INTRODUCTION

In clinical trials and other prospective studies, data on the status of participants at the time of enrollment and at specified times thereafter are used to compare the frequencies of primary and secondary outcomes among participants. Observations, measurements, laboratory specimens, responses to interview questions, and other documentation of each study participant's status may be collected repeatedly over a period of time. Typically, the data are processed, stored, and analyzed at a coordinating center. The study culminates with publication of findings and inferences based on statistical analysis of the data and other study results. Data management begins during the design of the data collection protocol and ends only after the final database for statistical analysis and data archiving is complete. Quality assurance should be built into a study's data management system and carried out concurrently with other data management activities. Otherwise, the ability to detect and resolve anomalous study data is compromised.

By the very nature of a multicenter study, data quality is a shared responsibility. Because all the data collected ultimately reside in a master database at the coordinating center, the investigators and staff at that center are in a unique position to check on data quality and to monitor for anomalous data recording, transcription, omission, or modification patterns as data accumulate. Nevertheless, if those responsible for recording the status of participants do not make their observations and measurements conscientiously and adhere to the study protocol, the most expert data management and analysis team cannot overcome the resulting deficiencies. Thus, quality assurance activities cut across functional and organizational boundaries.

The task of designing and implementing a comprehensive quality assurance and monitoring program often is undertaken by personnel at the study coordinating center. Such a program typically includes:

- Training and certification of study personnel
- Comprehensive documentation of operations and procedures at all participating centers
Table 1  Steps Taken at Resource Centers to Optimize and Monitor Data Quality in the Collaborative Ocular Melanoma Study

<table>
<thead>
<tr>
<th>Resource Center</th>
<th>Types of Checks/Actions</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echography Center</td>
<td>Confirmation of diagnosis</td>
<td>Expert interpretation of pre-enrollment photoechograms</td>
</tr>
<tr>
<td></td>
<td>Confirmation of tumor height</td>
<td>Measurements from photoechograms</td>
</tr>
<tr>
<td>Photograph Reading Center</td>
<td>Confirmation of diagnosis</td>
<td>Expert interpretation of pre-enrollment photographs</td>
</tr>
<tr>
<td></td>
<td>Development and progression of radiation retinopathy</td>
<td>Expert interpretation of followup photographs</td>
</tr>
<tr>
<td>Radiological Physics Center</td>
<td>Confirmation of radiation dosimetry</td>
<td>Recalculation; calibration site visits; mailed dosimeters</td>
</tr>
<tr>
<td></td>
<td>Compliance with radiotherapy protocol</td>
<td>Expert interpretation</td>
</tr>
<tr>
<td>Pathology Center</td>
<td>Confirmation of diagnosis of primary tumor and recurrence</td>
<td>Expert interpretation of microscopic sections</td>
</tr>
<tr>
<td>Coordinating Center</td>
<td>See Table 2</td>
<td>See Table 2</td>
</tr>
<tr>
<td>All Resource Centers</td>
<td>Training and certification of personnel</td>
<td>Didactic training; test cases; observations, etc.</td>
</tr>
<tr>
<td></td>
<td>Documentation of internal procedures</td>
<td>Operations handbooks and logs</td>
</tr>
<tr>
<td></td>
<td>Internal quality monitoring</td>
<td>Performance reports to quality assurance committee twice yearly</td>
</tr>
</tbody>
</table>

- High-quality data collection forms or other data recording instruments
- Concurrent data management systems that incorporate data edits to identify anomalous and possibly erroneous data with corresponding mechanisms for correcting or confirming anomalous data
- Automated systems to produce reminders and schedules to facilitate field site operations and data collection
- Assignment of responsibility for various aspects of quality monitoring
- Periodic site visits to study centers to observe operations and to review quality of data submission
- Periodic audits of the database against source documents
- Regular reports on details of the performance of all collaborating centers
- Regular reports on data quality that identify sources of errors and delays that limit the accuracy and timeliness of the database
- Corrective actions to be taken when problems are identified
- Revision or redesign of study systems, procedures, and documentation as needed to facilitate accurate and complete data collection and timely submission to the coordinating center for incorporation into the study database

The quality assurance program in one multicenter study, the Collaborative Ocular Melanoma Study [1,2], is summarized in Tables 1 and 2.
Table 2 Steps Taken by the Coordinating Center to Assure Completeness and Accuracy of the Collaborative Ocular Melanoma Study Database

<table>
<thead>
<tr>
<th>Stage of Processing</th>
<th>Types of Checks</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility review</td>
<td>Participant identifiers, eye, sub-study established; review of eligibility criteria; enrollment/initial visit time checks</td>
<td>Computer-assisted</td>
</tr>
<tr>
<td>prior to enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data entry</td>
<td>Valid identifiers; expected visit, form; data within time window</td>
<td>Computer check against patient inventory record</td>
</tr>
<tr>
<td>Initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Keying</td>
<td>Field type, ranges, valid codes</td>
<td>Computer validation using form-specific tables with generalized data entry program (table-driven edits)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data editing</td>
<td>Missing or ambiguous data, consistency of responses</td>
<td>Computer validation using form-specific tables with generalized data entry program (table-driven edits)</td>
</tr>
<tr>
<td>Within a form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between forms</td>
<td>Consistency of responses across forms and over time</td>
<td>Computer validation using form-specific tables with generalized data editing program (table-driven edits)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edit query processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At coord. center</td>
<td>Any keying error</td>
<td>Manual check of message against form</td>
</tr>
<tr>
<td>At field site</td>
<td>Any reporting error</td>
<td>Manual check</td>
</tr>
<tr>
<td>Correction processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing forms, query responses; status checks for patients at high risk of death</td>
<td>As for the original data form</td>
<td></td>
</tr>
<tr>
<td>Monthly reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to database freeze</td>
<td>Participant data files vs. electronic and paper records of participant identifiers to account for all participants</td>
<td>Computer-generated, hand-checked</td>
</tr>
<tr>
<td>Participant reported by more than one field site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmation of vital status of participants with recurrence</td>
<td>Letters to field site investigators after review of internal report</td>
<td></td>
</tr>
<tr>
<td>Monthly reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interim reports</td>
<td>Outliers; unusual patterns or responses</td>
<td>Manual review of reports</td>
</tr>
<tr>
<td>Prior to microfilming paper data forms</td>
<td>Any keying error; completeness of data records</td>
<td>Manual check, character by character, of sample of forms received vs. database</td>
</tr>
<tr>
<td>Field site visits</td>
<td>Record audits</td>
<td>Manual check of data submitted vs. clinic records</td>
</tr>
</tbody>
</table>
Guidelines for data collection forms are presented and discussed in the paper by Hosking et al. elsewhere in this issue. Performance monitoring reports are discussed in the paper by McBride and Singer in this issue. This paper focuses on quality assurance and monitoring mechanisms implemented as part of the database management system, mechanisms for monitoring the quality of the database, training and certification of personnel in data collection and data management procedures, and some quality reporting issues.

In multicenter studies, quality assurance mechanisms often are implemented as a set of feedback loops among different functional modules and across study components. Figure 1 diagrams a simplified quality assurance model that illustrates the feedback loop needed to manage data in such an environment.

The coordinating center investigators and staff must be alert to the possibility of error at each stage of data handling at field sites, within resource centers, at the coordinating center itself, and between study components. Some possible sources of errors in study data are:

- Deviations from protocol, or misinterpretations of the protocol, when making measurements and observations, or when preparing primary documents
- Inappropriate or uncalibrated equipment at field sites or resource centers
- Inaccurate, illegible, or incomplete data recording
- Inaccurate or incomplete data transcription to electronic files
- Errors or omissions in data and materials transferred between field sites and the coordinating center, between field sites and resource centers, and between the resource centers and the coordinating center
- Failure to obtain primary source documents to confirm data associated with primary or secondary outcomes, e.g., death certificates, autopsy reports, laboratory reports
- Excess data collection to the extent that it jeopardizes the quality of essential data
- Inadequate training of study personnel, especially new or replacement personnel recruited after the start of the study
- Intentional data fraud
- Undocumented changes or modifications to a local or central database
- Programming or procedural errors at the coordinating center that modify data inappropriately or corrupt the database
- Errors in summarizing and reporting data
- Misuse of statistical software or application of inappropriate statistical methods

Some of the concepts addressed in this paper have been described before. Overviews [3-6] have described methods of quality assurance and clinical trials textbooks [7,8] contain chapters devoted to quality assurance programs. Applications of statistical methods for performing and reporting on results of quality control schemes are also available [9,10]. Investigators from individual studies [11-15, for example] or groups of studies [16] have published articles related to specific aspects of quality assurance programs. Descriptions of the quality assurance program developed for the Multiple Risk Factor Intervention Trial filled an entire supplemental issue of Controlled Clinical Trials [17]. A panel discussion entitled
Figure 1 Data quality feedback.
"Quality Control Issues in Multi-Center Clinical Trials" covered many of these same topics [18]. The discussions in this paper consolidate and summarize current quality assurance practices, with emphasis on those aspects for which data management personnel frequently have major responsibility. These include monitoring data recording and data transfer to the central database from field sites and resource centers as well as data handling, performance monitoring, and quality reporting at the coordinating center.

