15. QUALITY ASSURANCE AND QUALITY CONTROL (QA/QC)

15.1   General Approach

Because the National Children's Study is a multi-site, multi-year study involving the collection of complex data as well as physical/medical measures, environmental samples, and biological specimens, quality assurance and quality control (QA/QC) are vital to ensure the data, measures, samples, and specimens are collected correctly and consistently across all sites and throughout all years. All NCS partners have long-standing reputations for conducting high-quality scientific research. However, as with all large multi-center studies, standard QA/QC mechanisms and procedures must be developed and utilized to assure data quality, integrity, completeness, and comparability throughout the Study. To accomplish this, a Quality Management Plan (QMP) and a Coordinating Center QA/QC plan will be developed, applied, maintained, and updated as needed throughout the Study. The QA/QC plan will specify QA/QC procedures and policies that will apply to Coordinating Center operations and also QA/QC procedures and policies that the Study will require of the four types of collaborators: Study Centers, laboratories, clinical testing facilities, and central repositories.

An individual will be assigned by the NCS Program Office to serve as the NCS Program Office Quality Manager. This individual and, as the study grows, his or her staff, will provide independent high-level oversight of QA/QC activities conducted by the Coordinating Center, Study Centers, Information Management System (IMS) contractor, laboratories, clinical testing facilities, and repositories. Examples of the types of activities the Quality Manager will perform include conducting independent audits/assessments of the NCS components, reviewing audit reports, and making recommendations to the Study Director and Project Officers on corrective actions.

The major tool for Study and data management, and thus Study QA/QC, will be the IMS. The IMS will not only provide an array of QA/QC monitoring functions, it will also track the QA/QC activities. There are three aspects of QA/QC related to the IMS: (1) the IMS will capture all Study data allowing for Study oversight of data completeness and production; (2) the IMS will capture all Study QA/QC data allowing for Study oversight of data quality, integrity, and comparability; and (3) specific QA/QC checks will oversee the IMS.

15.2   QA/QC Activities for IMS

The IMS is the computerized heart of the Study. It must support the collection, management, and storage of the study data and manage highly complex study activities involving thousands of staff and participants across the country. The electronic edits built into the IMS will be the key to ensuring data quality, and the monitoring and tracking systems it includes will be critical to ensure proper Study management. Since the NCS will be underway for such a long period of time, it is critical that the IMS be able to accept upgrades and new technologies without going out of service. These challenges require constant attention to quality.

15.2.1   IMS System Quality

The IMS will not be able to ensure the quality of NCS data unless it is itself a quality system that performs reliably, accurately, and according to specification. System quality begins with the team that builds and integrates it. A fundamental component of the quality system for the IMS is a contractual requirement that the IMS contractor must maintain ISO 9001:2000 certification and demonstrate CMM

Level 3 compliance on an ongoing basis. During the planning phase, the IMS contractor developed a CMM plan which defined internal roles and responsibilities, record-keeping requirements, and other quality-affecting parameters. The CMM plan ensures the organization's software development processes include visibility, oversight, and checkpoints throughout the software development life cycle.

It is an axiom in software development that the earlier an error or problem is found, the easier and cheaper it is to correct. Thus, the IMS contractor will perform early reviews of requirements and design specifications, working closely with Program Office and Coordinating Center staff, who are the subject matter experts. This process ensures that when software is built (or purchased commercially) and integrated, it will meet requirements. Source code reviews during actual development will further ensure that errors are caught as early as possible.

A key step in ensuring system quality is testing. The IMS will be tested in four stages. In the first stage, the developers and integrators will test each hardware and software component to ensure it functions according to specifications, a process called "unit testing." In the second stage, and in a separate process, an independent test team will examine the IMS requirements documents and prepare a detailed test plan for each IMS system. After initial training by the development team, the independent test team will execute the test plan against each of the systems, identifying problems and placing them into a formal defect tracking system. Each problem will be prioritized and tracked to resolution, and the systems will be retested until they pass. The third stage of testing will be performed by Coordinating Center and Study Center staff who will test each of the IMS systems using real-world study scenarios to determine if the systems perform their functions properly. This process is known as "acceptance testing," and systems cannot be fielded until they pass. The final stage of testing is ongoing. Whenever a system is enhanced, upgraded, or a defect is found and corrected, not only must the new or changed elements be tested, but also a "regression test" must be performed by the independent test team to ensure the changes do not adversely affect other functionality.

