Promoting Good Clinical Laboratory Practices and Laboratory Accreditation to Support Clinical Trials in Sub-Saharan Africa

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Abstract. Laboratory capacity in the developing world frequently lacks quality management systems (QMS) such as good clinical laboratory practices, proper safety precautions, and adequate facilities; impacting the ability to conduct biomedical research where it is needed most. As the regulatory climate changes globally, higher quality laboratory support is needed to protect study volunteers and to accurately assess biological parameters. The University of Bamako and its partners have undertaken a comprehensive QMS plan to improve quality and productivity using the Clinical and Laboratory Standards Institute standards and guidelines. The clinical laboratory passed the College of American Pathologists inspection in April 2010, and received full accreditation in June 2010. Our efforts to implement high-quality standards have been valuable for evaluating safety and immunogenicity of malaria vaccine candidates in Mali. Other disease-specific research groups in resource-limited settings may benefit by incorporating similar training initiatives, QMS methods, and continual improvement practices to ensure best practices.

INTRODUCTION

The Malaria Research and Training Center (MRTC) clinical laboratory has been in operation since 2001 and is located at the Faculty of Medicine, Pharmacy, and Odonto-Stomatology (FMPOS), at the University of Bamako, Mali. The MRTC clinical laboratory has provided clinical laboratory support for natural history studies based at the university and served as a central laboratory for studies conducted in the peripheral rural field settings. Malaria, leishmaniasis, filariasis, tuberculosis, and other tropical diseases are endemic to the region, and are the focus of a wide array of basic and translational research applications and clinical trials^{1–8} aimed at interventions to curb these diseases. Vaccine and drug studies are conducted under high quality control (QC)/quality assurance (QA) scrutiny, with continual clinical monitoring oversight, to protect study participants, and to ensure that the data generated can support licensure or expanded product indications. In general, candidate products are evaluated first in healthy adults in a non-endemic setting to assess safety and immunogenicity in the case of vaccines; and safety parameters, pharmacokinetics (PK), and pharmacodynamics (PD) in the case of drugs. Successful products may then advance to phase 1b evaluation in healthy adults living in an endemic setting, to first monitor safety parameters, and to measure immunogenicity or PK/PD. Children bear the burden of malaria infection in sub-Saharan Africa, and thus, phase 2 and 3 studies to monitor safety and immunogenicity of candidate products are conducted in this population.

Global harmonization to standardize the conduct of laboratories supporting United States-funded clinical trials are published and implemented by the U.S. Code of Federal Regulations (21 CFR). Guidelines and standards for the conduct of international laboratories that support clinical research are covered under the International Conference on Harmonization-

Good Clinical Practices (ICH-GCP), the U.S. Clinical Laboratory Improvement Act (CLIA), the World Health Organization (WHO)/Research and Training in Tropical Diseases-Good Laboratory Practices (TDR-GLP), by accrediting agencies such as the College of American Pathologists (CAP), and the International Standards Organization standard 15189 (ISO 15189). Much overlap exists between the relevant portions of these guidelines, however when taken together, these serve as the backbone for laboratories supporting clinical trials, termed Good Clinical Laboratory Practices (GCLP). Some of the challenges for implementing quality standards and practices in resource-limited settings (RLS) include staff training and education, physical infrastructure, financial constraints, climate extremes, and geographic isolation. Other challenges include a high rate of background pathology, a lack of normal reference values, a lack of local clinical laboratories, and expertise in pathology that often lead to failure to make accurate diagnoses.⁹ While overcoming these difficulties, the need to establish GCLP to yield quality clinical data to protect study participants remains of the utmost importance. Clinical trials with the U.S. Food and Drug Administration (FDA) oversight must incorporate the appropriate safety and immunogenicity readouts to measure physiologic responses to the candidate product and to guide clinical development. The National Institute of Allergy and Infectious Diseases (NIAID) selected Global Health Partnerships (GHP), of CLSI, as an implementing partner in the quality management systems (QMS) improvement activities at the MRTC. The focus of GHP is the improvement of laboratories in RLS. The GHP relies on international expertise, leadership, hands-on development, and implementation of consensus quality standards for improving such laboratories. The GHP Laboratory Strengthening Program is a structured approach using six core phases that involves assessments, training and education, mentoring and twinning, and continuous quality improvement. Using this approach, the laboratory staff was able to gain technical and operational skills to implement QMS and establish best laboratory practices.

