INTRODUCTION

Estimated global malaria cases have increased from a baseline of 224 million at the inception of the Global Technical Strategy for Malaria 2016–2030 to 241 million cases in 2020.2 Nigeria had 27% of global malaria cases and 32% of global malaria deaths—the highest reported by any country—which also accounted for an estimated 55.2% of malaria cases in West Africa in 2020.2 Nigeria is at the top of the highest burden countries. The high burden-to-high impact initiative helps to refocus attention on the countries with the highest burden of malaria on the basis of response elements, including better guidance, policies and strategies, and coordinated national malaria responses.3

Malaria case management remains a vital component of malaria control strategies, and surveillance is paramount in keeping track of the status of antimalarial drug efficacy by control programs. This helps combat antimalarial drug resistance, a major public health problem, which hinders effective treatment with recommended antimalarial medicines. The WHO recommends a protocol for surveillance of antimalarial therapeutic efficacy in endemic regions and advises that it should be conducted every other year to monitor antimalarial resistance. To allow for the collection of accurate and comparable data on drug resistance, the WHO recommends a systematic and uniform organization of drug efficacy monitoring.4 In Nigeria, the results of the national therapeutic efficacy study (TES) conducted in early 2000 influenced the updating of malaria diagnosis and treatment policy in 2005, when the use of artemisinin-based combination therapy was adopted. Subsequently, four rounds of the TES have been conducted in Nigeria.5 These were individual studies, with sample sizes adequate only for national aggregate data such that, delay arising from any site could delay the availability of the national data. It is noteworthy that the National Malaria Elimination Program (NMEP) and the Nigerian Institute of Medical Research (NIMR) are both domiciled in the Ministry of Health. Coordination of TESs across different sentinel sites was therefore reviewed to take advantage of the specialized capacity of the NIMR to conduct health research and manage these studies. A core team was set up with representation from collaborating partners, including the WHO, the U.S. Presidential Malaria Initiative (PMI) and the Global Fund, with the NIMR to provide oversight for the coordination of the 2018 TES in three sentinel sites in Nigeria. This initiative has resulted in a number of best practices and critical lessons learned. We present the planning, implementation, and coordination process of the TES activities carried out in three ecological zones in Nigeria, with the goal of establishing a sustainable model for routine antimalarial therapeutic efficacy monitoring.

MATERIALS AND METHODS

Planning of the TES. Initiation meeting by the NMEP. At its inception, an initiation meeting was held late in 2017 among the NMEP, partners, and NIMR leadership, led by its director general. The choice of the NIMR as the main public health research institution in Nigeria with a mandate for health research was emphasized along with NIMR technical support to coordinate the 2018 TES, leveraging on research
structures, facilities, and vast experience in the thematic areas was solicited. A follow-up 3-day workshop took place in Abuja in February 2018 to provide a mechanism for management of the TES and to delineate the role of the NMEP, the NIMR, and the partners (Table 1). The participants at the workshop agreed to adopt the WHO TES guidelines, and agreed on the antimalarials to be tested for their efficacy; artemether–lumefantrine (AL), artesunate–amodiaquine (ASAQ), and dihydroartemisinin–piperazine (DHP). It was decided to ensure that a study site be powered to have an adequate sample so that reporting per site could be valid independently. For 2018, the selected sites were Enugu in the east, Kano in the north, and Plateau in the central regions of the country (Figure 1).

The TES core team. The steering committee also known as the TES core team was constituted and chaired by an officer of the WHO Nigeria Country Office. The committee was mandated to select principal investigators (PIs) for each of the sites to work directly under the leadership of the NIMR and to meet every other week to assess progress of the TES, address challenges, and report to the leadership of the NMEP and the NIMR.

Selection of study sites and engagement of site coordinators. The NMEP had their first TES in 1989 (personal communication) and has increased the number of sentinel sites to cover all six geopolitical zones and epidemiological strata in the country, including mangrove, rainforest, Guinea and Sudan savanna, and the sahel. There are currently 14 sentinel sites, three to four of which are prioritized each year for a TES. The factors considered for sentinel site selection was guided by WHO criteria: population density; accessibility to and feasibility of supervision; epidemiology of malaria, especially intensity and seasonality of transmission; and population mobility and migration (Supplemental). Consequently, Agbani in Enugu State, Vom in Plateau State, and Kura in Kano State were selected for the 2018 TES. Principal investigators with experience in malaria research were selected under a subaward with the NIMR. The PIs then selected their site-specific investigating teams, which included two clinicians, two experienced microscopists, three study nurses, one data manager, one pharmacy technician, two laboratory technicians, one social mobilizer, one accountant, and one home visitor. The sites were health facility based, close to communities for easy follow-up. Each PI anchored the TES as provided by a tripartite memorandum of understanding with the NMEP and the NIMR.