Throughout the Study, the Coordinating Center will capture, track, and report IMS infrastructure outages as well as software defect reports, IMS help desk calls, and application error logs to compute an ongoing reliability factor that will be reported monthly and yearly. The IMS will include application event logs that will capture application failures along with reporting capability. In the unlikely event of a system outage, the Coordinating Center will document the outage with an incident report that describes the cause of the outage, the measures taken to resolve it, and the processes and procedures that can be implemented to prevent a similar future occurrence. Prior to implementation, the Coordinating Center will confirm the computation of the reliability statistics with the NCS Program Office.

15.2.2 IMS Data Quality

The IMS will be designed to maintain and ensure the quality of the NCS data throughout its life cycle from collection through analysis, storage and eventual archive. Quality, in this context, is defined in four broad dimensions. A data element must be:

- collected accurately;

- protected from tampering or inadvertent alteration or corruption;

- traceable and attributable to its original source; and

- associated with audit trails and decision logs that document all changes to it as well as the source and reasoning behind each change.

To support accurate data collection, the IMS will maintain calibration and test records for data collection devices and instruments, including questionnaire instruments. The IMS will also maintain records documenting data collectors' training and certification. To support data security, the IMS security features will include many technical and procedural checks and guards to protect data from tampering or corruption, including encryption, network firewalls, multi-factor authentication of users, and role-based access controls. To ensure that data are always traceable and attributable to source, each data element will carry associated metadata to document its history and context. IMS data management systems will use audit trails, include timestamps, and will identify the source as well as the nature of data changes. Decision logs will document the reasons behind any changes made to data post-collection as well as larger study-level decisions that may cause wholesale instrument or methodology changes.

The IMS will not only maintain data quality, it will provide the information needed to make improvements in data collection instruments, methods, and techniques. Edit reports produced by the IMS will document edit failures and their resolution. The IMS will use the edit failures to identify possible data collection or manipulation or metadata errors that will be used to compute an overall accuracy statistic for data collected by the IMS.

In addition to system reliability and accuracy statistics, reports and audits will be used to assess the quality of the IMS products at any given time in the project life cycle. Reporting on defects and change requests provides some useful quality indicators, such as team productivity and bottlenecks, evaluation of workload distribution, the need to insert more or less flexibility into processes, and overall schedule progress. Audits provide verification that processes are being followed and that traceability exists between coded software and requirements or change requests.

15.3 Training Data Collectors

Comprehensive training of Study Center data collection staff will be an important aspect of the QA/QC plan. Highly experienced Coordinating Center staff will develop and implement a carefully designed and thorough training program, including training manuals, training exercises, role-play scenarios, audio/visual tools, and certification procedures. The Coordinating Center staff will conduct initial training of Study Center staff using a "train-the-trainer" method to prepare the Study Center staff who will subsequently conduct the training and retraining for data collection at their site. The training sessions and materials will be structured around specific competency-based objectives using a variety of teaching strategies to maintain the active involvement of the trainees. The techniques used during the training will follow the fundamental concepts of effective adult learning theory and require extensive active participation of the trainees. A basic and important requirement of the training will be to give every member of the staff the tools he or she needs to gain respondent cooperation at every level of participation and to acquire the skills needed to combat nonresponse and promote continued response.

As part of the QA/QC plan, a training roster will be developed for each Study Center that will include the type of competency assessment or certification required for each Study Center staff person. Almost all of the training modules will require a competency assessment at the end of training before the trainee can begin data collection. For example, staff members who collect anthropometry data will be tested against the "gold standard" expert in a series of competency sessions at the end of training. Additionally some staff (e.g., phlebotomists and ultrasonographers) must have up-to-date certifications before they can begin data collection. The team responsible for the training will determine the competency criteria. As training and certifications are completed, the training roster will be updated to indicate the training and certifications received. The roster will be maintained through the IMS.