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Early planning, assessments, and infrastructural improvements.

Before beginning the clinical trials at our site, MRTC clinicians and NIAID investigators held a strategic planning meeting to identify clinical laboratory platforms that would provide high-quality readouts to support the studies. During the earlier years of operation, the clinical laboratory staff operated in very constrained quarters, which not only was a safety concern, but a laboratory quality concern by impeding specimen processing and one-directional workflow. Based on assessment by MRTC and NIAID staff, it was determined that a larger space to accommodate adequate spacing between instruments was a priority. This, coupled with more bench top space for processing, would be needed to adequately support clinical trials. Through the positive working relationship between the NIAID and the University of Bamako, a larger space was secured into which the MRTC clinical laboratory expanded, increasing the working area by nearly 6-fold. Laboratory equipment and staff were permanently moved into the new space and used the CLSI standard *Laboratory Design; Approved Guideline—Second Edition* (GP18-A2), a reference to redesign the laboratory layout and workflow, with regards to improving safety and quality. Separate laboratory bays were established to enable one-directional workflow, and to segregate laboratory subspecialties. The following bays were created: Specimen Receiving/Initial Processing, ELISA/Immunology, Hematology, Chemistry, and Microscopy. Robust, validated, FDA-approved clinical laboratory equipment (described later) were selected that would provide accurate readouts yet would be feasible for use in our setting. In RLS, user-friendly laboratory technology and the flexibility to self-repair some equipment is important, because many times local technical expertise is limited. To ensure continuous, stable, power supply, voltage compatibility was important for selection of instrumentation, particularly with blood chemistry and hematology machines. Frequent power surges and outages are commonplace in RLS, and therefore, back-up generators were important, particularly for laser-based instruments such as flow cytometers that can be adversely affected by a mere fraction of a second delay in power supply (Becton Dickinson, personal communication, 2008). The storage conditions for reagents and biospecimens in our studies are very important aspects of the pre-analytical process to ensure quality. Temperatures exceed 40°C in Mali, and it is important to ensure continuous climate control of shipments, transport, and storage of reagents, and of biospecimens in repository storage. All refrigerators, freezers, and laboratory room temperatures are monitored continuously by the viewLinc electronic environmental monitoring system (version 3.5.2, Veriteq, Richmond, BC, Canada). Temperature probes record data every 5 minutes and plot data points longitudinally. In the event any temperature is out of established range, an alert system is activated, notifying designated contacts in Mali and the United States by mobile phone short message service, and e-mail for corrective action. In addition to the viewLinc system monitoring and alarming temperatures for critical platforms, it provides 21 CFR Part 11-compliant records, an FDA requirement for clinical trials. Under these guidelines, applications require electronic records and hard copies signed by trained, approved laboratory staffs that are on the clinical study team. As the electronic records are created, they cannot be modified and provide an audit trail. Hard copies are printed and

signed by the laboratory as per standard operating procedures (SOPs). Hardware for the viewLinc system are calibrated and maintained annually by qualified technical staff. Although technical support for advanced laboratory equipment is typically lacking in RLS, we were able to establish working relationships with local and regional service providers such as that from Becton Dickinson ([BD]; Dakar, Senegal; Accra, Ghana) and Beckman Coulter (Abidjan, Cote d'Ivoire) for hematology equipment, which has been critical in the event of breakdowns or needing technical advice. One of the benefits to the working relationship with BD has been the provision of training on any BD instrument, as well as refresher training, in phlebotomy and GCLP, at NIAID research sites in Mali, Uganda, Tanzania, and India.