Advocacy visits and site assessment. Advocacy to the state Ministry of Health (MoH) was then conducted to kick-start the fieldwork. The NMEP, accompanied by the investigating team members, visited each state MoH to advocate for support of the state government to create awareness and to solicit the buy-in of the state MoH. The Honorable Commissioner of Health and other relevant health personnel were briefed on the purpose of the TES as a national assignment, and the PI and team members were introduced. Thereafter, site assessment was conducted using the site selection checklist provided by the NIMR. Key features examined included Health Management Information System (HMIS) records of malaria prevalence for facilities; clinical and laboratory facilities, including the clinical examination room, general laboratory, pharmacy or medical store, and office space for data management; and availability of transportation for patient follow-up.

Development of standard operating procedures and training activities. A list of 26 standard operating procedures (SOPs) describing defined activities necessary for the successful conduct of the TES was prepared by the NIMR team in consultation with the core team (Supplemental Table 1). Roles identified for the different participating institutions in the Nigerian 2018 TES

<table>
<thead>
<tr>
<th>Institution</th>
<th>Institution type</th>
<th>Role</th>
</tr>
</thead>
</table>
| NMEP        | Ministry of Health | • Involved in the Nigeria TES as coordinating partner.  
• Guide selection of sites.  
• Convene partner meetings.  
• Submit protocols for institutional review board/ethical approval.  
• Lead advocacy visits to participating state.  
• Monitor adherence to study protocols.  
• Update TES data in the National Malaria Data Repository.  
• Grant permission for data use and publications.  
• Ensure results are disseminated, published and used to inform policy.  
• Coordinate TES implementation process.  
• Ensure adherence to study protocols.  
• Develop a framework for fund management and financial accountability.  
• Engage selected participating principal investigators and institutions for execution of the TES at each site  
• Coordinate quality assurance/quality control and molecular analysis.  
• Procure centrally and ensure provision of all items needed for the drug TES, and distribute supplies to sites in a timely manner.  
• Engage services of expert microscopy readers to certify the competency of laboratory scientists participating in the study. |
| NIMR        | Public medical and health research | • Provide technical supervision while chairing technical meetings.  
• Provide data collection tools and template protocols for the TES.  
• Provide quality-assured antimalarial drugs.  
• Mediate decision making in gray areas.  
• Provide support for review meetings. |
| WHO         | United Nations health agency | • Provide support for TES implementation.  
• Provide supplies and technical support. |
| PMI         | Funding/technical partner | • Provide financial support and accountability.  
• Provide capacity building for finance personnel. |
| Global Fund | Funding partner | • Update TES data in the National Malaria Data Repository.  
• Monitor adherence to study protocols.  
• Submit protocols for institutional review board/ethical approval.  
• Provide technical supervision while chairing technical meetings.  
• Provide data collection tools and template protocols for the TES.  
• Provide quality-assured antimalarial drugs.  
• Mediate decision making in gray areas.  
• Provide support for review meetings.  
• Engage services of expert microscopy readers to certify the competency of laboratory scientists participating in the study. |

NIMR = Nigerian Institute of Medical Research; NMEP = National Malaria Elimination Program; PMI = U.S. Presidential Malaria Initiative; TES = therapeutic efficacy study.
Appendix 1). The SOPs were presented during the training workshop along with key performance indicators and checklist guides to be used for monitoring field activities. There were two major training sessions for the TES. The first was orientation training for members of each team (clinicians, microscopists, nurses, and a data clerk) at the NIMR. This was organized by the NIMR from May 21 to 24, 2018, and included didactic lectures and hands-on practical sessions for both the laboratory and data personnel. Two microscopists were assigned to each site and they had 4 additional days of training. Pre- and post-training test results for each of the two microscopists per site on their combined written, picture, and slide tests for detection, species, stage identification, and counting are presented in Figure 2. During the second training session, which occurred at the study sites, a stepdown of the NIMR training was conducted for other members of the team, including alternate members that may have been needed to replace key personnel. This stepdown training was held during the study kickoff (dry run), and was facilitated by team members and visiting monitoring supervisors from the NIMR and the NMEP, who attended or facilitated the first training at the NIMR. An abridged agenda and slides used during the NIMR training were used in the stepdown training at prechosen dates agreed upon for each of the study sites. This activity ensured standardization of training activities across the sites.

