From: Cagen, Stuart Z SHLOIL-SHOIL-SHS <stuart.cagen@shell.com>
Sent: Tuesday, October 16, 2007 7:16 PM (GMT)
To: Tsai, Shan P SHLOIL-SHS <Shan.Tsai@shell.com>
Subject: FW: Shanghai Health Study QA/QC team activities
Attach: APIDatabaseAuditPlanv1.pdf; Cagen, Stuart Z SHLOIL-SHOIL-SHS.vcf

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For our discussion

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-----Original Message-----
From: Jmricewas@aol.com [mailto:Jmricewas@aol.com]
Sent: Tuesday, October 16, 2007 2:00 PM
To: jennifer.b.galvin@conocophillips.com; Cagen, Stuart Z SHLOIL-SHOIL-SHS; Clegg, Patsy M SCC-DCS/22
Cc: jarnotb@api.org; whiter@api.org
Subject: Shanghai Health Study QA/QC team activities

Hello Jennifer, Stuart and Patsy,

This is to bring you up to date on ongoing QA/QC team activities in advance of the team conference call that is scheduled for Friday, October 19 at 0900 EDT, and to ask your input on a proposal to more closely define the scope of the formal QA documentation that is now under consideration (draft workscope attached). The new workscope has been drafted by Carl Mao, on behalf of Pharm-Olam, a firm which regularly conducts QA/QC monitoring and evaluation for the pharmaceutical industry. Pharm-Olam was identified by API as a potential successor to Judy Baldwin for professional QA/QC assessment, and has been engaged for the past few months in familiarization with the SHS program and its key worksites in Shanghai, Colorado, and California.

Some concern has been expressed by QA/QC team members that the Pharm-Olam audit might become too all-encompassing and too intrusive, and that it might unduly distract SHS personnel from their primary tasks. This is especially applicable to the exposure assessment project, which needs to be finished before Yimei Zhou is reassigned by ExxonMobil from the SHS at the end of 2007. In response to this concern -- and I need your input and concurrence on this -- it seems to me that it is **the case-control study and its supporting elements, the JCML/case ascertainment nexus and the Shanghai & Colorado databases** that principally require formal QA/QC audit, to help validate the CC study. In contrast, those elements of the SHS research program that are developmental in nature and not amenable to definition by SOPs should not be a focus of the Pharm-Olam audit. These would include the EA program, and the DP and ME studies. Unless you have concerns about this approach, I intend to propose this narrowing of focus by the Pharm-Olam effort when the team convenes by conference call on October 19. I would appreciate your response ASAP.

I would add a private observation that there is probably much to be said for involving a firm like Pharm-Olam in the QA/QC effort at this time. While Judy Baldwin's withdrawal for reasons of health was widely considered a calamity by the investigators, their longstanding familiarity with Judy and hers with them might have led to a less critical and dispassionate audit than is ultimately desirable. In short, she may have been a bit too close to the investigators. While there will be some nervousness among the investigators as they adjust to the new audit team, the final outcome may be better for the

SHS overall.

The QA/QC team had also planned to review the status of the extensive preliminary dataset that was to have been delivered to Otto Wong by the end of September. Gail Jorgenson is pivotal to that undertaking, and both she and Sherilyn Gross (Richard Irons' alter ego at the University of Colorado) have been added to the QA/QC committee. Unfortunately, one of Gail's family members was involved in a serious automibile accident 2 weeks ago, and it is not clear at this time whether she will be able to participate in the conference call this Friday.

The constructive involvement of Pharm-Olam personnel in the formal QA/QC audit puts the formal charge to the QA/QC team back on track, and I expect from now on to convene monthly conference calls which will include the appropriate Pharm-Olam senior staff. In order to encourage free discussion of the draft audit plan I have not invited the Pharm-Olam people to participate in the October 19 conference call.

I look forward to your response, and to keeping in more frequent contact as the final stages of the Shanghai Health Study develop.

