Epidemiology Projects

A Introduction

This section will summarize the development status of the exposure assessment for the AML/NHL case control study, the DP and ME studies, including equipment procurement, staffing, training, questionnaires and other support materials, and quality assurance. Additional discussion of AML/NHL case-control progress will be referenced by Dr. Wong in a separate document.

B Equipment and Software Issues

As discussed in Section IV, a Dell Dimension PC system was delivered to IPHS in February. This supports their database migration to SAS, which will improve data queries in support of our

studies. In February, using a test license copy, we successfully imported a test set of data from the current IPHS Foxpro database. The SAS software license involved negotiations with IPHS and the SAS Institute in Shanghai. We signed the software agreement in March. The package includes SAS Base, FSP, Assist, Stat, Access ODBC, Format, Graph, and Insight. Two of the IPHS staff selected to work on the projects attended a 2.5 day SAS Institute training course in April. This activity was not provided in the system software contract (Cost approximately $ 400 per person). The remaining Foxpro data sets are being converted to SAS, with expected completion at the end of August 2002. IPHS's entire data set is divided into three different subsets with unique structures and codes that span from 1952 to 1986, 1987 to 1997, and 1997 on. The total database is likely to remain in three subsets, each with its own structure, but IPHS plans to harmonize the exposure codes and adapt them to one structure. Dr. Yang Shi Xin, a senior IPHS emeritus staff member will work with Professor Liang from Fudan University to develop the translations of the three different coding systems to one common code system. The plan is to use the national code system that was used for the 1952 to 1986 database. EMBSI and Fudan University will also provide additional advice and technical support on the software issues of the conversion process.

Four UltraRAE benzene selective detector systems and expendable supplies for them are on order from the supplier, but await clearance from Chinese customs. These devices will be used in the molecular epidemiology projects in site selection and in the case control projects for screening measurements on the initial visits to work sites. These work site visits are part of the exposure assessment for case or control work histories.

C Personnel

In February, 2002 a joint conference was held with representatives from Fudan, IPHS, SMCDC and JCML staff to establish an agreement on staffing projections and supporting budgets for each institution regarding exposure assessment. Identification of positions, together with a brief description of responsibility and current status is provided in Table.

D Questionnaire Development

Exposure assessment is being harmonized for both AML/NHL case control and DP studies. We have developed a two level questionnaire approach for use in the case control and disease progression studies. The initial level is used for all cases and controls. The second set of questionnaires covers a broad range of relevant jobs and industrial segments in much more detail. The initial questionnaire for the AML/NHL and DP studies evolved from a draft provided by Applied Health Sciences that has been subjected to extensive review and revision jointly by all investigators, from the US and China. The questionnaire will be used to collect information from subjects (or surrogates only if necessary) about their medical, medication, employment, exposure, and lifestyle. Questionnaire pilot testing began in April, 2002 and continues with periodic collaboration between staff and investigators. The current Chinese draft was pilot tested starting on April 23, 2002 by Miao Lizhuang and Junming Dai from Fudan University. The initial pilot results from eight patient interviews at Hua Shan Hospital in early May led to discussions and revisions in formatting and clarification of some of the questions. Another, more

detailed pilot test of the revised Chinese draft was initiated in mid-May. This second stage pilot test will cover other hospitals that are signatories to the project. The continued pilot testing will also add in queries for relevant data from the IPHS database.

Second level job-specific questionnaires were initially derived from a set of standard occupational exposure history questionnaires published by Dr. P. Stewart of the US National Cancer Institute. These have been extensively reviewed and edited in order to provide a point of departure for our projects. Most of these were originally developed for use in an NHL study. The original NCI set covered 63 trades/jobs/industries. A total of 13 were discarded because they duplicate information obtained in our first level questionnaire. However, we added several new job/exposure categories, and may add additional as needed if we uncover unique jobs during continuing pilot tests or in early stage investigations following project startup. Our current revised set retains 50 specific jobs adapted from the NCI set, three new jobs, and additional generic modules on aspects such as dermal contact, degreasing, welding/burning/cutting/soldering, ventilation systems, and use of personal protective equipment. We anticipate that these will provide additional discrimination of subjects' work and potential exposure history, building on the initial questionnaire. The editing and development of additional question segments in English is complete and undergoing translation into Mandarin. Piloting of these will be completed, starting in late May of 2002.