Dry run. The 1-day stepdown training session was followed the next day by a 1-day dry run. This was done to test all the processes, with the intention of mitigating against the possibility of any operational failures onsite. The dry run was conducted across the three sites with the support of the NIMR and the NMEP, giving team members the opportunity to put last-minute finishing touches to ensure a smooth take-off and proper running of the study.

Coordination of TES activities. NIMR coordination structure. The NIMR established an in-house TES committee for the coordination of field activities. The committee, led by the head of the Malaria Research Program, reported directly to the director general and the chief executive officer of the NIMR. The committee engaged PIs on a regular basis and ensured that field activities were carried out on schedule. The PIs participated in finalizing the study protocol, implemented the TES study protocol, adapted site SOPs from the core SOPs, and submitted the TES data to the NIMR within the stipulated time frame. The committee also appointed clinical consultants, a WHO-certified microscopist, a data manager, and a report-writing consultant to ensure the quality of the fieldwork and prompt delivery of progress and technical reports. Other activities of the committee included appropriate and timely delivery of study supplies (laboratory and field consumables) to the study sites. Furthermore, data entry on the REDCap® platform, coordination of scheduled
field supervision, monitoring of timelines and deliverables, planning of meetings, and data cleaning, validation, and analysis in consultation with the report-writing consultant were overseen by the committee. To avoid bureaucratic bottlenecks with the PIs’ institutions, each PI was awarded a subcontract with a surety by a senior colleague from the respective institutions, with funds transferred directly to individual PI to cover site-specific expenses and day-to-day running of the study. The sites were provided with a narrative reporting template that was submitted to the director of the NIMR TES by the due date on completion of the study.

Field activities. The study took place at three sites—1) Agbani District Hospital, a 15-bed secondary health facility in Nkanu-west local government area (LGA) in Enugu State, southeastern Nigeria; 2) Vom Christian Hospital, Jos South LGA, Plateau State; and 3) Kura General Hospital in Kura LGA, Kano State—from August to October 2018.

Children 6 months to 8 years with fever (>37.4°C) or a history of fever in the 24 hours preceding presentation at the study clinic, who weighed 5 kg or more, and had a *Plasmodium falciparum* monoinfection with an asexual parasite count ranging from 2,000 to 200,000 parasites/mL of blood as determined by malaria microscopy were recruited. Protocol required that the parents give written informed consent; 7- and 8-year-old children were required to give their assent before they were recruited into the study.

The study design was a two-arm, prospective, open-label randomized study using the modified WHO 28-day follow-up protocol for AL and ASAQ, and 42-day follow-up protocol for DHP. Study participants in Kano and Plateau were randomized to receive AL or ASAQ, whereas participants in Enugu were randomized to receive either AL or DHP.

The sample size was calculated for each treatment arm and drug to allow the efficacy of AL, ASAQ, and DHP to be evaluated independently. As a result, a sample size of 73 participants was required per site to 184. Participants were randomized to treatment arms using block randomization (blocks of four), which was generated centrally at the NIMR and sent to sites in sealed envelopes.

Each site kept four logbooks for screening, recruitment and, drug allocation, parasite count, and drug dispensary/treatment. Clinical information and demographic information were acquired during screening from each potentially recruitable participant, after which rapid diagnostic testing was conducted. Malaria microscopy was conducted for those participants noted as positive by the rapid diagnostic test to obtain counts and identify parasite species. Each study participant with *P. falciparum* only and within recruitable parasitemia range were then randomized to one of the two treatment arms per study site, and listed accordingly in the treatment logbook. Clinical parameters for recruited participants who provided informed consent were documented in the case report form (CRF) along with study medications administered and concomitant drugs (e.g., paracetamol) given during the study or already being taken by participants. Study medications were administered orally by a study nurse or clinician, after which subjects were observed for 1 hour to be sure the medicine was retained. If a participant vomited within 30 minutes of drug administration, the treatment was repeated and the subject was watched for another 30 minutes. If vomiting occurred again within an hour of the first treatment, parenteral therapy was instituted according to national guidelines and the participant was withdrawn from the study, but monitored thereafter for safety. All participants were asked to return on days 1 and 2 to conclude their drug administration. They also all returned on days 3, 7, 14, 21, and 28 for the AL and ASAQ arms. In addition to these days, for the DHP arm, they returned on days 35 and 42. On the day of presentation (day 0), finger-prick blood samples were obtained from all screened participants to make duplicate slides of thick and thin blood film for microscopy, for hemoglobin determination (HaemoCue Hb®, Angelholm, Sweden) and also to make dried blood spots on Whatman 33 filter paper. Similar samples were collected on the follow-up days, and any other day of recurrence of parasitemia, except that only one microscopy slide was made. Patients who failed to report at the clinic for the scheduled visit were visited in their home by community health workers. They were also asked to return to the clinic on any other day, if new concerns arose.

