Implementing a quality management system using good clinical laboratory practice guidelines at KEMRI-CMR to support medical research [version 2; peer review: 2 approved]

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Abstract

Background: Good Clinical Laboratory Practice (GCLP) is a standard that helps ensure the quality and reliability of research data through principles of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The implementation of GCLP includes careful documentation of procedures, competencies and safety measures. Implementation of GCLP is influenced by existing resources and quality systems, thus laboratories in low- and middle-income countries may face additional challenges.

Methods: This paper describes implementation of GCLP at the Kenya Medical Research Institute-Center for Microbiology Research (KEMRI-CMR) as part of a quality system to support medical research. This study employed assessment, twinning (institutional mentorship) model, conducting relevant training workshops and Kaizen 5S approaches to implement an effective quality management system using GCLP standard. This was achieved through a collaboration between the KEMRI/Wellcome Trust Research Programme (KWTRP) and KEMRI-CMR. The aim was compliance and continuous monitoring to meet international GCLP standards in a way that could be replicated in other research organizations.

Results: Following a baseline assessment in March 2017, training, mentorship and a cycle of quality audit and corrective action using a Kaizen 5S approach (sorting, setting in order, shining, standardizing and sustaining) was established. Laboratory personnel were trained in writing standard operating procedures and analytical plans, microbiological techniques, and good documentation practice. Mid-term and exit assessments demonstrated significant declines in non-
conformances across all GCLP elements. KEMRI-CMR achieved GCLP accreditation in May 2018 by Qualogy Ltd (UK).

**Conclusions:** Involving all the laboratory personnel in implementation of quality management system processes is critical to success. An institutional mentorship (twinning) approach shows potential for future collaborations between accredited and non-accredited organizations to accelerate the implementation of high-quality management systems and continuous improvement.

**Keywords**
Good Clinical Laboratory Practice, Quality Assurance, Quality system, medical research, quality management system.
Introduction

Medical laboratories play an important role in disease diagnos- is, treatment guidance, drug resistance monitoring and surveil- lance of diseases of public health interest (Gershy & Rotz, 2010; Martin et al., 2005; Wians, 2009). According to Nkengasong (2010), 20% of clinical trials in Africa have been suspended due to serious Good Clinical Practice (GCP) breaches, which mainly impact on participants’ safety and reliability of the data generated. This can be addressed by implementing integrated, tiered and harmonized operations, and a well-functioning laboratory quality system (Nkengasong, 2010). Moreover, the emergence of the recent Ebola virus disease epidemic in West Africa in 2015 emphasized the need to rapidly develop better laboratory systems that will foster increased accuracy and reliability of the data generated (Gostin et al., 2015; Heymann et al., 2015), which have often been the traditional meaning of quality in medical laboratories (Harteloh, 2004). In medical research, it is imperative to note that generation of reproducible and re-constructible results can be achieved when the clinical laboratory operates under a robust and mature quality management system (QMS) that complies with the GCLP standards, thus providing an excellent path for the success of conducting medical research.

What is the GCLP standard?

GCLP is a standard that supports both the research and clini- cal aspects of Good Laboratory Practice (Ezzelle et al., 2008). It was developed to support and strengthen research laborato- ries performing human clinical trials and provides a platform for monitoring the global conduct of clinical laboratory work performed under harmonized operations (Marcella et al., 2009). This standard was developed by merging the principles of Good Clinical Practice and Good Laboratory Practice in conjunc- tion with the regulatory authorities and accrediting bodies, and was the same approach adopted by the British Association of Research Quality Assurance (BARQA) to develop the Good Clinical Laboratory Practice standard (Stiles et al., 2003). The GCLP standard focusses on the building blocks of a quality system, which includes assessments, assay validation and verifica- tion, training of personnel involved in the research, organization and personnel, specimen management, laboratory equipment, reagents, records and reports, laboratory safety, quality control and proficiency testing programmes, laboratory informa- tion systems, and the overall quality management plan of the laboratory (Marcella et al., 2009). The expectation of implement- ing the GCLP quality system is that data of high quality will be generated when the laboratory complies to the GCLP guide- lines. In addition, it provides guidance on the development of a quality system that ensures integrity, validity and reliability of clinical trials data.