The quality assurance and monitoring program should include periodic reports to the data collectors, the sponsor, and the study leadership group on the timeliness, completeness, reliability, and consistency of the accumulated data. Information on the quality of the study database is an important component of the presentation of statistical analyses and interpretation of the study data. It is helpful to summarize near the end of the study the quality assurance and monitoring methods employed and the results achieved to guide investigators in future related studies.

Marinez et al. [19] defined the objective of data management in medical research studies to be control of both loss of data and introduction of errors so that errors do not bias study findings. They added: "Ideally, one seeks an error-free study rather than merely control of errors. In most situations, however, the resources required for an error-free study are unreasonable." Thus, a primary consideration in most studies is the size and scope of the quality assurance and monitoring program.

ROUTINE AUTOMATED DATA EDITS

Guiding Principles

In a data quality assurance program implemented without cost and time constraints, coordinating center personnel would be able to check every item of data with equal thoroughness. However, the staff working on a particular study always must choose, in conjunction with the study leadership and other resource centers, which data items should be checked as well as the nature and frequency of that checking. In general, quality assurance and monitoring programs should focus on issues central to the study design and the study analysis plans. In a randomized clinical trial, data on primary and secondary outcome variables, the integrity of the randomization process, and eligibility of enrolled participants have the highest priority for quality assurance and monitoring. Data on the intervention and on other aspects of protocol compliance are also important but may be assigned lower priority, depending on the purpose of the study, while data related to ancillary measurements may be given the lowest priority. For the highest priority data, quality assurance should occur as close as possible to the point of collection. "Check early and check often" applies particularly to this class of data.

It is important to plan and implement the data edit system prior to implementation of data collection. The Stroke Data Bank added an error detection and correction mechanism near the end of the study [20]. Such a delay may create difficulties at many levels of the study.

The extent of data edits at any stage of processing depends on the amount of "context" available. For a simple example, consider the sequence of digits 4102764775. Formatted as (410) 276-4775, the sequence is recognizable as a North American telephone number. However, unless some additional context is available (in the
form of a criss-cross directory or a telephone at hand), it is impossible to know whether the string of digits represents a working telephone number or not. The complexity of data checking increases with the amount of data collected.

Selection of Data for Checking

An important decision is allocation of quality assurance and monitoring resources to various aspects of a multicenter study. Responsibility for much of the remote monitoring typically is assigned to the data management staff at the coordinating center. However, those individuals require advice and guidance from the study leadership to select subsets of the data that should receive special emphasis. Typically, data that are simple to monitor are checked routinely, even when they are not those most important to the study goals. One guideline for selecting data to monitor is to check all correctable items and all other items important to the study outcome. Many data items are checked immediately during processing; others may be checked periodically at defined points in time.

Data should be edited and opportunities for correcting anomalous data should be provided throughout all phases of a study. Accumulated data may be reedited or subjected to special edits during closeout of participant follow-up, as discussed in the paper by McBride and Singer in this issue. An initial check of validity of identifiers typically precedes other edits of the data. A common sequence of checks on data items includes (1) simple variable type and data range checks within each form, often during data entry; (2) consistency checks among items within a form; (3) consistency checks across forms within a visit; and (4) consistency checks across visits over time.

Types of Data Element Checks

A primary responsibility of the coordinating center is to guarantee that all of the data collected for a specific study participant are identified by that participant's unique identification code. An alphanumeric identifier consisting of a number and a text name code is one convention for constructing unique identifiers. A namecode that is an acrostic of the participant's name helps to identify improper recording of identification numbers. A check digit (an algebraic function of the other digits in the identification number) can be useful. A check digit or name code can be implemented as a separate variable or as part of the identifier. Study identifiers also may be needed. In the Southwest Oncology Group (SWOG) and other multicenter groups in which the same group of investigators is conducting a number of studies with a single coordinating center serving all studies, the participant number (the same across all studies for a participant enrolled in more than one) and the study number (unique for each study) are both required to update or retrieve data for an individual participant [21]. The first check made for a new data record typically is one to assure that the data record is unique and that neither the participant nor the visit (or examination) has been misidentified.

The most basic data element checks relate to both data type and data range. Numeric values and alphanumeric codes should be checked for validity and range. Appropriate numeric ranges for continuous variables may be difficult to determine; one must use caution when referencing the normal ranges for a given biochemical analyte in a table or book. In most studies, the participants enrolled are by
Data Quality Assurance

design different from the population for whom the normal ranges for biochemical variables were defined. Normal ranges are useful guidelines, but experience with individuals similar to study participants or data from a pilot study may show how these ranges need to be refined for study purposes. If neither data on similar individuals nor pilot study data are available, data from participants enrolled early in the study may be used to develop ranges for those enrolled later. Edit ranges may change during the study, for example, as the physical status of study participants changes; edit checking programs or logs must document when and why a change to a range is made. Some multicenter study protocols require that all biochemical measurements be made at a central laboratory. Multicenter studies in which measurements from a variety of field site laboratories are accepted may need to take the field site instruments or assay kits and the local reference values into account when designing quality assurance programs and when analyzing data. Categorical variables often are handled in the data edit system with a data code “table lookup” system that is easy to modify when new codes are added.

Time and date fields should always be validated. Database management software allows checks for the validity of entries into a date field. For example, a date entered as 02/29/93 would be rejected. However, only appropriate training and instruction will guarantee that 06/07/90 refers to June 7 rather than July 6, or vice versa. Instructions on entering incomplete dates such as in “I had my heart attack sometime in 1974” must be provided to field site personnel. Most commercial database management systems do not accept blank fields for month and day in a date field. Estimated dates (e.g., when July 1, 1974 was imputed although only the year 1974 is known) should be marked (“flagged”) in the database to note the imputation. Those who analyze the data must be familiar with the coding conventions employed in a particular study.

The checks on the acceptability of dates and times include determining that the date of a visit or a patient’s birth date or a diagnosis date is reasonable. For studies in which examinations must occur within specified intervals (“time windows”), comparison of the actual dates of examinations or procedures with the allowable interval during data editing may result in rejection or deletion of data. The consistency and sequence of dates and times within a form can be checked to determine whether the interval between any two dates or times on a form is undesirable, unlikely, or impossible. Finally, comparisons of dates across forms completed during the same follow-up interval or clinic visit and across examinations over time can be made to assure the proper chronological order of sequential events. It should be noted that all of these sequence checks depend on recording of the necessary information during data collection.

The validity of data may be dependent on the level of training of personnel and their familiarity with the study protocol. The identification of those who examined the participant, completed the data forms, and keyed or transmitted the data should be recorded and a system for identifying and verifying qualified personnel incorporated into the data edit system. In a study that requires study-specific certification to perform certain procedures, study-assigned personnel identifiers can be used to monitor compliance. Data submitted by uncertified personnel may be rejected from the database or may be flagged to note that data quality may be suboptimal.
Routine Data Edits at the Key Entry Level

Field site data generally are recorded on paper data collection forms, even in a distributed data system. Well-designed forms are important whether paper forms or a computer screen system are used to capture data. Form design considerations are discussed in the paper by Hosking et al. elsewhere in this issue. Data gathered on a paper form must be keyed or scanned to convert them to an electronic format. Considerations for selecting data entry software and designing data entry systems also are reviewed in the paper by Hosking et al. in this issue.