Jerry

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vCard Version: 2.1 | Revision: 20060707T154808Z

Database Audit Plan (Draft Outline, Version 1.1)

Shanghai Health Study

Principal Investigator: Richard Irons, PhD

Case-Control Study of AML and NHL (PI: Otto Wong)
Disease Progression Study – AA, MDS, AML, BP (PI: Fu Hua)
Molecular Epidemiology Study – Benzene-Exposed Workers (PI: Fu Hua)
Joint Clinical and Molecular Laboratory (Clinical and Molecular Research Center)

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Date draft: Sunday, September 09, 2007

Signature page

Reviewed and approved by

Y. Carl Ma, PhD Audit Lead	Date
Anthony Orlando, PhD VP, Global Data Division Pharm-Olam International	Date
Richard Irons, PhD Principal Investigator	Date
Jerry Rice, PhD Chairman of DB Audit Charter	Date

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1 Objectives and Scope

1.1 Objectives

The primary objective of this data quality assurance process is to facilitate successful completion of the Shanghai Health Study (SHS) through development, implementation and management of an independent data and process quality assurance and control program. The focus of this audit is to be on the Shanghai Health Study as a whole, rather than on specific protocols, existing QA/QC measures that have already been established by individual principal investigators for individual protocols or other SHS elements will not be replaced by this plan.

1.2 Scope

Expanding the above, this audit shall ensure that a rigorous system for data and process quality assurance and control is in place and functioning (defined processes, roles and responsibilities, process reviews, project timeline with goals & milestones, and key metrics) to provide oversight and assurance addressing the following:

(1) data and process quality control are robust and sustained;
(2) data capture, analyses and transfers are done in a timely, accurate, complete, consistent and secure manner;
(3) data tracking and progress reporting is on-time and accurate;

The above scope can be detailed into following concrete actions:

(1) documentation audit: this involves all necessary procedural documentation including standard operation procedures (SOPs) of clinical/diagnostic laboratory and data base management, data capturing forms (including laboratory diagnosis reports), study conduct professional training documentation and process; and other relevant documentations that were used during the conduct of the study.

(2) database audit: this involves database structure, computer system (server, including system security), software associated with the server(s) that maintain database, database access security, database exporting system (supporting SAS?), database reporting system, data point verification against original paper data, among others.

The scope will be augmented by the procedures described in following sections.

2 Procedures

This section outlines the procedures the audit to follow. The procedures are arranged in the order in which the audit will be conducted.

2.1 Documentation Audit and Review

The diagnosis of disease in case-control and disease progression protocols followed *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues* (WHO 2001), while Molecular Epidemiology study followed (to be provided by Richard Irons)

(1) Protocols. It has been understood that the protocols have been updated a number of times during the past time since they were initially drafted. All updates for the protocols are necessary to be reviewed so that the actual audit process will be guided under these changes.

(2) Data forms. All forms used in the study for data capturing, including all revision and/or updates should be available for review; these include the questionnaires for the study, among others that were used.

(3) SOPs. All SOPs that were used during the conduct of study should be available for review; this especially includes the SOPs for the clinical/diagnostic laboratory.

(4) Professional training documentation. All training documentation/materials should be available for review.

(5) Interim reports. All up-to-date interim reports as described deliverables in the protocols should be provided for review.

(6) Other documentation. Any other documentation that was associated with the conduct of the study should be provided for review.

Detailed review reports of the above shall be prepared and reviewed by the relevant personnel as means to guide and regulate the audit progress and successful completion of the study.

2.2 Database Audit and Review

In order to ensure database were correctly established and robustly maintained and data were accurately recorded, database audit shall consist of three major parts.

2.2.1 Computer System and Software Audit

(1) Database design structure review, to ensure appropriate relational data structure and normalization are in place to accommodate such complex study data. Database design plan/process flow will be needed for such purpose.

(2) Computer server(s) will need to be reviewed, including security and stability of OS, software used in developing and maintaining the database; Internet/Intranet infrastructure, among others.

(3) Database functionality (e.g. SAS data export)

2.2.2 Laboratory Audit

The central laboratory will be audited.

It as been learned that the Joint Clinical and Molecular Laboratory (JCML) was established as a part of this program, mainly for clinical diagnosis of sampled subjects. It has also been learned that the laboratory has staff trained in US and sent back to Shanghai to conduct actual diagnosis work.

The following should be included in the audit:

(1) Staff training materials or training program certificates;
(2) Staff education background;
(3) Staff work experience;
(4) Laboratory facilities documentation;
(5) Laboratory data transferring/transmission capability;

among others.