We have collaborated with Dr. Wong to initiate a number of investigations to develop information that will be needed for the exposure assessment work. Two notable projects are a) a review of benzene in paints and solvents in commerce in China and b) a review of Chinese publications that contain data on benzene exposure, such as case reports and survey reports. Additional information on these and other projects is outlined in the Applied Health Sciences report.

A detailed 18 page site inspection checklist has been developed to guide the field exposure assessment team in collecting data and information needed to support the exposure assessment for a subject's work history. The document is in review for comments and revisions by other investigators on the project. The field exposure assessment team training course (see below) will include lectures and workshops to build the knowledge to use the checklist. We will pilot test the checklist using personnel from Fudan University prior to September training. We also plan additional piloting by the trainees following these courses.

E Training

A schedule has been established for training of questionnaire administrators and the field exposure assessment team, with emphasis on the disease progression and case-control study processes. The training for the molecular epidemiology support team is simpler and shorter and will be derived from the other courses. The first training courses are slated for mid September of 2002, to be conducted with support from Fudan University. We also plan to hold a short refresher course closer to project startup. In-the-field training by a core team will also be provided during the early phases of the actual field investigations. The course contents are outlined, and the bulk of the course materials are drafted in English. We plan to complete courses materials by early July in order for them to be translated into Mandarin by early August.

A separate questionnaire administrator course is designed to provide interviewers with the capability to uncover relevant details of the study participant's medical history, use of medications, work history, initial information on exposure potential, and lifestyle factors. The training will include an overview of the projects, issues such a biases and blinding in epidemiology studies, and how the data from the interviews is a key component of the projects. Dr. Gary Krieger, who will participate in this training course, is developing a series of case studies to use in developing the attendees knowledge of workplace hazards and work practices. We plan to include a several role-playing workshops, built around case studies, using both the first level and selected second level questionnaires.

Field exposure assessment team training will involve IPHS/CDC inspectors as attendees. These persons have firsthand experience with Shanghai area work places. We will teach them additional inspection practices directed at gathering information to support assessment of a participant's exposure history. The course includes an overview of the studies, review of the questionnaires, and how the work site inspection is integrated into the exposure assessment process. We have developed specific inspection modules on evaluating ventilation system, and evaluating use of personal protective equipment (such as respiratory protection).

F Quality Assurance

The central Shanghai CDC laboratory has recently obtained certification (Number 0585), granted by under ISO Guide 25, which applies to analytical measurement laboratories. A copy of the certificate is attached to this report. The China National Accreditation Laboratory granted the certification on January 18, 2002. This accreditation includes a broad review of quality assurance practices, one of which is demonstrating proficiency by satisfactory performance in a round robin testing program organized by the CDC in Beijing. Since 1995, the SCDC central laboratory has been conducting semi-annual proficiency tests of the district CDC laboratories. Independently, SMCDCP and EMBSI laboratories are currently collaborating in an external validation and standardization of analyte recovery and analysis which is anticipated to be completed by the end of September.

The early era (e.g., prior to the early 1970's) industrial hygiene measurements for benzene were collected in glass syringes and analyzed by a colorimetric procedure. Mr. Xu Yi-sheng of CDC will provide publications and a report to document comparisons of that method to its successor. We intend to use this information to determine correction factor is needed to compare those early results to the current charcoal tube collection and gas chromatographic analysis method. Should this prove inadequate, we will perform the necessary methods comparisons.

DP, Case Control Resources and Responsibilities. REVISED May 2002

Position	FTE (People)	Duties	Experience or Person	Where	When Needed
Questionnaire coordinator.	1	Oversee conduct of interviews, training of interview team	Full-time PhD (Dai Junming)	Fudan	Before April pilot
Questionnaire administrators	3	Conduct interviews	MS or BS	Fudan	Fall
QA coordinator	1	Oversees all data, conduct audits	MS, English skills (Miao Lizhuang)	Fudan	Summer
Data entry	2	Enter data from questionnaires, and abstracted medical records	BS or clerk, 1 full time	Fudan	Ready at data flow start
Initial exposure assessment classification, and expert panel	1	Interpret exposure questionnaires, assign to y/n/?. Decide approach to follow-up. Provide expertise in final assignments.	Yang Shi Xin, Liang You-xin Others	IPHS, Fudan	Lead by pilot April?
Database query	1?	Query and report relevant database contents	Ding He Bao, ?	IPHS	By summer for database conversion, familiarization
Special investigators	2	Obtain data from medical records, previous physicians, etc. Chase down missing data.	Clinical experience	CDC, hospitals	
Project coordination	1	Manage all aspects of the project. Makes critical decisions, overview of controls	Dr. Wang Xiaoqin clinical & control and Ye Xibiao (EA)	Fudan	By pilot April
Field exposure assessment	5	Work site investigations, sampling and characterization, analysis	Field experience	IPHS	
Analytical support	0.5	Analyze samples from field investigations		CDC	Ready at project start