When key entry is performed at the field site, data may be entered using a commercial database management system (DBMS) and stored in a field site database. Data also may be entered and stored directly in the study database maintained at the coordinating center by transmission of data over a telephone line or network. Another approach is to enter the data using data entry software that does not interact with a DBMS; in this case only within-form edit checks are possible. These checks typically are limited to those at the data item level and consistency checks between items on the same form. However, an ancillary database or table lookup system can be used in conjunction with data entry software so that critical data, such as the validity of a participant or examination identifier, can be checked.

When data are keyed into a DBMS and stored in a field site database, between-form edit checks are possible. As discussed in the paper by McFadden et al. in this issue, an advantage of a DBMS is that both simple within-form edit checks and sophisticated edit checks of consistency throughout the database can be performed. However, logistical problems can arise in data correction, database synchronicity, and control of data and reports when databases are maintained at both the field sites and the coordinating center. These issues also are discussed in the paper by McFadden et al. in this issue. Unless data are entered directly into the master study database, the field site database must be transmitted to the coordinating center and merged with the study database.

Resource centers are often able to transmit data directly from laboratory instruments to the coordinating center, thus eliminating the need for data transcription and key entry. However, this method of data capture does not eliminate errors in participant and sequence identifiers.

Routine Data Edits at the Central Database Level

When data enter the main database in two steps, i.e., first, through data entry at the local field site or resource center and, second, by transfer to the study database, further edits typically are performed at the coordinating center when data are added to the main database. Edit programs are used to check the data for agreement between forms (records) and adherence to the requirements of the programs that define the database. The number and types of edits may be based upon the extent of editing at the field site or resource unit. When less editing is feasible at the field site, the data typically are edited more thoroughly at the coordinating center than data that already have been checked exhaustively.

Disagreements or inconsistencies between data records are expected to account for most of the discrepancies detected by central edits when data are keyed at the field site without the benefit of an ancillary database or table lookup system. These discrepancies usually are detected between new data and data previously stored in the database for a particular study participant. When new data records
for a participant are checked against a local field site database, fewer between-form discrepancies are expected during editing at the coordinating center.

Consistency checks are made routinely when data are added to the study database. The data from multiple forms for an individual participant at a single visit or examination are checked for the following:

- All forms (i.e., data records) are appropriately labeled with a valid participant identifier or set of identifiers.
- All forms expected for this participant for this visit were received.
- All data were collected for the participant in the allowable time window for the visit.

After the forms within a visit are checked, consistency checks for a participant across time are made. Preliminary checks include the following:

- All data are labeled with the proper identification codes or, conversely, all of the data known to have been received for a participant are resident in the database.
- All data are consistent regarding age, race, gender, and characteristics that are not expected to vary across all forms for a participant.
- The sequence of the examination identifiers and test dates is correct.

The edits performed when data initially are added to the central database are followed by further batch edits in most multicenter clinical trials. The coordinating center staff prepares data screening programs that are run on a regular schedule, e.g., daily, weekly, or monthly, to check for inconsistencies within and among records currently in the database. The routine edits may be performed just before the database is copied ("frozen") for data analysis or before reports are generated on a regular daily, weekly, or monthly schedule. These checks typically are too complex or too protocol dependent to include as a part of the database definition programs and, therefore, are not implemented immediately on entry or receipt of each data item. Examples of such periodic routine edits are participant medication monitoring systems or checks of patient-specific data for extreme or unexpected changes that may suggest errors in observing, recording, or transferring data. Missing forms checks may be done later, as part of the quality monitoring process. Such checks should not be done manually without automated verification. All edit programs, whether for routine or special processing or for immediate or batch processing, must be carefully documented to guarantee consistency and to facilitate description of the edit process in reports or manuscripts.

Edit programs require careful checking and testing, both when implemented initially and whenever revised. Two types of mistakes are possible: an anomalous value or condition should have produced an edit query but did not, or an edit query was produced in error when the data were acceptable as reported. The first mistake is more difficult to detect without thorough testing and comparison with data records with known problems. The second mistake, even when undetected at the coordinating center, usually is called to attention by field site or resource center personnel who receive such a query. New checks on data quality can and should be added as close to the source as feasible. When a new check on data quality is added, the current database is edited retrospectively for that condition or set of conditions to assure uniformity of data handling.
Checks on Database Quality During Data Analysis and Reporting

Two types of analyses and reports may reveal problems with data quality. The first type consists of analyses and reports designed to uncover marked differences between field sites with respect to data patterns or variability as well as comparisons of original and repeated assays, measurements, or observations to assess reliability. Data patterns unique to a single field site or single examiner may indicate either unconscious examiner bias or intentional misreporting. Such analyses and comparisons are important throughout data collection so that problems can be detected or more reliable methods implemented early in the study. Discovery of systematic biases or unreliable methods late in the study may require that some data collected throughout the course of the study be discarded.

The final data editing stage occurs when unusual values or unusual changes in data not previously detected are observed during statistical analysis or during the presentation of these analyses to clinicians or other experts. Additional checks of the data should be performed on a regular schedule when anomalies are found during statistical analyses.

Handling Anomalous Data

When an anomalous or discrepant data item or data form is identified at the coordinating center, the individuals who use the database for preparing reports or analyses or for communicating deficiencies to the field sites and resource centers should be aware that these data values are suspect. A policy that addresses unresolved discrepancies in the database must be formulated, taking into account all of the needs of the study. The policy adopted must be well documented.

One way to protect coordinating center staff from misinterpretation of anomalous data is for these data to be stored outside the master database and inaccessible for analysis purposes until confirmed or corrected. In some systems, entire data records are prevented from entering the database until every data field has passed all checks [22,23]. When this approach is taken, discrepant data records are stored temporarily in a secure location for resolution. Field sites must be encouraged to resolve anomalous data items in a timely manner. A query database that accepts records containing anomalous data can serve as an appropriate temporary storage location. Corrections must be processed promptly so that the data record can be added to the master database after anomalies have been resolved and be made available for analysis. This option is reasonable only when data are not needed for analysis immediately and when corrections or confirmations are returned and processed rapidly.

Another option is to store the status of each item in the database using a "status field" that contains readily interpretable codes, such as "acceptable," "unacceptable," or "currently under review." These status fields may double the size of the database and increase the computing resources used when retrieving or analyzing the data. However, this approach allows those summarizing the data to select information based on the status of the item in each record. A third option is to use status codes for a few key variables. A fourth option is to use a status field for each complete data record (or form) that denotes "all accepted" or "some anomalous data" depending on the outcome of edits.
**Study Data Query**

**Section 1:**

Date of Query 04/12/92

Patient Identification 123456 Form 17
Visit Date 4/9/92 Visit Number 12
Item Questioned 7a

Description of Query: You have provided pill count data of (Item 7a = 58) for ACE Inhibitors on a patient you notified us had discontinued ACE.

**Section 2:**

Date of Response 04/13/92

Form to Correct 17 Item to Correct 7a
Correct Value 0

Explanation: This person wasn't on ACE.

Certification number FSSSCI

**Section 3:**

Date of Correction 04/15/92
Explanation: Changed 58 to 00 as requested

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Figure 2 Data edit query example.

**RESOLVING DISCREPANCIES: DATA QUERIES AND RESPONSES**

**Content of Data Queries**

Anomalous data are reported to the appropriate field site or resource center through data queries, i.e., data discrepancy reports sent to solicit confirmation or correction of questioned data. These customarily are produced as “turnaround documents” because of the query feedback loop that must be completed (Figure 1). Queries are sometimes referred to as edit messages, edit reports, or data anomaly reports. An example of a query is shown in Figure 2. The query example includes
an identifying title, a question section from the coordinating center, a response section from the data originator, and a documentation section for the coordinating center. The format for the query should be established by coordinating center personnel and explained to data originators during training. Queries usually are prepared by the coordinating center staff either manually or, preferably, by specialized computer programs. Queries should follow a standard format for a given study or group of studies with common field site personnel.