Laboratory processing. One of each day 0 duplicate slide was stained with 10% Giemsa for 15 minutes for quick reads to determine whether parasitemia qualified for recruitment. The other slide was stained with 3% Giemsa for 1 hour and preserved for later reads. Slides were stained with 3% Giemsa for 1 hour on follow-up days. Parasite densities were determined by reading the thick blood smears and counting the number of asexual parasites and the number of leukocytes for 200 high-powered fields. Slides were considered negative if no parasite was detected after reading 200 high-powered fields. The presence of gametocytes was also recorded. Thin blood smears were reviewed for non-*P. falciparum* infections. Two microscopists read all slides independently, and parasite densities were calculated by averaging the two counts. In case of >20% variance in counts between primary and secondary microscopists, a third microscopist read the slide, and the average of the two closest parasite densities was retained.
Dried blood spots collected on day 0 and on the day of parasitological failure were processed in the laboratory as described previously. Recrudescence and reinfection were differentiated by genotyping a panel of 12 neutral microsatellite markers. The fluorescently labeled heminested polymerase chain reaction (PCR) products were separated using an Applied Biosystems 3500 XL series Genetic Analyzer and visualized using the GeneMapper software version 5.0 (Applied Biosystems, Foster City, CA). Data generated were analyzed using Gene mapper and GENALEX 6.5.

Field supervision and monitoring. Monitoring activities were schedule for three visits according to WHO recommendations, including the initiation, interim, and end-line supervision visits.

First, the core team and the NIMR TES focal person visited each site to conduct stepdown training and a dry run, and to verify that the PIs had all the necessary resources for the take-off of the efficacy trial at each site to proceed on schedule. The second visit was made by an expert WHO-certified malaria microscopist, a data manager, and a WHO-certified clinical trial monitor. The WHO-certified microscopist provided technical support to the site microscopist with repeated visits, cross-checking and validating a random selection of 20% of day 3, and 10% of days 0 and 7 Giemsa-stained blood smears against data recorded. All parasitological failure cases for days 3, 7, 14, 21, and 28 were also cross-checked. The data manager reviewed the CRFs and logbooks for completeness of data, and discrepancies and inconsistencies in data collection. The same process was applied to electronic data in the CRFs as captured by REDCap, as well as data captured on the WHO spreadsheet. The WHO-certified external clinical trial monitor ensured protocol compliance, including verifying that all trial documents were accounted for, consents were obtained appropriately, source documents and all records were correct and complete, all required data were in participants’ files, drug doses were recorded, side effects to the medications administered were noted, and reasons for exclusion and loss to follow-up were documented correctly. In addition, the clinical trial monitor also looked for breaches in risk management in the TES, errors and loss of data resulting from inadequate backup procedures, and noncompliance with protocol, ethics, and safety and security measures. The third visit was a wrap-up/ closeout visit.

Each of the visits was conducted with the aid of a key performance indicator review form and consisted of a 2-day observation and interaction period with the site team, and a debriefing meeting with the team PI at the conclusion of the visit. All field visit reports were submitted to the NIMR TES secretariat for appropriate action during review meetings.

Review meetings. There were two types of review meetings. Two virtual meetings were held with each of three different cadres of personnel: PIs, laboratory works, and data managers. These meetings provided an opportunity for cadres from different sites to share their experiences, challenges, and burning issues that needed to be addressed. There were also two in-person review meetings organized by the NIMR. The NIMR TES focal person compiled monitoring field reports for the review meetings held by the tripartite TES core team. The core team performed a risk assessment, devised solutions to problems encountered by the investigating teams as reported by the monitors and in a feedback mechanism, and developed means to effect correction to noncompliant events reported by the monitors as needed. If a visit showed many deficiencies (protocol violation, poor slide quality and microscopy reading), additional follow-up visits were planned to assist and effect correct protocol execution.