Molecular Epidemiology Study Resources. REVISED May 2002

Position	Full Time Equivalents (People)	Duties	Experience or Person	Where	When Needed
Medical records abstraction, interviewer	1	Abstract data from medical records and conduct interviews	Medical background Ding He Bao (draft questionnaire ARS by June 20)	IPHS	By June pilot
Sr. occupational physician	1	Oversees consent, physical exams	Lu Lin	Hua Shan Hospital	June
Exposure assessment team	4	Measures and estimates exposure	MS plus	IPHS, Dr. Liang at Fudan	Lead in by June
Bone marrow analytical support	0.5	Analyze bone marrow metabolite samples	MS	CDC, Hua Shan	
Exposure samples analytical support	1.5	Analyze workplace samples	MS	CDC	At start
Data entry	1.5	Enters questionnaire data, medical record data	BS, clerk	Fudan	By September
QA coordinator	0.5	Oversees data quality, conducts audits	(Miao Lizhuang plus another for	Fudan	Share with AML/NHL DP study
Position	Full Time Equivalents (People)	Duties	Experience or Person	Where	When Needed
Field QA/QC exposure assessment	1.0		IH or occupational/public health background	Fudan	In August
Project Coordination	1	Manage all aspects of project. Decision making	Zhou Shi Zhong and Zhu Surong,	IPHS, Fudan	In place
Project liason	1	Coordinate between the	Ye Xibiao	Fudan	In place

		various groups in the study			
Sample collection coordinator	(In lab budget)	Sample ID quality assurance, transport	JCML	JCML	In August

VI Project Database System Development

A Review and Selection of System Architecture

Provisional planning of the database system was based on the use of a standard PC platform supported by FileMaker Pro software. However, subsequent assessment revealed that this architecture did not meet essential characteristics required for Project database management, patient confidentiality or database security and that alternative strategies needed to be considered.

1. Assessment of Commercial Clinical Data Management Solutions and the Yale Trial/DB Data Management System

Before opting to develop a customized data management system, research was conducted to identify packaged solutions for use as the research data system. The review of DBMS architectures provided in the next section was an integral first step to both identifying the appropriate DBMS and limiting the scope of packaged product alternatives. It is important to note that a DBMS would have to be purchased or licensed separately as it is typically not included in the cost of a packaged solution alternative. During early evaluations, it became apparent that commercial clinical data management systems were aimed at supporting clinical drug trials and were primarily employed in the pharmaceutical and biotechnology industries. Much of the functionality of the systems reviewed focused on accommodating and analyzing data associated with such areas as pharmacokinetics and toxicogenomics. The systems were not viewed as appropriate alternatives and the product costs were prohibitive. However, one non-commercial solution was evaluated further.

Trial/DB was developed by a group within the Medical Informatics department at Yale University in response to the Yale Cancer Center's need for a Clinical Trials database Over a two week period, this system was reviewed in depth and a dialogue established with the leading developer. At the outset, Trial/DB appeared to offer some of the features required UCHSC-Fudan University Health Effects Data System project. It also offered some advanced features for the dynamic creation of study forms, export of datasets, and data randomization. However, upon further review, limitations of the system became apparent. While the data system accommodates a majority of clinical data required be stored by the UCHSC-Fudan University Health Effects Data System, it does not accommodate exposure data and would need to be extended to store employment history, exposure data, and user data modifications. Discussions with Prakash Nadkarni in the Yale Medical Informatics Department who was the lead developer on their effort, indicated that the application and database would require serious restructuring. He communicated that "there is possibly less than 20% overlap between the functionality you need and what TrialDB provides". He also stated that the level of customization of TrialDB and unneeded functionality could be a large hindrance in maintaining and further developing a modified Trial/DB system. The types of modifications needed were not advised. Other issues were also weighted in review of the system. The number of database tables, complexity of table relationships, and the static nature of a few key programming elements were seen as future