The QA/QC plan will include periodic staff retraining. Refresher training may be necessary to introduce new Study procedures and forms and to sharpen data collector skills. This will be done throughout the Study as a standardized means of delivering new information. The Study may identify a Study Center whose study staff members, when audited, are not passing standards or whose data do not correlate with standard examiners, and may decide to conduct refresher training at that Study Center. As the Study progresses, some attrition among Study Center staff is expected. This will make it necessary to train new staff. There may be a need for special training during the course of the Study, for example, to teach techniques for improving response rates among special populations (e.g., minorities, very young mothers, or single mothers), or to elicit feedback from interviewers on the effectiveness of outreach materials and the need for new items to target specific groups. Remedial training may be necessary when data collectors do not meet acceptable performance standards as identified using QC measures.

15.4 QA/QC for Data Collection Activities

QA/QC procedures will be developed and applied to all Study data collection and management activities including interviewing, taking physical and medical measurements, collecting and handling environmental samples and biological specimens, and processing the collected data. QA/QC procedures regarding maintenance and calibration will be developed and applied to the measurement equipment used in the Study. There will also be QA/QC procedures developed and applied to the environmental and clinical laboratories and testing facilities utilized.

All Study data will be carefully and thoroughly reviewed and edited for consistency and range checks. Inconsistencies, anomalies, and outliers will be identified, examined, and verified when necessary. For example, participant demographic characteristics will be checked against reported health conditions and medical events for logical consistencies, and blood pressure measurements will be checked for end-digit preferences. All data collectors will be directly observed, indirectly monitored, and evaluated for quality issues such as protocol adherence and inter-rater reliability measures.

Study staff will observe Study Center data collection staff to evaluate procedures and protocols during participant identification activities, while completing the interviews, while collecting specimens and samples, and while taking physical measurements, during the field pilot tests and dress rehearsals. After this initial period, Study staff will conduct at least one in-person audit in the field per data collector per year to monitor interviewing techniques and all other data collection activities. Data collectors will be observed while conducting the home visits as well as the clinic visits. Study staff will develop a standardized electronic form for use by auditors in evaluating performance during these observations.

The Study will assign senior staff, trainers, or trained designees to conduct the field audits. The field auditors will record the results of each audit item on the form and will use the completed forms as the basis for providing rapid feedback. Individual and/or group feedback may be provided. Completed observation forms will be kept for the duration of the Study and will be used to assist in identifying topics for review during refresher trainings.

The procedures described above will be applied to all data collection activities, but there will be additional QA/QC procedures developed and applied to each of the specific types of data collection activities. Sections 15.5 through 15.9 summarize these additional QA/QC procedures.

15.5   QA/QC for Interviewing

Re-interviews, or "verifications," will also be used to monitor interviewer work. The verification will confirm that the interview was conducted and verify a few selected responses. Verification QC will be conducted by telephone by Coordinating Center staff. Cases to be verified will be selected through the IMS as work is completed. All of an interviewer's work will be eligible for verification regardless of the final disposition. Typically, 10-15 percent of each interviewer's cases will be selected for verification. Only a certain number of highly objective questions will be selected for verification, both to reduce respondent burden and to protect against discrepancies due to legitimate response changes. Interviewers will be told their work will be verified but will not know the number of cases or the procedure for selecting cases. If at any time verification indicates the possibility of falsification, the Coordinating Center will begin a 100 percent verification immediately of the interviewers' work. The Coordinating Center will report verification rates and results through monthly progress reports.

Falsification will be further substantiated through the use of digital time stamp reports and tracking GPS coordinates. A systematic review of digitally entered time stamps for work done by each interviewer will be an important indicator of potential problems in the field. These time stamps will generate several reports that will be routinely reviewed by Study staff. Any unusual or suspicious pattern in the digital entry trail must be explained and will trigger a higher validation rate for the interviewer.