In the question section (Section 1 of Figure 2), each query must identify the data items being questioned. The example in Figure 2 gives the form identifier, participant identifier, visit type, date and sequence number of the data form (or screen) associated with the query, and the data item(s) in question. Identifying information typically is followed by a description of the problem detected. The description of the anomaly may be generated from a menu, manually, or by an automated system that creates customized messages.

Using a manual anomaly description system, a staff member at the coordinating center may interpret error messages generated by the database programs and compose a detailed, easy-to-understand description of the problem, and write or key this description into the question section of the query. In a menu-driven anomaly description system, a staff member selects from common standard queries on a menu and has the option of selecting “other” and composing a unique or unusual query [24].

Automated anomaly description systems generate a customized query for each anomalous data item or set of items. Computer programs generate customized reports that clearly state the problem detected. These automated reports are sent to the data originators. This approach has proven to be a reliable method of notification in the Bypass Angioplasty Revascularization Investigation Study [25], the Collaborative Ocular Melanoma Study [1], and the Macular Photocoagulation Study [26], among others. This method of generating query documents is the most efficient in terms of coordinating center personnel time. The query may be printed and mailed or telecopied, or it may be transmitted to a special file in the local computer system at the field site or resource center.

Field site staff read the question section and complete the response section (Section 2 of Figure 2). In some instances, an error in one field may cause correct data in another field to fail an edit check. Adequate space should be provided in the response section of the query for field site staff to modify one or more fields in addition to the one questioned, or some other mechanism must be provided so that corrections can be reported for items not identified as anomalous by the automated edit system (see Figure 1 of the paper by Hosking et al., this issue). Some automated systems print all related edit information (related forms, fields, and values) used to generate the query. This additional information may expedite the anomaly resolution process.

A brief explanation area in the response section also facilitates query resolution. The explanation provided by the field site may aid the coordinating center staff in determining that the query response is correct.

The documentation section (Section 3 of Figure 2) contains information regarding the resolution of the query. The example includes the date of the correction, a brief explanation of the action taken, and the certification number of the coordinating center staff member who was responsible for the corrective action.
Communicating with Field Sites About Data Anomalies

The coordinating center should notify the field site or resource center personnel from whom the data originated in a standard and expedient manner when data are questioned. A system must be in place to document when the query was generated and the data originator was contacted. In the Diabetic Renal Disease Study [27], a coordinating center staff member writes each query on a query form to be telecopied to the site. In the North American Symptomatic Carotid Endarterectomy Trial [28], the query is sent as an electronic mail message [29]. In clinical trials sponsored by industry, such as drug company studies, the questioned data items are often marked on the paper data form and then telecopied or mailed to the field site. In automated or semiautomated query systems, the question portion of the query is computer-generated as a report that is sent to the data originator by regular or electronic mail.

Fax machines (telecopiers) and electronic mail provide for inexpensive, rapid, and well-documented communication. Express mail may be too expensive, and regular mail may be too slow. Telephone notification is acceptable only when detailed paper documentation of the calls is kept at the coordinating center and the field sites. Telecopying queries may be the most efficient procedure in small studies. Electronic mail systems are easy to implement and efficient provided that personnel at each center have access to electronic mail.

Queries may be sent whenever an anomalous data item is encountered, or they may be accumulated and sent in batches. Queries generated from routine scheduled edits are sent in batches after the edits are performed. The advantage of sending queries daily is that field site staff have the opportunity to resolve a few discrepancies at a time and are not overwhelmed with a large batch of queries that arrives less often. Also, the closer in time the queries arrive relative to initial data collection, the more easily field personnel can recall the event in question or retrieve documentation. However, in a study in which few patients are seen or data flow is slow at each site, query batches may reduce the likelihood of individual queries being lost. Batched queries facilitate concentrated review of data records to prepare responses.

Field Site Responses to Queries

Data originators respond to queries using the system established by the coordinating center. The form in which a response is returned typically depends on the form of the original query. Telephone responses are generally unacceptable, unless they are followed by mailed or telecopied documentation or, in special situations, detailed documentation of telephone calls is maintained in an auditable form. Written response by telecopier may be appropriate and has become more common. In the Southwest Oncology Group (SWOG), one of the cooperative cancer research groups sponsored by the National Cancer Institute of the National Institutes of Health, the field sites respond to queries by resubmitting the data form in question to the coordinating center with corrected data penned in colored ink. In some drug company studies, the corrections are marked on the discrepant forms, signed, and dated and the forms are sent back to the coordinating center. Electronic mail messages are used to respond to queries in some studies. Either paper or electronic records may provide adequate documentation. Query responses in the
Table 3  Query Response Times by Field Site

<table>
<thead>
<tr>
<th>Field Site</th>
<th>Number of Queries Sent</th>
<th>Response Time</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤7 Days</td>
<td>&gt;7 Days</td>
</tr>
<tr>
<td>1</td>
<td>200</td>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>225</td>
<td>180</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>175</td>
<td>158</td>
<td>2</td>
</tr>
<tr>
<td>Overall</td>
<td>600</td>
<td>488</td>
<td>56</td>
</tr>
</tbody>
</table>

Correction of the Database

Data should be corrected or other appropriate action taken as soon as a query response is received at the coordinating center. Saving all corrections or confirmations until just before preparation of a report increases the opportunity for loss or misuse of data. Furthermore, a correction to one item may result in a new discrepancy that must be resolved.

The method of data correction is a function of the format in which the data originator responds to the query and the way in which the anomalous data were stored initially. When field site personnel respond with unformatted text, the text must be read and interpreted by the staff at the coordinating center. When field site personnel respond with strictly formatted text, the text may either be read...
by a coordinating center staff member for appropriate action or coding or the
response may be treated as raw data for processing by special database correction
programs.

When the discrepant data are stored as a simple grid with rows and columns
of numbers (flat file), the data can be corrected by applying an error correction
program to the file. Manually editing a flat file by overwriting the original values
using a text editor is not advised; tabbing over to column 14 on line 3 to change
a 6 to a 9, for example, offers many possibilities for error. The recommended
approach is to utilize an error correction program written in the language used
for data management. After the flat file is revised, it may be added to the study
database immediately or marked (flagged) so that it will be added to the study
database automatically at a later time.

When the discrepant data are stored in a database — whether it is the main study
database or a special query database for discrepant data — the data usually can
be corrected using the data screen display component of the database management
package. These components provide a view of a portion of the database similar
to the appearance on the paper form and permit overwriting of incorrect values.
In an automated system, the data typically are corrected using programs that read
the formatted field site responses as raw data and subsequently correct the data
in the database. When a large series of similar data anomalies are detected through
routine edits or data analysis and resolved with the field sites, an error correction
program may be used to correct all of the data automatically without introducing
transcription errors. Coordinating center staff must be trained never to change
data, even when an apparently obvious error is encountered, without confirming
the change with the field site or resource center personnel responsible.

Whatever the method of correction, all initial edit checks need to be repeated
for the “corrected” data to assure that correcting one or more data field(s) improved
the overall quality and consistency of the database and did not create new discrep-
ancies. A mechanism is required to allow the study database to accept data that
fail electronic edit checks and yet are determined to be acceptable, e.g., unusual
values or observations that nevertheless are correct. In this sort of mechanism,
data are marked as permanently anomalous to bypass editing in future. A common
example of this would be a valid measurement that is outside the usual range for
study participants because of an unusual characteristic of the participant or the
measurement situation. Typically, the database administrator consults with clini-
cians and statisticians to determine when anomalous data may be stored in the
database. Inclusion of unusual data values confirmed to be correct should be the
rule; exclusion should take place only in rare circumstances. Documentation is
required to justify acceptance of the anomalous data items. This documentation
should include information on the edit being bypassed, record identification, field
to be bypassed, date of the bypass decision, and a brief explanation of the reason
for bypassing the record and accepting an anomalous value. Documentation may
be maintained either on paper or in an on-line file or log maintained by the database
administrator for this purpose. This task should be entrusted to (and undertaken
by) designated personnel who have a complete understanding of the study data-
base. Responsibility for bypassing edit checks is generally vested in a senior staff
member, such as the database administrator, who is fully accountable for all such
actions.
As previously noted, many studies require documentation of query response times, missing query responses, and other logistical data relevant to the queries as part of performance monitoring and database quality monitoring. As part of performance monitoring of the coordinating center, summaries of the time it takes the coordinating center personnel to correct anomalous data once the originator provides the appropriate data correction information should be generated.