limiting factors. The level of complexity would prevent most users from being able to interact directly with the database and would increase considerably the amount of time required in development even compared to starting "from scratch." Throughout the development process and into system maintenance, the database/software engineer would require support from the individuals in the medical informatics group. This was not seen as a possibility since the data system is not a commercial product and product support is not available. Furthermore, Trial/DB is a system in evolution, and we were warned that application/database bugs exist and can present themselves at any point. Therefore we decided not to pursue the Trial/DB as an alternative but to develop our system from the ground up.

The proposed system, while it may lack some of the functionality offered by Trial/DB, provides a solution customized to the requirements of the UCHSC-Fudan University Health Effects Data System. Because the system is being developed from the ground up and with emphasis on reducing both the database complexity and the time required for future system maintenance, it was seen as a much more viable alternative. As the project shifts from development to implementation, and responsibility from database engineers to database administrators, the simplicity of the system and ease of maintenance will be important. Also, the system is being developed with a view to accommodating future functionality without overhauling the existing system.

2. Selection of System Architecture

We conducted a detailed scope and feasibility analysis in March, 2002 as a prelude to the selection and design of the final system architecture which was completed in May. The following (3) candidate system architectures were contrasted and compared as possible DBMS solutions: Oracle, Filemaker Pro and Microsoft Access. A number of databases, such as DB2 and SQL Server, and their associated development tools were also considered but are not reviewed here. Instead, Oracle was chosen to loosely represent this class of high end DBMS, given their closeness in cost, implementation, and scalability. Freeware databases, such as MySQL, were eliminated, due to their limited offer of development tools and database client software. (Note: database client software must be available to individuals who will be accessing the UCHSC-Fudan University Health Effects Data System locally and remotely).

The essential features required for the UCHSC-Fudan University Health Effects Data System include:

1. Storage accommodation of data relating to the health effects of benzene and the pathogenesis of hematopoietic and lymphoid diseases in a relational database.(Must be able to store character data in both English and Simplified Mandarin)

2. Intranet deployed data entry interface to govern data processing, insure data integrity and reliability, and allow selected access to data based on individual user permissions.

3. Environment for administering study protocols as they relate to the assignment of study subjects, management of biological samples, preservation of subject

confidentiality, and the tracking of data modifications.

4. Secure common point of access to the clinical or research database for both local and remote users, both in Shanghai and in Colorado.

5. Internal database links to identified external databases, allowing investigators to view and export required data in an external database.

6. Platform for automating the migration of datasets from the clinical database at Fudan University to the University of Colorado Health Sciences Center.

7. Integration of SAS/ACCESS to make data available in various formats for use in statistical analyses.

Additional requirements for the implementation of the database system include:

1. The initial version of the system must be operational by November 1, 2002. Subsequent versions will provide functionality beyond that listed under the system's essential features.

2. The system must allow for the implementation and utilization of SOPs within clinical data management to assure compliance with regulatory requirements.

3. The technology used to develop the system, in addition to supporting documentation, must provide for a minimal amount of time and cost needed to maintain the system.

4. The system must implement database backup and recovery processes to eliminate the possibility of permanent data loss.

The tables below are provided as a summary of the rationale we used in the selection process. Each candidate system is reviewed individually with respect to the essential features of UCHSC-Fudan University Health Effects Data System. As a result of this exercise, it became evident to us that Oracle provided the best alternative. Its globalization architecture, security features, scalability and development tools can be extended to address present and future system requirements. Economic feasibility, which is a limiting factor with Oracle products in the commercial world, is not an issue in light of Oracle's Research Alliance Program with Universities. Specialized features, such as Oracle's Internet File System, can be developed to allow users to share large image files without having to implement a separate software layer. The initial configuration of a customized Oracle DBMS is time consuming and sometimes complex, however, once implemented, the system's reliability, functionality, and flexibility. Once developed, the system will require limited maintenance; data entry, control, and analysis processes should be optimized; and require a minimum of investigators' time to maintain. Finally, the database and interface design can accommodate the needs of future research studies that may be leveraged on this project.