Implementing QMS. The CLSI and NIAID had assessed the laboratory with the end goal of it becoming an international center of excellence for supporting clinical trials. Implementing QMS, and therefore the logic of accreditation, would enable the laboratory to be capable of supporting clinical trials of the NIAID, the University of Bamako and its partners, according to FDA criteria. Upon assessment, deficiencies were identified and primarily included: documentation practices and SOPs, one-directional workflow, space utilization and technical expertise in urine sediment and blood differential microscopy. To remedy the deficiencies and move toward accreditation, an action plan was written, containing specifics on intensive hands-on training initiatives followed by competency assessment, facilitated by CLSI consensus documents, companion products, and checklists for implementing QMS. To facilitate the total QMS plan, one delegate for QC and one for biosafety were selected for implementing the activities. Two NIAID-established clinical field sites in rural Mali were selected for our vaccine trials: Bancoumana and Donéguébougou. Although the field site laboratories were not CAP accredited themselves, the laboratories are served by the same staff, and QMS and laboratory subspecialty expertise was implemented at each site for contiguous quality across our program. Instrumentation used to evaluate enrolled subjects included AcT Diff Hematology Analyzer (Beckman Coulter) for clinical hematology, Vitros DT 60 Chemistry System (Ortho-Clinical Diagnostics, Rochester, NY) for blood chemistries, and VersaMax ELISA Microplate Reader (Molecular Devices, Sunnyvale, CA) for serology/immunology. Duplicate clinical hematology instrumentation (AcT Diff) was maintained at the MRTC clinical laboratory and was compared with the instruments at the field sites for precision and accuracy per CAP and CLSI guidelines, and the data maintained longitudinally with Levy-Jennings charts to ensure QA. Concepts of QA/QC, laboratory documentation requirements and safety were introduced to the laboratory in the initial phases of the QMS improvement plan. Identifying local solutions to local problems, such as those in biohazardous waste management, as well as trouble-shooting and problem solving were instrumental to successfully solve problems encountered. Rigorous technical training involved many aspects of the clinical laboratory to include: gross evaluation of specimens, performance of blood cell identification, manual differentials, instrument flagging, estimation of white blood cells (WBC) and platelets, urine sediment microscopy, standardization between technicians, establishing reference intervals, documentation of corrective action and follow-up on QC, as well as CAP proficiency testing (CAP PT). Vehicle

transport of specimens from the field to the laboratory is organized between laboratory staff and drivers who receive training on blood-borne pathogens prevention, and basic chain-of-custody concepts according to our SOPs at the MRTC for specimen transport. Upon reception, specimen evaluations are immediately performed with regard to being under maximum allowable time between collection and processing (e.g., < 4 hours for hematology), and specimen quality (e.g., icterus, clotting, hemolysis, insufficient volume, breakage, spillage, and temperature). Any one of these criteria could deem a specimen as rejected, with prompt notification of the clinical team for recollection and documentation requiring corrective action as required by CAP. Clear delineation of roles in the personnel plan was established to better balance workload and personnel competency into all bench area techniques. As per CAP checklist requirements, all staff was required to receive oral and practical training in each bench area, receive a competency assessment administered by qualified personnel, and to perform each applicable technique annually.

Equipment and assay validation. Validation of laboratory equipment and assays supporting clinical research are critical aspects of the QMS. Laboratories cannot merely rely on the pass/fail of manufacturer supplied controls, but should evaluate each platform on the basis of accuracy, precision, limits of detection (LOD), limits of quantitation (LOQ), linearity, tolerance range, and robustness as per ICH Topic Q2 (R1) 1995 *Validation of Analytical Procedures*, Westgard guidelines and CLSI guidelines.¹⁰ Immunogenicity assays may not have a “gold standard” and frequently are optimized and standardized at each laboratory for evaluation of specific vaccine candidates. Assay optimization and standardization in each setting should follow performance evaluations according to the previously mentioned standards and guidelines. Proficiency, as described later, is of critical importance when implementing an assay in a given setting, as well as transference of the technique to other sites. For the automated hematology and chemistry platforms in our laboratory, LOD, LOQ, linearity, tolerance ranges, and robustness were established by using progressive standard specimen dilution or a commercially available known concentrate specimen. The CLSI standard *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP06-A)* was the reference used for the laboratory SOP.