Study Center interviewers will be required to edit all work before finalizing the data collection case. After completing each case, the computer will display any outstanding data collection activities and exams which the Study Center staff would review and finalize. If the data are collected at a home or birth visit or some other facility, it will be further reviewed at the Study Centers before uploading to the IMS. If necessary, the interviewers will receive immediate feedback to rectify any problems. After this edit, the completed work will be uploaded to the IMS. There will be built-in editing procedures in the IMS that will support a further review of the data. For example, all text entries in the questionnaires, as well as other critical data items, will be reviewed. Whenever possible, the Study Center coordinator or an assistant will re-edit 10 percent of each interviewer's work.

15.6   QA/QC for Collecting and Handling Samples and Specimens

All procedures for the collection of environmental samples and biological specimens will have data collection forms specific to each specimen or sample to be collected. These forms will be developed to allow the monitoring of data quality across the Study. All procedures and corresponding forms will be evaluated regularly for effectiveness, and, if a modification is required, changes will be implemented seamlessly and the modification will be documented. On a periodic basis, all parties affected by the procedure and data collection forms will be solicited for any needed modification or update.

Observing or auditing the work of sample collectors will be done to evaluate procedures and protocols as described in Section 15.4. In addition, Study staff will observe sample labeling at the collection site and processing, storage, packaging, and shipment of biospecimens and environmental samples to ensure these activities are conducted according to Study procedures.

In addition to conducting visits to observe field procedures, the Study will establish a schedule for regular reviews of biospecimen and environmental sample data, problem logs, equipment logs, maintenance records, and calibration results for all field work. Review of biospecimen and environmental sample data can be considered an indirect observation, a variation on the method of direct observation that may be suitable for some collection tasks, either as a substitute for or supplement to the

field audits. During an indirect observation, field staff performance will be monitored after the activity is complete, for example, by review of data from completed collection forms and comparison of the collection data to the laboratory results of analyzed specimens. The resulting data can be used as a measure of the quality of data collection or specimen collection.

All Study Centers will be required to keep logs of reported problems with specimen and sample labeling, processing, transfer, and shipment. These logs will be maintained on the IMS, as would similar logs from the biorepositories and analytic laboratories. The Study will track these logs on the IMS to identify, investigate, and resolve these types of problems with the Study Centers, laboratories, and repositories and to make recommendations for modifying procedures as necessary.

All biospecimen and environmental sample measurement equipment used in the field will be required to have regularly scheduled maintenance and logs of the maintenance, operating status, and all calibration results. The written procedures will describe, in detail, calibration procedures for all biomedical and environmental measurement equipment. If a particular instrument is required to be calibrated prior to each use, the Study will specify these calibration tests as well. Study procedures will include instructions on how to handle situations where equipment does not meet the specified calibration criteria. Study Center staff will be trained to calibrate and maintain all instruments and equipment in accordance with the approved procedures, including equipment that may need to exceed manufacturer recommendations because of extensive use.

The results of equipment maintenance and calibration activities will be automatically tracked in the IMS. If missing logs, failed calibrations, drifting, or other problems are found, the Coordinating Center will contact the affected party to discuss and correct the problem. If needed, a site visit will be made to observe the questionable equipment and procedures.

The Coordinating Center will work with the NCS Program Office to develop procedures designed to address the need for resampling and duplicate or repeat collection of samples. These procedures could apply to collection of most biospecimens or environmental samples (e.g., more blood, urine, or breast milk, or another dust, air, or soil sample). The Study will identify quality control samples to be used, including specifications as to their content, number of samples to be obtained, possible sources, and assurance of the quality of the samples and specimens.

15.7   QA/QC for Environmental/Clinical Labs, Repositories, and Testing Facilities

The Study will require all laboratories to submit the standard operating procedures, which will be used for the NCS. These documents will be logged and evaluated to ensure the standard operating procedures are written in accordance with current guidelines and other regulatory requirements, as well as Study procedures. Revisions will be requested as needed. All current and past standard operating procedures will be submitted and maintained electronically in the IMS, which will be easily accessible and searchable by the NCS Program Office.