	Candidate 1 - Oracle DBMS
Key Benefits	• Provides a completely integrated solution for developing a scalable relational database and deploying an intranet-based application. • Database size requirements will never be a limiting factor and Oracle's Data Encryption and Sharing security features meet the highest standards of data transmission. • User security and permissions can be applied on multiple levels (i.e. table, schema, database). • Much of the complexity of data processing logic can be implemented and enforced on the database side, removing the need to require the application layer to control the key business logic. • Oracle offers a full suite of development tools, a proprietary procedural language, and full support of object-oriented development. These features allow for the development of a database and interface to meet any functionality requirements, present or future. • Oracle's Globalization Support architecture allows you to store, process, and retrieve data in native languages, including Simplified Chinese.
Limitations	• Commercial licenses of Oracle are expensive and the cost is usually prohibitive for small companies. (Note: Discounted rates for Higher Education) • Initial configuration and development of database and intranet application is a complex process and requires a considerable amount of development time. • The variety of development features and number of database management processes can be overwhelming and difficult for the novice user to maintain.
DB/Application Software needed	• Oracle 9i Database and Application Server – Enterprise Edition (Programming IDEs for PL/SQL or Java will incur no additional expense) • Data modeling software (e.g. Erwin 4.0 or Enterprise Architect) • Internet Explorer or Netscape Navigator (version requirement not identified yet)
***Cost of Database and Application**	• Approximately $3500 (cost of Oracle biannual license* renewal included) (*See document ORAP.doc – Oracle Research Alliance Program)

Software*	

	Candidate 2 - FileMaker Pro DBMS
Key Benefits	• Can quickly develop a database solution using development wizards and sample databases/templates. • Provides seamless integration with Microsoft Office, such as allowing users to easily import data from Microsoft Excel. • Users can share files between Windows and Mac OS over a local area network, an intranet or the Internet. • Can create custom application solutions for distribution on the web capable of fast interaction with FileMaker Pro databases. • New ODBC and JDBC drivers allow for interaction with SQL databases, such as Microsoft SQL Server and Oracle. • Cost effective solution as a consumer-level database and is relatively easy for non-technical individuals to create and share databases in a workgroup.
Limitations	• Does not support Simplified Chinese • Does not provide any real security unless it is deliberately implemented by the developer. • FileMaker's security schemes are somewhat esoteric and FileMaker's passwords are not inherently tied to individual users, but rather link up with "groups" that the database designer can define. • Limited capability for implementing complex logic in the application layer. • Many steps required for selecting and exporting specific datasets for analysis. Support of SQL (Structured Query Language) is limited to simple SQL DML statements (i.e. INSERT-UPDATE-SELECT-DELETE). • Data transmitted over a network is sent in the clear (i.e. unencrypted and unscrambled) and passwords or sensitive data can be captured by hackers.
DB/Application Software needed	• FileMaker Pro 5.5 Unlimited • FileMaker 5.5 Developer

	• Data modeling software (e.g. Erwin 4.0 or Enterprise Architect) • Internet Explorer or Netscape Navigator (version requirement not identified yet)
***Cost of Database and Application Software**	• Approximately $1,800

	Candidate 3 - Microsoft Access DBMS
Key Benefits	• Microsoft Access provides a simple and flexible Database Management system with an integrated environment for developing a relational database and forms application. • Regular users of Microsoft products will be familiar with its Windows "look and feel" as well as the tight integration with other Microsoft Office family products. • An abundance of wizards lessen the complexity of administrative tasks and guide users through the tasks of developing a relational database and creating forms. • Single file system makes it a simple task to upload, download, or copy and paste entire databases to other computers. • The developer and client can easily exchange prototypes of a database design, without having to recreate and run new installations for each updated version.
Limitations	• Microsoft Access is a low capacity database system and is designed to efficiently manage relatively small numbers of database records. (2 Gigabyte file size limit) • Microsoft Access runs best as a singer-user system and structural design limits performance as the number of concurrent users increases. • Implementation of complex logic in a forms application can be a difficult process and requires a considerable amount of development time. • Microsoft Access uses a one file system and embeds many of it's ease of use tools into the actual MDB file, data tables, and form objects. Since all of the objects and tables reside within one file format, the system may perform sluggishly when transmitting high

	volumes of data. • Supports Simplified Chinese, but can cause configuration issues when implementing a global platform.
DB/Application Software needed	• Microsoft Access 2000 – comes standard in Microsoft Office 2000 • Microsoft Windows 2000 Server • Microsoft Visual Studio 6.0 or later • Internet Explorer or Netscape Navigator (version requirement not identified yet)
***Cost of Database and Application Software**	• Approximately $3,000 (This estimate does not assume that Microsoft Office or Server is already available, which it may be through the university license)