Local reference ranges and critical values. It has been shown that age, genetics, infections, and nutrition can play a role in baseline hematology parameters.^{10,11} In many RLS, manufacturers’ suggested reference ranges for clinical laboratory results are used for evaluating patients. Use of inaccurate reference ranges can lead to falsely including or excluding patients enrolling in studies, and potentially affect accuracy of evaluating the safety of products in a given population. Several populations have been evaluated in natural history studies and clinical trials at our field sites in Mali; mothers, infants, and young children in natural history studies, healthy adult men and young children in phase 1 and 2 studies. Each representative population may have their own unique reference range for hematology and blood chemistry measures. Because large validation studies to determine local reference ranges are lacking in Mali, we conducted a transference study to establish local reference ranges according to CLSI guidelines.¹⁰ Briefly, blood specimens from 20 volunteers who provided written informed consent were used to establish ranges

for 15–59-year-old healthy males (from phase 1 study screening) and 2–3-year-old healthy children (from phase 2 study screening) whose mothers provided the written informed consent. Healthy volunteers were defined as such by being ambulatory, normal physical examination, and a lack of clinical malaria or other clinical infections. An established reference range, from a similar setting, was then used as a comparator. In our case, we established local reference ranges in comparison to a large reference range study conducted by our colleagues in Uganda.¹¹ Our local reference ranges were then verified after statistical analyses composed of specificity and sensitivity calculations, as described elsewhere.^{10,11} It is possible that reference ranges can apply broadly across similar settings elsewhere; however, transference studies according to CLSI guidelines should be performed for the new population, matched for age and gender. Critical values are posted at each bench station in the clinical laboratory for quick reference by technicians. These are defined as laboratory results that represent a pathophysiologic state at such a deviation from the normal reference values, as to be life threatening or which requires immediate medical intervention by clinical staff. Laboratory staff report test results with critical values by telephone immediately, upon verification of accuracy according to instrument-specific SOPs, to the appropriate clinical investigators in charge of care.

Clinical laboratory subspecialties. Technicians completed rigorous clinical laboratory subspecialty training to support clinical trial readouts. Subspecialties include: manual and automated hematology and biochemistry (for safety parameters), immunology/serology (for immunogenicity measures), and blood smear parasitology (for diagnosis and efficacy outcomes). Subjects enrolled in clinical trials were pre-screened for abnormal chemistry readouts including alanine aminotransferase (ALT), serum creatinine (creat), and abnormal baseline hemoglobin (Hb), absolute leukocyte count, absolute lymphocyte count, and platelet count, all of which are clinically significant and may confound the interpretation of study results. These parameters were subsequently followed to assess safety, with abnormal values recorded as adverse events in the study databases and reported. Malaria blood smear microscopy is a known cause of error in field trials and can be the source of false results and costly delays.^{12,13} At the field sites, blood smear microscopy was performed by certified technicians after completing a rigorous certification process, involving established slide sets composed of over 240 unique slides of known parasite densities and species to determine specificity and sensitivity of the technician compared with a senior, certified reference reader. Certification occurs at a threshold of $\geq 90\%$ specificity and sensitivity, and with demonstrated speciation of *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium vivax*. Staff re-certification occurs every 2 years, or before starting a new study. During the initial training among the MRTC clinical laboratory staff, six of six laboratory staff (100%) passed the certification process. The laboratory staff now serves as a training resource for other researchers in Mali and elsewhere. (Figure 1 illustrates one such certification activity, which the MRTC clinical laboratory staff provided for a research team at the University of Bamako this year.) Our procedure for malaria blood smear microscopy is detailed in a comprehensive SOP. Briefly, the blood slides were made with 10 μ L of EDTA blood made into thick and thin smear preparations