The Coordinating Center will work with the NCS Program Office to define and implement procedures for monitoring the performance of the laboratories, testing facilities, and repositories. The monitoring will continue throughout their performance. The performance monitoring will include implementing external QC through use of split duplicate and other QC samples and review of those results. Reports will be developed to ensure production standards are met; to identify inconsistencies and inaccuracies in specimen type or labeling; to identify results that fall outside of expected parameters; to identify any trends in analysis over time; and to review internal standardization and proficiency sample analysis conducted as part of accreditation or certification programs. On-site observation will be done to

verify that procedures adhere to the NCS procedures and to verify equipment calibration procedures and internal QC. The Study will institute a methodology for regularly receiving data from the laboratories (monthly or semimonthly) to ensure quality and production standards are maintained. The Coordinating Center will perform this task by verifying the laboratory QC data and production levels are within acceptable parameters set forth by the NCS Program Office. The Coordinating Center will provide the results of the verification process to the NCS Program Office on a monthly basis.

The Coordinating Center will generate data collection forms for all audits and data collection mechanisms. Based on the data elements collected, the Coordinating Center will generate reports for the NCS Program Office. The Coordinating Center will request the input from the NCS Program Office into what data elements would be needed for reports of varying types. Based on these requests, the Coordinating Center will ensure all data are collected in a timely manner and any discrepancies will be reconciled.

The Coordinating Center will submit the audit procedures for each type of facility to the NCS Program Office to approve prior to any site audit. The Coordinating Center will arrange for and oversee audits of all laboratories and repositories before samples are sent, and every six months thereafter. All laboratory audit inspectors will have initial training and refresher training for current guidelines and will maintain training levels throughout the Study.

The audit staff will conduct six-month on-site laboratory reviews. Prior to the audit visit, the Coordinating Center will work with the NCS Program Office to address any particular concerns for the specific site to be audited by developing a site-specific audit plan. During the audit visit, the audit staff will operate from the approved standard operating procedures as well as from the site-specific audit plan of all Study-related equipment calibration documentation, internal assay QC specimen or sample results, and environmental control logs. The audit team will verify all components of the Study-related procedures conducted at the site, including staff training, procedures, security, environmental monitoring. The team will document any deviations or violations uncovered, as well as the corrective actions the site implemented to rectify them. The team will also work with the sites to obtain copies of all necessary documents and maintain these documents as a tracking mechanism for site performance. The Coordinating Center will document all findings and report to the NCS Program Office within one month of the site visit.

The Study will develop and implement procedures to work with laboratories to improve performance on an as-needed basis. The Coordinating Center will submit the procedures to the NCS Program Office for approval prior to implementation. The Coordinating Center will draft a procedure that addresses distributing QC specimens or samples. The procedure will address methods for distribution from the source to the Coordinating Center, the Study Centers, and the central repository, including sample handling and storage, as appropriate. For stable samples and analytes, many QC specimens may be ordered and sent out at one time; however, for unstable samples, there may need to be a steady stream of QC samples shipped out to the various entities.

The IMS will also specify the frequency with which each Study Center will insert the QC specimens and samples into the sample stream. This will primarily be by affixing a bar-coded label to each QC specimen or sample as if it were an actual Study specimen or sample during collection of actual specimens or samples. No sample type identifying information will be provided to the laboratories, (e.g., for environmental samples), and the surface area or volumes will not be provided. This will help prevent the laboratory from knowing which specimens or samples are QC checks.

The Coordinating Center will ensure that all QC specimens and samples are tracked in the IMS regardless of the source of the material. Ideally, the sources would enter the specimen/sample

information directly into the IMS. The IMS will have a specimen and sample tracking system (STS) component to track the shipment, handling, and results for all specimens and samples. The STS should have a set of specimen/sample ID numbers for QC specimens and samples that look like actual sample numbers.

15.8 QA/QC for Physical Measures Data Collection

QA/QC measures will include periodically reviewing equipment logs, maintenance schedules, and calibration results. Study staff will conduct any duplicate data collection specified in the Study documents, will ensure that all data collection forms are completed accurately in the field, and that all data such as ultrasound images and digital photographs are collected, labeled, and transmitted in accordance with specified study procedures. Study staff will document data maintenance efforts in the form of log files, summary operating procedures, and logs of changes to data.