Tracking Corrections and Other Changes to the Database

In any data management design, a system for tracking changes to the study database is essential for data quality assurance. A complete chronological history of database transactions ("audit trail") should be an inherent component of a data management system for troubleshooting data inconsistencies, data integrity, database rollback (i.e., restoring or returning the database to its contents at a certain point in time), and prevention of database degeneration. Audit data should include (1) unique record identifiers, (2) field name to be modified, (3) old and new data values in that field, (4) date of modification, (5) operator performing the modification, (6) person authorizing modification, (7) a brief explanation of the modification, and (8) identification of the update utility performing the modification. These audit data may be generated either manually or automatically, contingent on the sophistication of the data management system. Automatic auditing should be an integral function of all database update subsystems purchased or programmed for a data management system. If several update utilities are employed in a study, they all should store audit data in a shared audit table to provide one central source for the database history.

MONITORING ACCURACY, CURRENCY, AND INTEGRITY OF THE DATABASE

Monitoring Completeness and Currency of the Database

The data management responsibilities of the coordinating center are not merely reactive, i.e., acceptance, processing, checking, storage, and analysis of the data sent from the field sites and resource centers. The coordinating center personnel must maintain automated systems for noting when study participants are due for examinations or other data collection contacts, checking the database for receipt of the expected information, and assuring that all information expected for the participant is accounted for. Typically, reports to field site and resource center personnel are sent periodically to indicate time windows for participant contacts that have closed without receipt of the expected data, incomplete information received for a study participant, or materials overdue at resource centers. Often items that have remained overdue for more than one reporting period are flagged in some way. Similar information may be summarized as part of periodic reports on performance of individual field sites.

Periodically, the coordinating center may send each field site and resource center a summary of the data received for each study participant. These reports assure these centers that all information has been received. Verification of the completeness of these reports by field site and resource center personnel assures the coordinating center that information has not been lost either in transmission to the
coordinating center or during processing at the coordinating center. Frustration may occur initially when missing data are attributable to violations of time windows. The emphasis on complete and rapid reporting may be increased during the final stages of a study as the database is prepared for final manuscripts and for archiving. Field site and resource center personnel should be alerted to the need for special attention to data reporting.

Monitoring Timeliness of Data Submission

Studies in which a data monitoring committee is charged with periodic review of accumulating data rely heavily on field site personnel and resource center personnel to report participant data promptly after collection. The reports described in the previous section may prompt timely data submission although their primary purpose is to encourage complete data submission. However, the coordinating center personnel can only request the data that are expected, i.e., those scheduled for collection at routine contacts or anticipated based on events that have been reported at a routine contact or examination. Adverse events and primary outcome events such as deaths may occur at any time. Typically, the coordinating center staff learns of such events only from reports from the field sites; it is not possible to prompt the field site personnel to submit a report. However, depending on the condition under study and the type of data collected, it may be possible to anticipate some events on the basis of data submitted from routine contacts. For example, in the case of some neoplasms, death rapidly follows a diagnosis of distant recurrence. Thus, the data management system may initiate inquiries regarding vital status at frequent intervals following a diagnosis of metastasis. In addition, participants who have had several consecutive missed contacts or examinations may trigger special requests to the responsible field site to intensify efforts to contact the participant or to examine the participant at home.

Investigators at many coordinating centers find it useful to produce periodic reports on the timeliness of data submission, both to recognize sites and personnel who adhere to established schedules and requirements and to identify those who do not. In such reports, the emphasis typically is on data concerning the primary and secondary outcomes of interest, with less attention to ancillary data.

It is important that reports concerning data submission deficiencies not be sent only to the person who appears to be at fault. Often a letter to the principal field site investigator is more effective than a series of routine requests to the local data coordinator or to another member of the field site staff. Field sites or resource centers with persistent reporting delays may require special site visits or other corrective action by the study leadership committee.

Monitoring Accuracy of Data Collection

Retention of paper data collection forms is recommended for quality monitoring purposes. When the data form is completed and signed by the individual who performed the examinations, test, or procedure, the data form may provide a more complete record of the findings than routine records maintained independently of study records. Furthermore, the handwriting of the person who recorded the information is preserved along with any other explanatory notes about the data. With paper forms, a subset of the data reported can be selected and compared
with independent records to verify accurate reporting of selected information, such as dates of examinations or procedures and key examination findings. Even when paper forms are not used for initial data recording, it usually is possible during data audits to verify dates of examinations and identities of examiners from appointment schedules and billing records. When data are abstracted from medical records and entered directly into a paperless system, record abstracting may be repeated for auditing purposes.

**Monitoring Accuracy of Data Entry**

The quality of data entry must be monitored. Some of the errors made during data entry typically are detected during later edits. However, some are very difficult to detect except by comparison to the completed data collection forms. Furthermore, the time required to find and correct key entry errors may be a significant component of the workload in some settings. It should be noted that such checks are needed regardless of whether 100% rekeying (double independent data entry with comparison or data entry and verification) is employed routinely.

To determine rates of key entry error, a random sample of data fields is selected for checking. A broad cross-section of data should be examined including single- and multistroke fields and both numeric and alphanumeric fields. Logistically it may be easier to select randomly a subset of forms and to assess all fields on these forms, rather than to select a totally random sample of data fields.

Neaton et al. [31] have given a summary of several methods of data entry, both central and distributed, and their respective performance in a single clinical trial, the Multiple Risk Factor Intervention Trial. Error rates also were compared to those of a number of other studies. They concluded that 10 keystroke errors per 10,000 fields was achievable using several approaches to data entry. A review of error rates achieved in different settings is given in the paper by Hosking et al. in this issue.

Double entry by two different key entry persons is preferred when there is a constant heavy flow of data forms with an emphasis on production and key entry operators take a "key-what-you-see" approach. Such an approach may not be feasible or necessary in some data management systems. Some related issues are given in the paper by Hosking et al. in this issue. Even with 100% rekeying, it is possible for two individuals to interpret the recorded responses incorrectly in the same way, particularly if the design of the data collection form or completion of the form is less than ideal.

In a system with double entry of all data, decisions must be made regarding whether the accuracy of each keying is to be monitored or only the accuracy of the second or adjudication keying, i.e., is monitoring directed at assessing the performance of individuals or the performance of the system? Often both types of information are desired, particularly when process error rates are excessive. Reproducibility of the system typically is easier to check than individual operator accuracy because of the manual step required in all checks of accuracy. Key entry software and most database management software provide utilities for comparisons of data entry records. Blumenstein [32] has reviewed options for verifying study data.

Considerable planning and motivation is required to develop a system for comparison of keyed data with original records. These checks may be part of an
ongoing program or may be scheduled only occasionally. As with other quality monitoring checks, the attitude of personnel regarding this task is influenced heavily by the priority given to it by the coordinating center investigators. These individuals must seek to instill in all study personnel pride in high-quality performance and a nearly error-free database.

When reporting on data entry error rates, it may be desirable to distinguish between key entry errors made during initial transcription of data from the forms and errors made in entering responses to edit queries. Similarly, depending on the diversity in types of data collected, types and lengths of fields, and changes in data collection over time, error rates may be presented for individual form types, different item types, or different time periods as well as by key entry operator, pairs of operators, or field site.

Most coordinating centers have automated ways to compare data files to assess reproducibility, but special purpose programs may be required to track and report information on data entry accuracy. It is important that a coordinating center director not commit to quality checking of 10% of key-entered data when checking even 1% of the records may require a large investment of time and personnel and may provide sufficient data entry error estimates. Furthermore, data entry errors may represent only a small fraction of all errors introduced during processing. Residual errors in the database (see the section “Monitoring Quality of the Data Management System” below) after all edits and corrections are complete may be more meaningful and therefore may deserve more attention.

Monitoring Accuracy of Data Transmission

In a study with distributed data entry and electronic data transmission from field sites or resource centers, mechanisms are needed to check the accuracy of data transmission [33]. Methods of data transmission between centers are discussed in the paper by McFadden et al. in this issue. Most data transmission software has a system that confirms that the data sent from the field sites are the same as the data received at the coordinating center. When data are transmitted electronically, paper forms need not be sent from the field site to the coordinating center [34] as long as quality monitoring has shown the telecommunication process to be reliable. A data transmission quality assurance and monitoring system should be in place when any telecommunication system is used.