FIGURE 1. Sensitivities and specificities of blood parasite microscopy qualifying staff and sensitivity of seven qualifying microscopists trained by laboratory staff compared with known slide sets of various known parasite densities. REF = reference reader expert.

on the same glass slide, then dried, and fixed and stained with Giemsa. Slides were then read by two blinded, certified microscopists, followed by a third microscopist read if the first two reads were discrepant by the following criteria: 1) discordant positive and negative results by two technicians; 2) 50% discordance at parasitemia of 1–999 parasites/ μ L; or 3) 25% discordance at parasitemia > 1,000 parasites/ μ L. Slides are read systematically, vertically, and horizontally with parasites and leukocytes counted simultaneously using a manual counter. According to our SOP, in phase studies parasite counting proceeds until 300 leukocytes have been counted, the slide is considered negative only after scanning the entire thick smear, and WBC counts are used in the quantification formula to determine parasitemia. Typically in sub-Saharan Africa, high quality clinical microscopy is lacking, exacerbating the conditions of those with underlying pathology, leading to inadequate care.⁹ Upon initial staff assessment, deficiencies in technical expertise were found for clinical microscopy of urine sediment and blood differentials, therefore, substantial training and proficiency testing of the staff was conducted to support our vaccine studies. Urine sediment microscopy data were then collected, which were composed of cellular elements, casts, and crystals, as part of the patient safety profile to screen for acute renal toxicity or other diseases. Blood cell differentials to screen for toxic changes to blood leukocytes, erythrocyte, and platelet abnormalities were also collected as part of the safety profile. The capacity to perform standardized, high quality, on-site microscopic evaluations for patient safety profiles is important not only for guiding the clinical development of our candidate products, but for ensuring proper clinical management of patients by providing results with quick turnaround time.

Enzyme-linked immunosorbent assay (ELISA) optimization and verification. Enzyme-linked immunosorbent assay is

a common platform used to measure antibody responses to malaria vaccine antigens.^{3,4,6,14} Our standardized *Plasmodium falciparum* blood-stage antigen ELISA has been described in detail previously.¹⁴ A Malian technician was trained to perform the ELISA at the NIAID in a course that included theory, good pipetting practices, standardized buffer preparation, the ELISA SOP, data collection and analysis, and documentation. To demonstrate accuracy and precision, the technician had to proficiently perform the ELISA procedure on three consecutive days. Briefly, standards were tested on one plate on Day 1, 49 sera specimens were tested with multiple plate coating antigens on Day 2, and 22 sera at different concentrations were

FIGURE 2. Enzyme-linked immunosorbent assay (ELISA) qualification comparison between trainer and trainee using 19 unique serum specimens and two coating antigens (MSP-1, AMA-1).

TABLE 1
Quality assurance and CAP's external quality assessment schedule

Analysis	Platform	IQA	EQA
Hematology	Automated (AcT Diff)	Manual/calibrators/daily controls	3 × annually
Chemistry	Automated (Vitros)	Calibrators/daily controls	3 × annually
Blood parasites	Microscopy (Manual)	Double reading	3 × annually
Malaria	Immunochromatographic (RDT)	Control bands	3 × annually
Apical Merozoite Antigen-1	ELISA	Control	2 × annually
Merozoite Surface Protein-1	ELISA	Control	2 × annually
Anti-dsDNA	ELISA	Control	3 × annually
Hepatitis B surface antigen	Immunochromatographic (RDT)	Control bands	3 × annually
Anti-hepatitis C	Immunochromatographic (RDT)	Control bands	3 × annually
Pregnancy (hCG)	Immunochromatographic (RDT)	Control bands	2 × annually

IQA = internal quality assurance; EQA = external quality assessment; ELISA = enzyme-linked immunosorbent assay; RDT = rapid diagnostic test.

tested with multiple antigens on Day 3. A plate “passed” QC when the average of four blanks is < 0.100 optical density (OD), R^2 value is > 0.994 for standards run in duplicate, $< 20\%$ coefficient of variation (CV) for all specimens run in triplicate, and there are no more than two outliers among the standards and blanks. The pipetting technique, adherence to the SOP, timing all incubations using a timer for up to six plates, and being able to analyze a complex data set with SoftMax Pro software (version 5.3, Molecular Devices, Sunnyvale, CA) and Microsoft Office Excel 2007 (Microsoft, Redmond, WA) all must be demonstrated.