2.2.3 Database Audit

This is the most important part of entire audit process: physical and actual data points will be checked against original paper data recorded from various sources, including laboratory reports. Overall critical variables for this audit will be disease diagnosis and exposure assessment, including questionnaire data that are associated to these two aspects. All other variables are considered secondary at this time.

The following will be actual data audit process:

(1) Randomly select 10% of all participating subjects, this roughly represents 1500 currently available subjects;

(2) Conduct 100% critical variable value check, and calculate error rate, on the selected subjects;

(3) Conduct 10% secondary variable value check, and calculate error rate on the selected subjects;

(4) Calculate overall error rate. The database is considered to pass the quality examination when such overall error rate is no more than 0.5% and critical variable error rate is no more than 0.1% (These error rates may change upon further understanding of the study. The calculation of error rate can be seen in following sections).

(5) 100% programmatic check using SAS for overall accuracy of data captured for critical variables and selected significant variables including certain laboratory parameters. Such check based on frequency counts for categorical or descriptive data and outlier check for continuous data.

The 10% sampling may be selected proportionally based on study size, participating investigation sites, among other factors. This shall be detailed after initial Shanghai visits scheduled for October 9-29, 2007.

Failure to achieve a cumulative acceptable error rates will result in additional audit inspection of 5% of the study subjects. All errors reported as a result of this inspection will be corrected resulting in a 0.0% error rate upon completion of the audit for critical data.

SAS datasets created for each batch of rolling audited subjects will be saved in dated electronic files. These SAS datasets will be used at the completion of the audit to programmatically compare the data at the time of audit to the draft database through the use of a standard SAS PROC COMPARE program. This process is for the purpose of documenting any changes made to the data from the time of audit until draft database. These listings are produced on a per subject basis and remain with the working copy of the CRF. Discrepancies are noted directly on the PROC COMPARE listings. No error rates are calculated for this segment of the audit.

2.3 Calculating and Reporting Error Rates

Error rates are calculated using the following formulas:

Total # of Data Points for Audit per Dataset = (# of Data Enterable Variables) X (# of Records)

% of error = (Total # of Reported Errors / Total # of Data Points) X 100

Data "enterable" variables are data items which can be changed in the clinical database by study personnel. The number of records subject to audit for each subset of rolling audit subjects is reported on a SAS PROC CONTENTS produced with each batch of audit listings.

Error rates for all subsets of subject data having completed the audit process will be maintained and monitored. Cumulative error rates across all subsets are also maintained

and monitored as the rolling audit progresses. Only the final cumulative error rates across the study will be reported in the final database audit report.