The Kenya Medical Research Institute – Centre for Microbiology and Research (KEMRI-CMR)

The Kenya Medical Research Institute (KEMRI) is a Kenyan government parastatal that regulates and conducts research in human health with the aim of improving wellbeing, and the for- mulation and implementation of policy formulation, while collaborating with other global research organizations. It has its centers widely spread around the country that perform research focusing on different fields (KEMRI, 2018). Even though KEMRI is the leading medical research organization in the coun- try, some of its centers do not have up-to-date quality systems in place to support medical research. There is an urgent need to establish an effective quality management system using GCLP guidelines to support clinical trials and other studies.

KEMRI-CMR, based in Nairobi, is one of the oldest KEMRI research centers. Research has focused predominantly on tra- ditional and molecular characterization of enteric pathogens in communities and in hospital attendees, in addition to their transmission, virulence and antimicrobial profiles. To promote and support its research activities, KEMRI-CMR engaged its sis- ter organization KEMRI-Wellcome Trust Research Programme (KWTRP), to assist in the development of a quality system using GCLP guidelines. The KWTRP, based in Kilifi, has been actively undertaking microbiological research since 1992, pre- dominantly on invasive bacterial infections in children, including surveillance and antimicrobial treatment trials. KWTRP has been GCLP-accredited since 2007. Here, we describe how the quality management system was implemented at KEMRI-CMR using GCLP guidelines to support medical microbiological research with the goal of gaining recognition of the quality of their management system by attaining GCLP accreditation. The GCLP standards developed by BARQA was selected for this project because the mentor laboratory (KWTRP) had been accredited using this GCLP standard and it would be easier to replicate the same in the mentee laboratory (KEMRI-CMR).

Methods

Methodology used

This study employed assessment, twinning (institutional mentorship) model (Makokha et al., 2014), and conducting train- ing workshops to build a competent laboratory workforce and
utilizing Kaizen 5S approaches to implement an effective quality management system using GCLP standards (Stiles et al., 2003).

Baseline, mid-term and exit assessments
The QMS implementation progress was evaluated by performing assessments using a GCLP accreditation audit checklist, developed by Qualogy Ltd UK (Qualogy, 2018) (Table 1). This checklist consists of 12 sections of 15 questions, which covered the entire quality system elements defined by GCLP guidelines obtained from Qualogy, Ltd, and had a total score of 270 points. The audit checklist questions were asked by the mentors from KWTRP to the auditees (laboratory staff from KEMRI-CMR).

In total, three assessments were performed throughout the process to establish the laboratory’s performance and progress towards GCLP accreditation, as well as determining any remaining gaps. In March 2017, a week after the initial engagement, a baseline assessment was conducted at KEMRI-CMR, using the GCLP accreditation checklist (Qualogy, 2018). This assessment was performed by the laboratory quality officer (mentor, from KWTRP and its results provided the basis for developing KEMRI-CMR-specific actions. A mid-term assessment was conducted 3 months (June 2017) after the baseline assessment, following a GCLP training workshop and corresponding GCLP assignment elements assessed using the GCLP accreditation checklist developed by the mentor laboratory (KWTRP). The exit assessment was performed three months (October 2017) after the mid-term assessment by an independent auditor from KWTRP who was not involved in the training, and was the final assessment in readiness for the GCLP accreditation audit by Qualogy UK Ltd.

Twinning (institutional mentorship) model
The twinning (institutional mentorship) model was also employed to implement QMS (Makokha et al., 2014). This was conducted during the period of May-June 2018. Using this model, a total of 24 laboratory staff from the mentee laboratory (KEMRI-CMR) were paired to the mentor laboratory (KWTRP) to learn and subsequently implement GCLP processes in their laboratory upon their return. A total of 12 laboratory staff from KEMRI-CMR were twinned with staff from KWTRP in the month of May 2017 and another 12 laboratory staff twinned in June 2017. To facilitate the twinning relationship, the laboratory quality officer (mentor) spent 1 week at the mentee laboratory to provide mentorship and coaching for the GCLP process.