*Cost to develop and implement candidate database management system is not reviewed in detail. As a rough estimate, a FileMaker solution would most likely take half the time to develop/implement as the other two systems, but would not meet essential features of the system outlined in the project scope.

B Review and Selection of System Architecture

1. Selection of Computer Hardware

Review of candidate hardware was limited to Oracle Certified Hardware Configurations that are system stacks of hardware and software that have been integrated, stress-tested and pre-installed, offering the fastest and most cost-effective and reliable method of deploying Oracle software. These configurations were used as a template for identifying the best possible hardware configurations. However, we ruled out the purchase of a preinstalled system given the added costs involved. The category of server was selected was primarily on the basis of cost. Candidate suppliers evaluated included Compaq, Sun, and Dell. The Compaq ML530 and Dell PowerEdge 4600 were found to be relatively comparable systems with the Dell surpassing the Compaq only in regards to internal data storage capacity and processing speed. The UltraSPARC processors of the Sun Enterprise 220R are known for faster processing in comparison to the Intel Xeon processors, however processing speeds have been shown to curtail greatly with the addition of internal disk space above 300GB. Two key factors eliminated the Sun Enterprise 220R as an option: (1) the system would require running Sun's proprietary Solaris operating system and (2) the system was found to cost upwards of $8,000. In addition, only the Compaq and Dell provided for a RAID 5 configuration with optimal fail-over protection (redundancy and back-up) on the mirrored system drive. This feature was seen as an essential requirement given the emphasis on reliable database backup and recovery processes. Though the Dell PowerEdge 4600 outdistanced the Compaq ML530 in the areas of data storage and processing speed, the

Compaq ML530 was found to be more than sufficient for meeting the server requirements of the UCHSC-Fudan University Health Effects Data system. Ultimately, the costs of the hardware configurations played the decisive factor in choosing the Compaq ML530. The Compaq ML530 could be purchased for roughly $1,500 less than a Dell PowerEdge 4600 and further research had established that the ML530 had performed well when used as an Oracle Database and Application server. Two ML530 are being deployed as the major nodes of the UCHSC-Fudan University Health Effects Data system: one each as a designated server on the UCHSC and Fudan IT networks, respectively.

2. Operating System Review and Selection

The Oracle9i Database and Application Server support platforms including: SunSPARC Solaris, Windows NT/2000/XP, Linux, HP-UX, Compaq Tru64, and AIX. Solaris, HP-UX and AIX were quickly eliminated as options given their hardware dependency and the selected hardware configuration (i.e. Compaq ML530). The Compaq Tru64 OS was not considered since the developers working on the data system do not have experience using the operating system and are not familiar with its configuration. We initially (and may ultimately) preferred using Linux (RedHat 7.2 distribution) as the server operating system as a result of the noted stability of Oracle databases running on Linux. Linux offers system administrators complete control over all system processes and Oracle Services, which is a needed capability during times of database backup and recovery. At present, the server has been configured as a dual boot operating system (Windows 2000 and Linux). This configuration was implemented as a method of testing the stability and functionality of an Oracle9i Database and Application Server running on both operating systems. Early assessments have revealed a few inefficiencies with the Oracle9i Application Server running on Linux. In particular, shared library file dependencies in XClient Windows Desktops, GNOME and KDE, are causing faulty interactions with Oracle Forms Builder IDE. Current time constraints prevent troubleshooting this issue at present and development is moving forward on the Windows 2000 Server operating system. Prior to deployment, this issue will be investigated thoroughly to identify a possible resolution.

Project investigators and IT engineers met in June to identify data system storage requirements with respect to exposure analyses. These requirements will be used to standardize the format and content of all exposure data entry forms and provide a method for extracting data for analysis.