Overall technician qualification on the ELISA depended upon successful completion of four components: 1) assessment of the pipetting technique by observation and comparing 3 days of ELISA results with that of the trainer, with a “pass” given if at least 80% of the specimens are similar to the qualified trainer’s results, as illustrated in Figure 2 (i.e., the calculated units [in our assay, the dilution to obtain an OD = 1.0] are $< 20\%$ different, for those specimens within the acceptable range of OD = 0.25–2.5; percent difference is $100 \times [\text{Units}_{\text{trainer}} - \text{Units}_{\text{operator}}] / \text{Units}_{\text{trainer}}$); 2) subjective rating of operator performing the entire ELISA procedure with care and with attention to detail; 3) subjective rating of general laboratory technique and safety; and 4) maintaining appropriate records in the laboratory notebook and/or other documents as required by SOP. Additional Malian staff members were trained according to the aforementioned process

either by the first certified technician or by NIAID staff traveling to Mali.

Recertification of the technicians occurs annually or before the ELISA being used in a new study. If the technicians had been performing ELISA routinely, recertification requires 1 day of ELISA results being compared with a trainer’s or previous results on the same specimens and standards. The NIAID and MRTC laboratories share data by posting on our internal SharePoint website for verification between laboratories and continual monitoring. Reagents, such as aliquots of standards, antigens, and antibodies, were prepared in bulk at the NIAID under approved SOPs and shipped frozen to Mali under cold-chain. Pipettes are calibrated annually in the United States and then returned for use in the laboratory in Mali.

Good documentation practices. Documentation is the foundation of GCLP and is critical for ensuring high-quality laboratory data. The CLSI documents were important resources for establishing QMS, using more than 100 of the CLSI standard documents as references for what was required to meet regulatory and accreditation requirements for documentation practices. Training in the technical writing of SOPs, policy manuals, and safety procedures was conducted; documents were translated and back-translated from English to French, the primary language used in the higher education system in Mali. Additionally, a supply chain management and inventory tracking system was implemented in accordance with GCLP guidelines to ensure proper handling of reagents

FIGURE 3. College of American Pathologists (CAP) proficiency testing survey. Key quality indicator tool to monitor CAP proficiency testing surveys from 2007 to 2009 for blood parasites, hematology, and biochemistry.

TABLE 2

Key quality indicators (KQI) for continual improvement	
KQI	Corrective action threshold
EQA	100%
QC (overall)	100%
QC (results out of range)	< 10%
Specimen labeling errors	< 5%
Patient identification errors	< 2%
Specimen rejection	2%
Reporting critical results	98% reported < 1 hr
Corrective action documentation	100%
Maintenance records	100%

KQI = key quality indicator; EQA = external quality assurance, QC = quality control.

and supplies requiring a cold-chain. As part of the CAP checklist requirements, the laboratory developed the Quality Manual, consisting of all laboratory procedures, policies, and key quality indicators (KQI). The KQI serve as a self-monitoring tool to show continual process improvement, and include documentation and graphic depiction of QC errors, CAP PT (Table 1), specimen identification, specimen rejection, test run errors, turnaround time, critical values notification, and safety incidents (Figure 3 and Table 2). All documentation, including SOPs and policies, are reviewed and approved annually by the Laboratory Director.