Data collation and report writing. All information on study participants was recorded in their respective physical CRFs and entered daily into the REDCap equivalent on the NIMR server. REDCap ensured real-time monitoring of data from the study sites centrally at the NIMR. Patient information and other relevant data were also entered onto a WHO spreadsheet provided for TESs. Primary end points were cumulative PCR-corrected analysis determined using the Kaplan-Meier estimator of the survival function for each arm. This was calculated for each treatment arm and included data from

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Types of training and participants for the 2018 TES in Nigeria</th>
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</thead>
<tbody>
<tr>
<td>Type of training</td>
<td>Training content</td>
</tr>
<tr>
<td>TES protocol review</td>
<td>• Ethical issues: protecting human research participants • Randomization, screening, enrollment, and follow-up procedures • Efficacy and safety end points • Data collection tools and analysis • Adverse events documentation • Drugs logistics</td>
</tr>
<tr>
<td>Patient management</td>
<td>• Antimalarial drug administration • Physical examination and follow-up of patients • Assessment and reporting of adverse events and serious adverse event</td>
</tr>
<tr>
<td>Malaria microscopy</td>
<td>• Qualities of a good microscopist • Slide preparation and staining • Malaria parasite detection • Malaria parasite species identification • Methods used to count parasites • Data capture and analysis • Use of the WHO spreadsheet • Application of REDCap</td>
</tr>
<tr>
<td>Data management</td>
<td></td>
</tr>
</tbody>
</table>

DPRS = Department of Research Planning and Statistics; NIMR = Nigerian Institute of Medical Research; NMEP = National Malaria Elimination Program; PMI = U.S. Presidential Malaria Initiative; TES = therapeutic efficacy study.
patients lost to follow-up or excluded from the per-protocol analysis resulting from protocol violation up until the final visit before exclusion or loss to follow-up. P values corresponded to the significance of differences in time to failure for the different sites from the log rank test. Secondary end points included PCR-corrected and uncorrected estimates of efficacy of the proportion of patients with early treatment failure, late clinical failure, late parasitological failure, or an adequate clinical and parasitological response recorded per protocol at the study end point.8

LESSONS LEARNED

In Nigeria, the NMEP has the mandate to formulate policy and guidelines, coordinate and support implementing partners, and provide oversight on malaria control activities. A TES is only one of the major activities of the NMEP, and this exercise has facilitated collaboration among stakeholders, enabling a more coordinated and efficient approach to achieving the objectives of a TES. Therapeutic efficacy studies are technically demanding, and this coordinated prototype reduces the burden on individual sites by sharing study costs and responsibilities among stakeholders. It has further provided a platform for benefiting from harnessed resources for training and capacity building.

Adequate training was provided to all TES personnel, with more intensive training provided to microscopists (Table 2). The first and second microscopists for each site showed overall improvement in post-tests over their pretests, improving their competence marginally. This was evident by the minimal discordant rate observed by the quality assurance models; sharing of expertise and best practices among sites assisted in achieving robust, reliable results that can be generalized, because the same protocol and comprehensive list of 26 SOPs (Supplemental) were applied to complete the TES at the different sites with different malaria endemicity in the country. Standardized data collection and analysis methods implemented across sites were coordinated, managed, and analyzed centrally. Funding made available directly to PIs guaranteed by respected sureties in their institutions ensured lack of delays in conducting studies resulting from lack of funds. Last, errors encountered in the execution of the study will not be replicated in the future because these were learning points for the stakeholders.

All sites concluded recruitment and follow-up of participants in the allotted 3-month timeline for the study at each site. Study results were promptly disseminated in the year following the study. Based on evidence from this study, DHF was promptly included as a treatment option in the policy guideline for malaria diagnosis and treatment in Nigeria.

<table>
<thead>
<tr>
<th>Enrolment period</th>
<th>Slides examined, n</th>
<th>Average discordance rate across sites, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td>100</td>
<td>2.9</td>
</tr>
<tr>
<td>Month 2</td>
<td>200</td>
<td>2.5</td>
</tr>
<tr>
<td>Month 3</td>
<td>200</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>–</td>
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</table>

CONCLUSION

This article has described the apex health research institute in-country (the NIMR), in collaboration with the NMEP, successfully establishing a platform for the coordination of the 2018 TES in Nigeria. Strategies effected a synergy of efforts from the researchers, funding and technical partners, politicians and policymakers, resulting in an operational model for timely delivery and sustainability of future TES coordination in Nigeria that can be adopted by other endemic countries.

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Disclosure: The study protocol was approved by the Nigerian National Health Research Ethics Committee (NHREC). Additional ethical clearance was obtained from the PI’s host institutional review committees; social approvals were obtained from the states. Written informed consent was obtained from the parents and guardians of enlisted participants, and were also obtained 7- and 8-year-old children. All core team members, monitors, and investigators in the TES were required to take the online course, Protection of Human Research Participants, and submit a clearance certificate to the TES director at the NIMR. This also formed part of the documents and requirements for ethical approval at the NHREC.

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REFERENCES