The mechanisms implemented depend on the type of transmission and previous experience with reliability of the system. Data files may be transmitted twice and compared. Data collection forms from which data were entered may be sent by mail following transmission of data files and the contents of the electronically transmitted files compared with the information recorded on the forms. Other approaches may be appropriate depending on the procedures followed in a specific study.

Monitoring Quality of the Data Management System

As noted earlier, the most important measure of the quality of the data management system and operations may be the residual error rate, i.e., the frequency of errors in the database after all processing and routine quality assurance activities have been completed. Typically, these checks to assess the residual error rate
must be made manually. In a paper-based data collection system, they include comparisons of the database contents with paper data records, including completed data forms, responses to edit queries, and voluntary corrections to the database submitted by field site and resource center personnel together with records of exceptions processed. In the centralized data management model, these comparisons are made at the coordinating center. In distributed systems in which the local database is considered the official database, such comparisons are made at the local field sites although they may be initiated by coordinating center personnel or others with a central role in the study. In a distributed system in which the coordinating center does not receive paper forms and a local database is not maintained, checks of this type typically are done during site visits. In the Modification of Diet in Renal Disease Study, a sample of data was selected from the database, printed, and taken to field sites for comparison with original source data.

In the Macular Photocoagulation Study (MPS), a random sample of the data forms received each month from the field sites and fundus photograph reading center was compared to the database after all processing of the forms had been completed and all edit queries resolved [26]. Thus, checks for residual errors typically occurred several months after initial receipt of forms. The checking was done prior to sending the paper records for microfilming so that the microfilmed records would be complete. Because forms were filed by date of receipt and all completed edit queries and voluntary correction forms were attached to the corresponding forms, retrieval of paper records was straightforward. A special program was used to list the key field values of each form received for which data were stored in the database during the time period of interest, to select a random sample of the forms, and to print the data record for those sampled. Key outcome data were printed from all records. Coordinating center personnel were assigned in rotation to two-person teams, one person to read data from the data forms and correction documents received from the field sites and the other to check the listing from the database. All coordinating center personnel, including the director and the secretaries, participated in this quality monitoring program. Initially, 10% of the database records were sampled; this percentage was reduced to 5% later in the study after the residual error rates had been demonstrated to be low, on the order of 4 fields in error per 10,000 fields [26,31]. Nevertheless, 100% of key clinical outcome data were checked for every participant and every visit throughout the study. Cumulative and interval residual error rates were reported to the MPS Data and Safety Monitoring Committee in each report. Parenthetically, this program had many benefits besides data management quality monitoring. All coordinating center personnel became familiar with the data forms and data management system. The changing composition of the monitoring teams often paired individuals who had little opportunity to work together otherwise; less experienced individuals had an opportunity to work in tandem with more experienced personnel. In addition, many suggestions for improving data management systems emanated from these internal monitoring checks.

Monitoring Delays in Responses to Queries

Just as there may be delays in submission of completed data forms by field site personnel initially, there also may be delays in submitting responses to edit queries. In paper-based centralized systems, a file of copies of the edit queries may be kept
at the coordinating center and the copy removed as the response is received. The size and contents of the file may be used to monitor delays studywide or at specific field sites. In larger studies with more sophisticated systems, a unique tracking identifier may be assigned to each edit query and that identifier retained in the database with the query and a status code. This record may be used to control corrections to the database as well as to provide the basis of reports on timeliness of responses [35].

In the Modification of Diet in Renal Disease Study, the coordinating center re-sent any currently outstanding queries on a monthly schedule. Queries with no response after 14 days were noted in the data management section of monthly reports to the study leadership committee.

DATA QUALITY REPORTS

Discrepancies and Error Corrections

Routine reports to the field sites, sponsor, and study leadership committees, and especially reports related to site visits or study reviews, typically include the number and types of errors, timeliness of error correction, and an assessment of the completeness and accuracy of the database. Regularly generated reports include information for individual field sites and resource centers that helps to isolate individual problems. The paper by McBride and Singer in this issue contains a discussion of reporting.

Performance reports may include the percent of error-free forms, a query-to-form ratio, and a summary of queries by form and item type. Forms or items observed to produce a disproportionate number of queries may require revision.

Queries may be categorized and query processing data summarized by type of query. It may also be useful to tally queries separately by stage of data flow, e.g., those generated immediately after initial data entry, those generated during batch editing, those found during quality audits, and residual anomalies discovered during data analysis.

In order for data regarding timeliness and method of query resolution to be available, sufficient information must be maintained electronically [22,35]. A record of the date the query was generated, the date the field site responded, and the date the coordinating center corrected or confirmed the values in the database must be retained. This information is useful for both field site and coordinating center monitoring. Therefore, reports should provide information for each field site and resource center as well as for the full study. Individual field sites or resource centers can be highlighted as desired to emphasize outliers.

Accuracy, Currency, and Completeness of the Study Database

Many factors contribute to the accuracy of the study database, as noted in the introduction to this chapter and in the section "Data Quality Reports." When the overall quality of the database is sufficiently high, it may be unnecessary to analyze and report error rates from different components of the data management system. However, when the quality of the database is unacceptable, e.g., there is a high rate of discrepancies between source documents and the database, there are substantial errors in data relating to primary or secondary outcomes, or there is a significant
difference in quality of the data contributed by different centers, it is important to analyze and report on error components. Error rates from different components of the data management system, as well as descriptions of the monitoring programs that yielded the estimated rates, may be summarized for coordinating center site visitors and other external and internal reviewers of data quality.

Resource Center Quality Monitoring and Performance Reports

There are two major sources of data in multicenter studies: information that originates from the field sites based on contacts with study participants and information that results from specialized analyses or expert interpretation performed at resource centers. Blood and urine specimens, electrocardiographic tracings, fundus photographs, radiologic scans and X-ray films, dietary diaries or interviews, and any number of other materials may be obtained at the field sites and shipped or transmitted to resource centers with special expertise in analyzing, interpreting, or coding such materials. These resource centers play a major role in standardization of study findings from the materials and in quality assurance and monitoring. Resource center procedures and data must be monitored concurrently with field site monitoring.

Specialized resource centers typically have ongoing internal quality assurance programs for each assay or process. Studies using such centers can utilize data from these internal systems as a basis for designing more refined quality monitoring schemes. In many cases, supplemental external quality control programs are developed to check the accuracy and reproducibility of data collected within the structure and expected data range of a given study or participant population.

The study leadership, in consultation with the coordinating center investigators, must decide on an appropriate level of quality assurance and monitoring for each resource center. The decision may depend in part on the extent of external monitoring of the center by other groups or agencies. For example, many medical laboratories participate in a program of external monitoring, such as those administered by the Centers for Disease Control and the College of American Pathologists. Study committees should assist the coordinating center investigators in determining the specific data fields or summary variables to be monitored for resource centers. Even in condensed form, some of the data coming from resource centers may be peripheral to the major study endpoints. Procedural data such as timeliness of analysis after receipt of specimens, timeliness of data submission to the coordinating center, and timeliness of feedback to field sites should be monitored.

Focusing quality assurance and monitoring on the data to be used for primary treatment group comparisons in a multicenter clinical trial or for primary outcome estimates in other types of studies is a reasonable starting point in the process of selecting data to be monitored and reported. Intense monitoring of four or five fields from a detailed nutrition record of 100 nutrients may provide sufficient accuracy and credibility to the nutrient data, particularly when adequate internal quality monitoring data are provided for review.

Different methods of quality monitoring are needed for different types of centrally processed items; methods also depend on whether the materials sent to the central facility are reusable and the length of time the specimens remain viable. For durable data, e.g., photographs, dietary recall records, and electrocardiogram
Data Quality Assurance

Tracings, samples selected for repeat evaluation typically include both a cross-section and several time points. The coordinating center investigators may need to revise the sampling scheme as the study progresses and repeat evaluations are performed. One selection method may be to divide the data into quartiles based on the entire range of values expected to be observed in the study and to sample equally from each quartile. Another system might emphasize areas prone to error or data associated with key study endpoints or critical values. Sampling with replacement permits evaluation of trends over time in interpretation of the same material.