CAP accreditation. The QMS efforts began in 2007 and with continued dedication from the staff, CAP inspection at the MRTC clinical laboratory was performed in April 2010 (Figure 4). After a thorough inspection by a CAP inspector, the laboratory received three phase II deficiencies. Two of the deficiencies were corrected on-site: addition of a label documenting "open on date" of a reagent, and the addition of parasitemia units (per μL) on one case report form. The third deficiency, which pertained to developing a more stringent KQI monitoring strategy, was addressed within 30 days to CAP. Full accreditation was received in June 2010. The laboratory completed a self-inspection in April 2011 with three phase II deficiencies noted: corrected use of personal protective equipment, late dated approval signature on a laboratory policy, and lack of a documentation of the training administered to drivers who transport specimens. The next full CAP inspection is scheduled for April 2012. The laboratory will need to have demonstrated continuous quality improvement with KQI to the CAP. The financial cost of QMS improvement and CAP accreditation could be considered costly; however, we feel that the cost of a halted or failed clinical trial is much greater and ethically more costly because of potential poor safety precautions, poor data quality, delayed results, inefficient consumption of laboratory consumables, or inadequate maintenance of costly laboratory instruments.

CONCLUSION

The MRTC clinical laboratory has provided a compelling argument to encourage the development of QMS programs encompassing GCLP and laboratory management in an effort to better support clinical trials and field studies. In our RLS, QMS improvement was undertaken using CLSI standards and laboratory advisors, resulting in CAP accreditation of our laboratory at the MRTC in 2010. To our knowledge, this is the first CAP accredited laboratory in West Africa. Quality laboratory testing is an integral part of clinical diagnosis, disease surveillance, and product evaluation. In developed settings, GCLP have proven to be cost-effective, provide reliable and accurate results, contribute to good patient care and safety, and promote a positive attitude toward testing from a patient's perspective. High-quality clinical laboratory capacity in this setting is extremely important for protecting study volunteers. We promptly identified and reported anemia adverse events in our pediatric phase 2 blood-stage malaria vaccine trials.¹⁵ Additionally, ALT caused by hepatitis A, was detected and reported in another phase 1b study in Mali.⁸ It is important for investigators to rely on clinical laboratory-assessed safety parameters, to guard against inadvertently facilitating disease transmission at study facilities and to properly evaluate symptomatic or asymptomatic elevations of ALT levels. Malaria microscopy results vary by microscopist and by level of experience and therefore it is important to establish robust, intensive microscopy training, particularly when involved in malaria vaccine or drug studies where prepatency period, parasite clearance time, or sterile protection may be measures of efficacy. Our efforts show that similar results can be achieved in a much more challenging location evaluating candidate products and in various human populations. Our efforts to implement high quality, standardized, and harmonized ELISA capacity have been valuable for evaluating vaccine candidates in Mali, building technical capacity, and saving in cold-chain shipping costs for analysis in the United States. Other disease-specific investigations may benefit by incorporating similar training initiatives, methods, and QMS to standardize and harmonize assays between the United States and endemic county sites, and between central developed laboratories and field sites. We have expanded the laboratory services to include several diagnostic tests for the screening of hepatitis B and C, double-stranded DNA, and chloroquine, and have plans to add testing for HIV-1/2. The addition of laboratory analytes or immunogenicity assays to the test menu are likely, and may include the addition of a standardized enzyme-linked immune-spot assay (ELISPOT) for enumeration of antigen-specific cellular immune responses to vaccine antigens. Although we have made great strides in improving laboratory performance, regular and on-going

FIGURE 4. Percent College of American Pathologists (CAP) checklist compliance, by self-assessment, April 2008 through April 2010.

advisement is imperative to sustain quality and improvements in capacity—up to and including—the achievement of accreditation. Regular assessment and re-training is necessary to sustain improvements achieved, to enable laboratories to grow, and to ensure quality diagnostics and clinical laboratory monitoring, particularly for laboratories that support clinical trials in RLS. The ability to serve as a center of excellence for training laboratory technologists is an added benefit of our QMS improvement and laboratory accreditation.

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