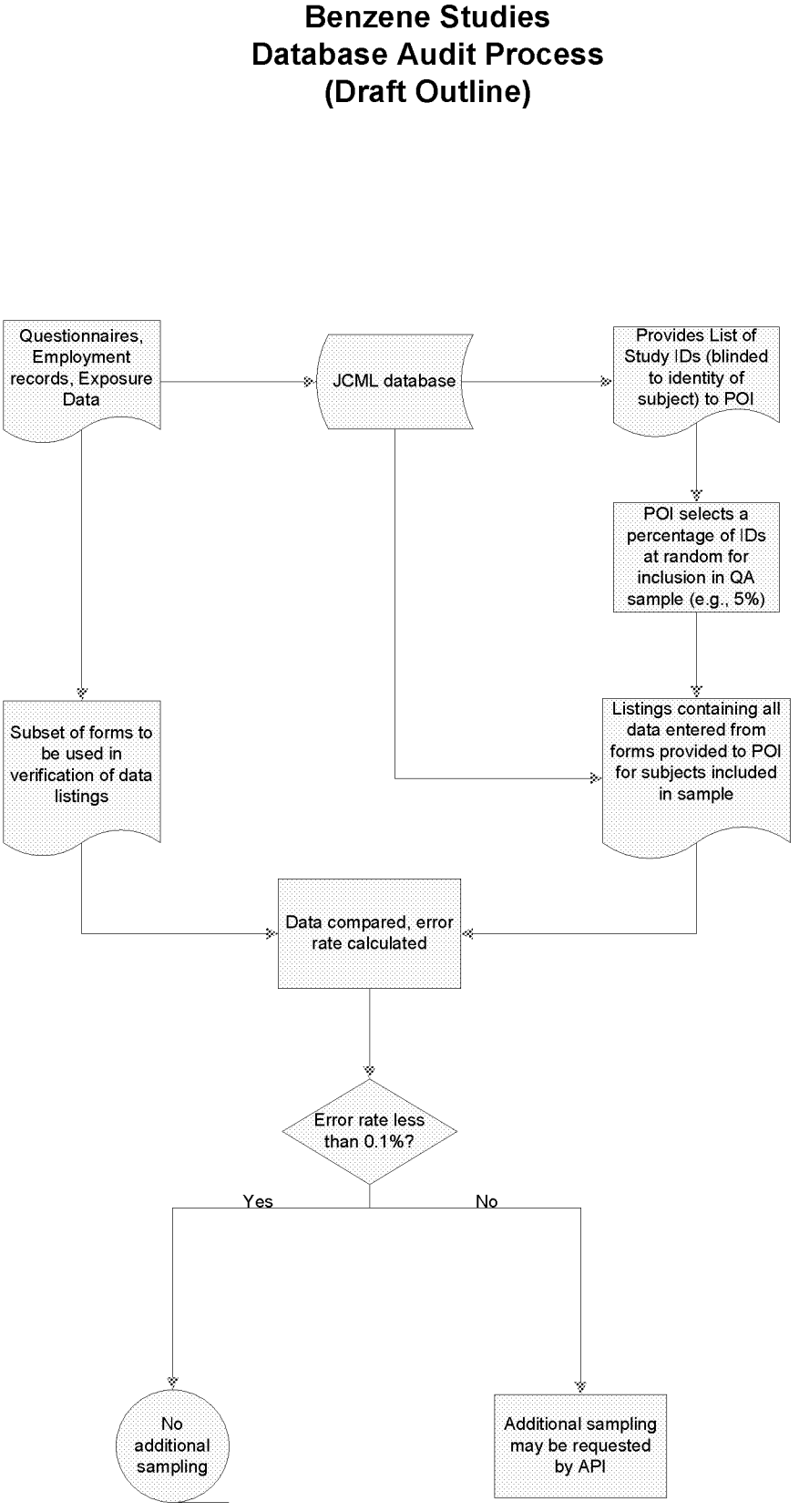
Immediate corrective action will be taken for any dataset not indicating an acceptable level of quality during the rolling audit process. Types of errors will be analyzed throughout the rolling audit process in order to assure consistency in processing and take corrective action when necessary.

Error rates on any additional audit inspection required because of failure to achieve an acceptable cumulative error rate will be calculated separately based solely on the additional data inspected. The < 0.5% error rate applies to any additional audit inspection.

2.3 Database Audit Forms

Database audit forms will be prepared after Shanghai site visits and will be submitted to QA Charter, together with the final audit plan for final review, before formal audit begins.

Figure 1 A draft overview of planned data audit process



3 Investigational Site Visits

For preliminary audit preparation, the following site visits are planned.

(1) University of Colorado Health Science Center (UCHSC) visit, meeting with Dr. Richard Irons, the principal investigator of the study, to have an overall orientation of the past and current on-going status of the study and the database. This visit has been conducted on September 7th, 2007 and the relevant information has been gathered and under organization for the audit.

(2) Fudan University Medical Center and other investigational sites in Shanghai, China. The purposes of this planned visit are: learn the first hand overall knowledge about the conduct of the study; overview relevant documents that may be further reviewed during the formal audit process; physical visits to selected investigational sites and meet with investigators; physical visit to the central laboratory where the diagnoses were performed for the clinical data, among others. This visit has been scheduled for October 9-29, 2007.

The overall objective of these visits is to have the final formal audit plan well amended and completed with detailed procedures specified; customized audit report forms developed/prepared, and training of audit staff to begin. All these are projected after Shanghai visit.

It was learned from the UCHSC visit that there are currently 28 Shanghai hospitals participating in the study conduct. This initial Shanghai visit is planning to visit 20-30% of these hospitals with the primary ones being visited and some remote/smaller scaled being considered for overall balance of information gathered.

Further investigational site visits are needed after the formal audit begins, which will be planned accordingly and as needed.

4 Audit Report

Upon completion of the planned audit, detailed audit report will be prepared in the previously identified scopes and submit to the QA charter for final review and approval.