Additional on-site observation audits of testing may include duplicate or repeat tests. Duplicate data will be collected on participants as part of the data collection protocol when the data are recognized as difficult to obtain. For example, in a typical ultrasound exam, each of the images will be taken twice to have at least two measurements of each type. Blood pressure measurements will be measured three to five times following a specific resting period. All measurements will be captured to allow an average reading to be computed based on an algorithm determined by the data analyst.

Gold standard examinations may also be used to measure the agreement between a recognized expert and an examiner by conducting examinations on the same participant during a single examination session. This type of QA is particularly relevant to some of the clinical examinations such as anthropometric measurements. The number of gold standard examinations required to assess the level of agreement, as well as acceptable levels of agreement, will be specified. The IMS will have the capability to generate a report that displays a side-by-side comparison of results from the primary and gold standard examinations. The gold standard examiner would be able to print and use this report to provide immediate feedback to the primary examiner. There should also be a program in the IMS that Study Centers run to produce inter-rater reliability statistics. If statistically significant differences between the gold standard and the primary examiner are identified, these will be addressed through retraining.

Replicate examinations, in which a second examination is performed on a participant by the same examiner as the primary examination, may be used to measure intra-examiner reliability on some clinical exams. Although replicate exams provide a good measure of reliability, they are burdensome for the participant and time consuming for the Study Center. Replicate examinations require that the participant return to the examination center (or the examiner return to the home) at a later date for a second-day examination. Not all exam procedures will be slated for inclusion in the second-day examination, and only those components that require this level of QA will be included.

15.9 QA/QC Activities for Data Management

The general approach to QA/QC for data management will be to rely on the approved procedures for ongoing structure to the program. Each procedure will include steps to facilitate identification of issues as they arise, support tracing problems to the source, and determine whether changes to procedures and/or the IMS will mitigate such problems in the future. QA/QC steps will be an integral part of each procedure and will be reviewed on an established basis but no less than annually.

The Coordinating Center will work closely with the NCS Program Office to ensure that NCS data are handled, processed, and managed with the highest level of quality. For data coding, the Coordinating Center will ensure metadata entry and maintenance, data review, and other manual data preparation procedures are performed properly. The Coordinating Center will ensure staff are trained and certified prior to beginning work and data management processes are designed specifically to identify errors resulting from data collection instrumentation or data processing activities.

A random sample of coders and data entry staff work will be reviewed by a second, more senior data management staff member or supervisor. Should consistent issues be identified, the staff member will be given additional guidance and training. If this guidance and retraining is not effective, the staff member will be removed from the project.

Automated edit software included in the IMS will be employed to detect item value, range, and inter-item logical inconsistencies, and checks will be implemented against historical data collected for the case. Results and resolutions of these edits will be maintained in automated form in the IMS. Any updates to NCS IMS databases as a result of data review will be accompanied by an annotation that includes the reason for the change, prior value, date of change, and authorization for the change, if required. Data management procedures will be fully documented and the documentation maintained online, accessible to data management staff. A log of all exceptional data management events will be maintained automatically within the IMS to support historical data questions.

Digital images will be used in several aspects of data collection such as radiology, pathology, or photography. Management of the digital images will include procedures for obtaining, transmitting, and storing images at the Study Centers and ultimately in image libraries in the IMS overseen by the Coordinating Center. A QA/QC protocol for management of digital images will be developed.

Approval guidelines for digital imaging equipment used in the Study will be developed. Study-approved protocols for technical parameters and measurements, calibration procedures and certifications, routine QC testing, and maintenance checks will all be addressed. Study Centers will be encouraged to participate in QA programs and certification programs for diagnostic imaging used in health care settings and will be expected to provide evidence of certification.

Procedures that ensure the capture of acceptable images for use in the NCS and the monitoring of images will be developed. Image transmission QC procedures that monitor the flow of complete image sets within the Study Centers and after transfer to the libraries will be addressed. Confidentiality and accuracy procedures for de-identification and anonymization of digital images, as well as ensuring accuracy in cataloging images, will be detailed in the QA/QC protocol. Evidence of robust backup, archival, and disaster recovery procedures will be required. Image files will be expected to be made available and accessible on secure Web sites.