3. Budget Analysis

Estimated FY1 costs for database development are $80,631 versus $84,313 budgeted for a positive balance of $3,682. Projected FY2 costs are now estimated to be $115,198, reflecting the changes described above, resulting in a negative balance of $30,794 for FY2.

Estimated Costs for UCHSC-Fudan University Health Effects Data System

Personnel:

1	System Architect & Database/Software Engineer (F/T 6 months salaried)	$35,000
1	Contract Database/Software Engineer (800 hours @ $45.00/hr)	$36,000
1	Oracle Database Administrator based at Fudan (400 hours @ $20.00/hr)	$8,000
2	Data Entry – system initialization data (already employed in clinical lab)	$0

New Hardware & Software

2	Compaq ML530 Server	$8,500
1	Server Interface Hardware for Development Client	$400
2	Back-UPS	$200
1	Oracle Database Server v.9i - Enterprise Edition (ORAP*)	$315
1	Oracle Internet Application Server v9i - Enterprise Edition (ORAP*)	$210
1	Technical Support and Update Subscription (ORAP*)	$660
1	Development Software and Reference Materials	$300
10	Oracle 9i Client Software (No additional Costs)	$0

* Oracle Research Alliance Program (discounted rate – see ORAP_Quote.xls)

Total Development Costs: **$89,585**

Projected Annual Operating Costs

Personnel:

1	F/T Database Administrator based at Fudan	**$10,000**
1	P/T Database Administrator/Engineer at UCHSC - PRA	$20,000

Expenses:

1	Oracle Biannual License Agreement Renewal	**$1,180**

Total Projected Annual Costs: **$31,180**

C Project Status Report - Deliverables

Deliverable	**Status**	**Comments**
1. Design of System Deployment Architecture	Complete	
2. UCHSC Server Installation and Configuration	Complete	System Array configured SCSI Hard Drives partitioned and formatted

		Dual OS (Windows 2000 Server and Linux Server) installed and configured
3. Oracle9i Database and AS Installation and Configuration on Development Client and on Server	Complete	
4. Database Schema (v 1.0)	Complete	Coded first version of schema generation script which includes (table definitions; relationship constraints; table indexes; and insert, delete, and update triggers on tables)
5. Database - System Analysis and Design	Incomplete	Completed Entity Relationship Diagram (v 1.0). **Domain Object Model (DOM) Document (v. 1.0) – waiting for feedback** Project Scope and Feasibility Analysis Document (v 1.0) – waiting for feedback User Requirements Document (v 1.0) and application architecture models will be completed by May 24, 2002
6. Database Schema (v 1.1)	Incomplete	Completion will be affected by timing of feedback on DOM

D Timeline of Project Database Milestones

Project Database Milestone	Estimated Completion Date
1. User interface design and prototype (will only illustrate appearance and navigation)	July 15, 2002
2. Database design completed and available for testing (will not contain PL/SQL application packages)	August 15, 2002
3. Fudan Server installed and configured	September, 2002
4. First "official" version of database and application developed and deployed on Fudan Server for testing	September 15, 2002
5. Database and Application Revisions completed	October 15, 2002

6. Final version of database and application completed	November 1, 2002

VII Project Management/Administration

A Overview

Project management activities have included: equipment purchasing and staff recruitment, both in the US and in China; personnel management; negotiation, review and management of UCHSC subcontracts; obtaining visas, arranging travel, registration, insurance, housing and training of Chinese personnel at UCHSC and other US locations; design and supervision of laboratory renovation, equipment installation and management of the daily operations of JCML; planning and implementation of database development; identification of reagent sources and negotiation of contracts for laboratory/exposure assessment supplies; coordination of laboratory procurement with study and clinical protocol requirements; development of strategies, documentation and administrative support for regulatory submissions and review in both the US and China; development of database and laboratory operating procedures consistent with College of American Pathologist guidelines; tracking of expenses and expenditure projections both at UCHSC and at Fudan University; meetings with Chinese, EMBSI and UCHSC collaborators; production of regularly scheduled progress and budget reports; responding to ad hoc API/Technical Committee requests for supplemental documentation and budgetary analyses, attending business and public affairs meetings in China and the US, meeting with business and government representatives in support of Project objectives.