For perishable or limited specimens, such as samples of blood or urine, an adequate sampling of randomly preselected collections should be submitted in duplicate to the central laboratories. The monitoring procedures thus serve to check the entire system from collection of the specimens through reporting of the results. Coefficients of variation (CVs) and coefficients of reliability (CRs) [36,37] give an indication of the variability between any two measurements. Technical errors also may be reported. Owen [38] reported for biochemical data in the Diabetes Control and Complications Trial a CV range of 1-10 and a CR range generally above 90%. The precision of the instrumentation must be considered when interpreting such results. Habig reported comparable numbers for the National Cooperative Gallstone Study [39]. McShane and Turnbull offer some suggestions on optimization of the samples selected and the timing of the submissions [40].

Quality assurance and monitoring of data from resource centers help to assure that study findings are reliable and credible and are not due to erroneous or inconsistent analyses at the resource centers. The cooperation of personnel at resource centers in carrying out quality assurance and monitoring programs is essential. Whenever possible, data analyzed in duplicate or reevaluated at specified intervals should be masked at the technician level to prevent the possibility of special handling for these items. Specimens may be resubmitted from the field sites following various protocols, depending on the type of resource center being checked [41]. Alternatively, a contact at the unit, perhaps a clerk or secretary who is routinely responsible for batching samples and preparing data forms, may be asked to prepare nonexpendable items for reevaluation. This contact may have to mask or otherwise alter the identifying information before repeat interpretations, codings, etc., are carried out. Jefferys [42] described some of the problems associated with masking of resource center personnel in quality monitoring.

For analytes that are stable over several months, the field sites may delay submission of duplicate items to the laboratory. Study labeling practices should be designed to assure that analysis of neither the original nor the replicate specimen is affected by results obtained on the other of the pair.

Some specimens may be of such poor quality that they are inadequate for initial processing or cannot be rechecked for quality monitoring purposes. For example, blood sample volume may be insufficient or an audiotape may be inaudible. Reports of results of data quality monitoring should include statements regarding the number of unacceptable specimens because ignoring them may lead to biased estimates of reliability or quality.

Coordinating Center Quality Monitoring and Reports

The coordinating center should have its own quality assurance and monitoring programs in place. Essential elements of this plan include documentation of all...
procedures, documentation of any extraordinary event that may have produced a data anomaly, and appropriate backup plans for loss of data or personnel. One aspect of quality monitoring is the time required for coordinating center personnel to process data received and to update the database. Other candidates for reporting are coding errors, data entry errors, programming errors discovered, and errors in interim reports. Quality monitoring of preparation of analysis data files or of performance of statistical analyses sometimes can be accomplished by duplicating procedures with different personnel and/or different software. Checks of stratification and treatment allocation in clinical trials in which these tasks are administered by the coordinating center should be performed and the results reported.

It can be disheartening to those with primary responsibility for data quality assurance and monitoring to discover that the net result of their effort is one sentence in the manuscripts that report the results of the study, e.g., a statement that the data from all groups of participants are equally complete, reproducible, and accurate and therefore that differences in data quality do not account for any difference detected in study outcomes. However, the alternative, i.e., that the data are not reproducible within prespecified limits, would be unacceptable. As noted in the introduction to this chapter, a more tangible result of these overall efforts may be a manuscript that describes the quality assurance mechanisms and the findings from quality monitoring and that provides useful information for future studies.

PROMOTION OF TIMELY AND ACCURATE DATA COLLECTION AND REPORTING

Training and Certification

In order to standardize study procedures, field site personnel should be trained and certified centrally. The field site staff may consist of local data coordinators or managers, key entry personnel, technicians, examiners, counselors, physicians, or dietitians, depending on the study design. The coordinating center investigators should take proactive measures to assure that these individuals understand the study protocol and design, including participant eligibility criteria and plans for analyzing primary and secondary outcomes of interest. Field site data coordinators and key entry personnel should be certified in study procedures for data entry, data transmission, and error correction. They also should be taught to use the study's system for electronic mail, if applicable, and other communication and tracking mechanisms. Because of the time and resources required for training and because of concerns about data quality, it is helpful to train two people at each field site for each task requiring study certification so that one individual is always available to the study.

It is prudent to include some review of medical and other research issues as part of the training program. Coordinating center personnel who participate in training programs for field site personnel often are dismayed by how little training in the medical aspects of the study local investigators have provided. Principles of good research practice regarding documentation and data handling should be reviewed. The quality assurance and monitoring program for the study should be described so that field site personnel know what to expect in communications with resource centers, in performance monitoring reports, and during site visits.
During training of personnel for the Bypass Angioplasty Revascularization Investigation, field site staff were given a pretest that included questions about the field site microcomputers and their operating systems, data collection procedures, and various study-related procedures. After the staff members completed training, a more detailed posttest (certification test) was administered and results were compared. Scores were better on the posttest, as expected, and the staff members reported that they were better informed and more comfortable in their responsibilities.

Physicians participating in the study likewise must be trained in all aspects of the study protocol, including data collection and reporting. Other quality assurance efforts are irrelevant if the physicians do not understand the basic principles of data collection and study design. In the SWOG, physicians responsible for research protocols must attend a workshop prior to initiation of new studies.

Study personnel typically are certified for a specific study when they complete initial training and pass competency tests for procedures or examinations required by the study protocol. Because of the nature of field site operations in some studies, certification may not be granted until an individual is observed by a site visitor who confirms that the applicable procedures can be followed in the local setting and that field site personnel have retained the skills taught during training. During annual meetings or site visits, recertification may take place. Recertification is especially important for field site staff who make difficult measurements for which measurement techniques are prone to drift over time. Examples of difficult measurements include dietary history interviews and anthropometric skinfold measurements. Personnel who do not meet recertification requirements may have their certification revoked or be scheduled for retraining. Edit checks may be added at the coordinating center so that after the date of decertification data provided by these individuals are no longer accepted or are flagged as being of lesser quality.

Field Site Management Aids and Reminders

Typically, data management staff at the coordinating center use programs that access the study database to create a number of aids for use by field site personnel. These aids may include data collection schedules tailored to each study participant to show target dates for examinations and contacts together with the acceptable time intervals during which each examination or procedure may occur to be accepted into the database; reminders of upcoming examinations; lists of participants for whom data reporting is delinquent; data records or other items associated with an examination that have not been received at the coordinating center; and lists of edit queries that have not been resolved. Some examples of such aids and reminders are listed in Table 4.

Considerations for Design and Production

By definition, management aids are closely linked to study operations within the field sites. Thus, design and production methods must be tied closely to the details of the data management model chosen for the study. For example, in a centralized model with paper forms, typically the coordinating center confirms receipt of each batch of forms received. However, in a study in which field site personnel are instructed to send data forms every day, each batch may be quite
Table 4  Examples of Field Site Management Aids

<table>
<thead>
<tr>
<th>Participant-Oriented Aids</th>
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</thead>
<tbody>
<tr>
<td>• Notice of eligibility for enrollment</td>
</tr>
<tr>
<td>• Confirmation of treatment assignment or registration</td>
</tr>
<tr>
<td>• Follow-up appointment schedule for a participant</td>
</tr>
<tr>
<td>• List of materials required to complete documentation of an event</td>
</tr>
<tr>
<td>• Participants due for examination/contact</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Database Transaction Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Confirmation of data accepted into database</td>
</tr>
<tr>
<td>• Confirmation of corrections applied to database</td>
</tr>
<tr>
<td>• Queries regarding anomalous data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missing Items Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Missing query responses</td>
</tr>
<tr>
<td>• Missing paper forms</td>
</tr>
<tr>
<td>• Missing electronic data records</td>
</tr>
<tr>
<td>• Missed examinations/contacts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Aids</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Roster of study-certified personnel</td>
</tr>
<tr>
<td>• Study personnel activity reports</td>
</tr>
</tbody>
</table>

small and a daily confirmation report may be excessive. Instead, the coordinating center may elect to confirm receipt of data forms on a weekly or monthly basis.

Many of the methods used to monitor database completeness and timeliness incorporate documents generated at the coordinating center that are useful both for monitoring and for field site management, e.g., lists of participant contacts that are due, overdue forms, and information missing from the database. These usually are generated centrally, although they may be produced locally in a distributed system with a local database.

When designing site management aids, the intended user and local circumstances must be considered. For example, lists should be ordered in a convenient sequence for field site personnel. Reports that are generated only rarely should be more self-contained and self-explanatory than those sent often. Reports sent using E mail or other electronic systems should be formatted to accommodate different computers and printers.

**Scheduling Aids**

A schedule of expected contacts with each study participant typically is generated from the data management system following enrollment. This schedule may be generated at the coordinating center and sent to the field site in a centralized system or generated at the field site in a distributed system. In prospective studies, this schedule uses the date of enrollment to compute target dates for data collection visits or contacts. Typically, the earliest and latest acceptable dates for each data collection occasion are printed on the schedule. The schedule also may include reminders about procedures to be performed on each occasion and other information to assist field site staff or checklists may be generated before each examination interval.

In addition to individual participant schedules, summaries of participants due for contact during the next month or quarter often are generated as reminders to
confirm appointments or to reschedule examinations so that data are collected within acceptable time windows. Lists of overdue contacts with reminders of the closing date of the time window also may be generated. As noted earlier, the design and schedule of these scheduling aids must be tailored to the needs and design of the individual study.

**Missing Materials Reminders**

Missing materials lists provide detailed information to field site personnel regarding those paper forms, electronic records, responses to edit queries, items required for personnel certification, biologic specimens, and other materials that have not been received at the coordinating center or at another resource center. Typically, one list is prepared for each field site; this list may be subdivided by the type of item. Participant identifiers and data collection occasion identifiers, such as dates or examination numbers, are provided.

**Other Aids**

In some studies it has been useful to print a confirmation of the treatment assignment or other information necessary for patient management following enrollment or registration of each participant. Sets of printed labels for laboratory specimens, data forms, and other materials often are produced for the use of field sites. Labels may be printed with study, participant, and occasion identifiers or multipurpose labels may be printed that require recording of this information. Bar code labels permit rapid logging of materials upon receipt at the coordinating center and other resource centers.

**Site Visits and Record Audits**

**Visits to Field Sites**

Site visits provide an opportunity to review with field site personnel issues relevant to quality of the study data. Initial site visits typically are conducted by a team that includes personnel from the coordinating center, another field site, and other resource centers. Later site visits may be the responsibility of a single individual or a team, depending on the perceived needs of individual field sites and study goals. Early in the study, site visit teams may focus on enhancing accrual of eligible study participants. Later in the study, site visitors may focus on protocol compliance and participant retention and follow-up. Throughout the study, site visitors may explore whether field site personnel are giving appropriate time and priority to the requirements of the study and that the effort devoted to study activities is consistent with funding provided by the sponsor. Meinert presented some considerations for site visitors [7]. Cassel and Ferris [43] provided a detailed account of a typical site visit in the Early Treatment Diabetic Retinopathy Study.

Site visits allow the site visitors to see the field site setting and to observe actual data collection; they also allow the field site staff to communicate concerns to the study leadership and the sponsor through the site visitors. They also give coordinating center staff members who conduct or participate in site visits an opportunity to check field site data management; questions to be investigated
may include whether forms have been stored appropriately and whether the designated key entry person has easy access to the local study computer. The coordinating center staff can check that any required backup diskettes have been created and stored appropriately.

Site visits provide an opportunity to review quality monitoring data related to measurement with the personnel who make the measurements. For example, if measurement of blood pressure is a key aspect of the study protocol, data regarding local digit preferences should be discussed with the individuals who make the measurements. However, care must be taken in these discussions because telling a technician that he or she has an excess number of terminal zeros may lead to a subsequent deficit for that digit. One tactic that has been found useful is to provide annotated summaries of data for discussion. In studies in which signed consent forms are not collected centrally, visits to field sites provide an opportunity to check that an appropriate consent form has been signed and that the date recorded is consistent with study policy, e.g., prior to randomization in a clinical trial.

Site visits provide the coordinating center investigators an opportunity to review the field site source data directly, a process now mandated for multicenter clinical trials sponsored by the NIH and all clinical research sponsored by industry. A key issue is how the field site source data should be checked against the data in the study database. Paper forms may be checked to verify data entry and transmission. However, such checks are not sufficient. The participant's medical record or another original source of data that was transcribed onto a paper form should be compared to the data reported. At a minimum, the dates of appointments or examinations should be confirmed. The details depend on the field site setting, the types of independent records maintained, and the importance of each item to the goals of the study. Other issues to consider are how much data to check for each participant, the sampling scheme to be employed, and whether field site personnel are notified in advance of the visit of specific records to be checked.

At the close of the visit to a field site, following an executive session of the site visit team, a preliminary report on the findings should be provided to the field site investigator and staff. Within a month after the site visit, a draft of the site visit report should be provided to the field site investigators for review and correction of errors of fact. The final version of the report may be provided to the study leadership committee or to the sponsor. The field site staff should be invited to respond in writing to this report. Subsequent visits to the field site should ensure that the problems identified previously have been addressed. The degree to which site visit reports are disseminated among the full group of study investigators depends on the nature of the study, the types of problems discovered, and whether responsibility has been vested in a special field site performance monitoring committee.

Site Visits to Resource Centers

Many study groups rely heavily on the professional qualifications and performance of resource centers. It may be important that the study leadership committee arrange for regular site visits to the study resource centers. The visits serve a number of purposes and may be organized to meet specific study needs. The morale of the resource center investigators and staff may be raised by site visits that confirm the reliance of the study on the center. Site visits to these facilities
Data Quality Assurance

Encourage personnel to produce data of consistently high quality from the inception to the conclusion of the study. Site visitors observe at first hand the procedures and interactions at the resource center and gain a greater appreciation of the technical and logistical challenges to the resource center personnel. Site visitors should judge whether resource center personnel are giving appropriate time and priority to the requirements of the study and whether study resources are sufficient to the work required.

Site visitors typically are selected on the basis of their knowledge of the scientific activities performed at the resource center or because of their role in the study. Expertise external to the group of study investigators may be required for comprehensive site visits to resource centers. Thus, experts can evaluate internal quality assurance and monitoring schemes already in place and use their knowledge to recommend external monitoring schemes so that these two aspects of quality monitoring are complementary.

Site Visits to the Coordinating Center

Coordinating center operations should be evaluated by individuals who have expertise in statistics and data management. Site visit teams may include representatives from the field sites and resource centers who interact with the coordinating center staff. Early in the study, site visitors may wish to review the central security, data management systems, data analysis and reporting plans, documentation and backup plans for loss of data or personnel, and the participant enrollment and treatment assignment system in place. Later in the study, site visitors may concentrate attention on statistical analysis or publication plans. These site visits are important to coordinating center quality monitoring. Canner [44] gave a detailed review of the approach used in one study to monitor the various activities of a coordinating center. Sedransk [45] provided another perspective.

SUMMARY AND CONCLUSIONS

In conclusion, the quality assurance and monitoring program is an integral and continuing part of study operations. A system must be devised and implemented by the coordinating center investigators, with the endorsement of the study leadership and support of the field site and resource center personnel. Proactive mechanisms for promoting high-quality data acquisition and reporting must be implemented. Data quality monitoring must address the entire process by which the data are gathered, transmitted, stored, and analyzed.

Data quality should be monitored continually, with summary reports prepared and distributed to the study leadership. Appropriate training and certification enhance data quality, and site visits allow data collection and storage processes to be observed directly. The quality assurance and monitoring system must be documented. It should be flexible enough so that new means of quality assurance or monitoring can be added when necessary during the course of the study. At the completion of the study, quality monitoring results should be summarized in a final report regarding the level of quality achieved by the study investigators and personnel.

Finally, for a quality assurance and monitoring program to be successful, the coordinating center investigators and personnel must provide prompt feedback
and suggestions for corrective action whenever a data quality problem is discovered. This need can be met only when the coordinating center staff understand data quality goals and are up to date with all phases of data management and reporting. Delays in initiating any stage of data management and quality monitoring may result in uncorrectable data problems. Thus, knowledgeable and efficient coordinating center personnel are essential to achieving good data quality studywide.

REFERENCES