B Analysis

1. Progress

Progress in individual areas has been described throughout this report. We have been reasonably successful in constructing and managing a far-ranging operation spread across two continents. At the present time we appear to be on schedule and under budget, with enough cash flow margin to function with the budgetary shortfall we have been given. In order to achieve these goals, management activities have been governed according to the following priorities: (in decreasing order of importance): develop a high quality and stable infrastructure with which to implement the Project; bring the Project on-line within budget; and to begin subject accrual in January, 2003. We initially underestimated the level of effort required to administer and manage certain aspects of the Project. There are a number of reasons for this, ranging from a requirement to provide detailed "hands on" management supervision in Shanghai to a need to significantly increase our focus of attention on contractual, governmental and bureaucratic activities: including the negotiation of contract terms for the procurement of equipment, Chinese bureaucratic requirements for importation of equipment, responding to US immigration and

consular resistance to the approval of visas for the training of Chinese personnel at UCHSC, and accommodating post-contractual Consortium requests for additional accounting and budget projections. We also adopted an aggressive strategy with respect to submission of clinical protocols for IRB approval that was successful but labor- intensive. Early submissions of study protocols were provided to Cancer Center and COMIRB staff in order to orient them to the size and scope of the project. An overview of regulatory and ethical issues was prepared to guide their deliberations by identifying potential areas of conflict between US and Chinese regulations and customs. The complete protocols were re-written and submitted in formats required by thee review groups.

2. Budget

As a result, management expenses are estimated to be $397,720 for FY1 compared to $374,119 originally budgeted. This includes an additional charge of $48,466 for preparation of semi-annual budget analyses and summaries requested by the Consortium. These summaries do not comply with generally accepted US accounting practice. Therefore, we have been required to support their preparation as a direct cost outside the normal University accounting system. Moreover, because they are based on a calendar rather than a fiscal year, we cannot use them to reconcile our expenditures or to project our operating expenses.

We have minimized the budgetary impact of these activities during FY1 through a combination of efforts, including the linking of personnel recruitment with the redistribution of personnel administrative responsibilities, and the contribution of existing resources when possible. These included a commitment of an additional 0.7 FTE to management in August, 2001 but deferral of billing until January, 2002. In addition, the Colorado Combined Institutional Review Board contributed an unprecedented 40 man.days to the formal review of Project protocols without levying additional charges (protocol review typically requires 1 man.day). However, they will now levy an annual fee for the maintenance of these protocols.

In many cases we will not be able to continue to defer administrative charges incurred in FY1 throughout the entire FY2, although these appear to be more than offset by the economies realized in the overall budget. Management expenses estimated for FY2 are $394,902 compared with $327,476 originally budgeted, resulting in a projected deficit of $67,426 in this category.

VIII Disease Progression Study Milestones

Begin lab staff training	Feb 2002	All
Questionnaire harmonization for DP/CC studies	Apr 2002	DP
Draft second level questionnaires in place	April 2002	DP
Questionnaire pilot	May 2002	DP
(UCHSC) Provisional approval	May 2002	DP/ME

Final Approval	Jun 2002	DP/ME
Hardware/networking in place	Aug 2002	All
IRB approval (Fudan)	Aug 2002	All
Training for questionnaire admin and field exposure assessment staff	Sep 2002	DP
Questionnaire finalized	Nov 2002	DP
Database operational	Nov 2002	All
First phase of JCML operation	Nov 2002	All
Recruit first case	Jan 2003	DP
Complete first exposure assessment of case/control series	Feb 2003	DP
Recruit 230th case (AML/MDS/AA)	Jan 2004	DP
460th case	Jan 2004	
Complete 690th exposure assessment of case/control series	Apr 2004	DP
CAP certification of JCML	Jun 2004	All
690th case	Jan 2005	
920th case	Jan 2006	
1150th case	Jan 2007	

IX ME Study Milestones

Draft questionnaire and abstraction form	Jan 2002
Pilot study for ME	Jul 2002
Metabolism Pilot Study Completed	Oct 2002
Phase 1 completed for first factory	Jan 2003
First factory exposure assessment complete	Feb 2003
First physical exams conducted for Phase IIA	Mar 2003
Ibid Phase IIB	Apr 2003
Last factory Phase I completed	Oct 2004
Last factory Phase IIA	Dec 2004
Last factory Phase IIB	Jan 2005
First publication submitted – Phase I	Mar 2005

*Dates in red are for milestones already achieved.