Conducting KEMRI-CMR laboratory training
The QMS mandatory training and other relevant training workshops were identified with the aim of strengthening knowledge, skills and abilities, and changing attitudes. The training was mainly delivered through workshops, coaching, and visits to KWTRP for a period of 2 weeks. Training was delivered by the lead mentor and two co-mentors. Subjects of the training sessions, alongside the trainer and the dates of training, are listed in Table 2. Once these sessions were complete, staff were assigned a specific area to implement when they go back to their laboratory. Kaizen 5S (Kobayashi, 2005) was implemented to establish the foundation for continuity of quality management system at KEMRI-CMR.

Data analysis
Data from the three assessments, training conducted were analyzed using Microsoft Excel and presented in tables and figures to extract their useful meaning.

Results
KEMRI-CMR performance
The KEMRI-CMR laboratory assessment performance is summarized in Figure 1 and Figure 2. All 12 elements in the GCLP accreditation checklist were improved at successive assessments (Figure 1 and Figure 2). The most improved element was the facilities and safety element, followed by quality control, external

<table>
<thead>
<tr>
<th>GCLP Elements</th>
<th>Total points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 1: Documents, records and reports</td>
<td>30</td>
</tr>
<tr>
<td>Section 2: Trial samples and management</td>
<td>14</td>
</tr>
<tr>
<td>Section 3: Organization and personnel</td>
<td>22</td>
</tr>
<tr>
<td>Section 4: Reporting of results</td>
<td>10</td>
</tr>
<tr>
<td>Section 5: Equipment, materials and reagents</td>
<td>33</td>
</tr>
<tr>
<td>Section 6: Internal audits and corrective action</td>
<td>15</td>
</tr>
<tr>
<td>Section 7: Retention and archiving of records</td>
<td>32</td>
</tr>
<tr>
<td>Section 8: Quality control and external quality assessment</td>
<td>21</td>
</tr>
<tr>
<td>Section 9: Planning of the work &amp; sub-contracting</td>
<td>17</td>
</tr>
<tr>
<td>Section 10: Conduct of work</td>
<td>24</td>
</tr>
<tr>
<td>Section 11: Confidentiality, blinding and patient safety</td>
<td>12</td>
</tr>
<tr>
<td>Section 12: Facilities and safety</td>
<td>40</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>270</strong></td>
</tr>
</tbody>
</table>

Table 1. Quality management system elements and their scores on the good clinical and laboratory practice (GCLP) accreditation checklist. Source: Stiles et al., 2003.
Table 2. Training sessions given to staff.

<table>
<thead>
<tr>
<th>Training</th>
<th>No. of staff trained</th>
<th>Trainers</th>
<th>Training dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological techniques</td>
<td>25</td>
<td>Lead mentor &amp; co-mentors</td>
<td>25–28 April 2017</td>
</tr>
<tr>
<td>KWTRP Exchange visits</td>
<td>24</td>
<td>Attached to section heads of KWTRP</td>
<td>1st group: 2–12 May 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2nd group: 19–30 June 2017</td>
</tr>
<tr>
<td>Good documentation Practice</td>
<td>25</td>
<td>Lead mentor</td>
<td>16 June 2017</td>
</tr>
<tr>
<td>SOP writing training</td>
<td>25</td>
<td>Lead mentor</td>
<td>7–9 June 2017</td>
</tr>
<tr>
<td>Improvement projects and Quality Indicator training</td>
<td>10</td>
<td>Lead mentor</td>
<td>6–7 July 2017</td>
</tr>
<tr>
<td>Confidentiality, blinding and patient safety monitoring</td>
<td>12</td>
<td>Lead mentor (myself) &amp; co-mentors (Joseph &amp; Robert)</td>
<td>20–21 July 2017</td>
</tr>
<tr>
<td>Method and equipment validation</td>
<td>10</td>
<td>Lead mentor</td>
<td>24–25 August 2017</td>
</tr>
<tr>
<td>Analytical plan writing training</td>
<td>26</td>
<td>Lead mentor</td>
<td>6–8 September 2017</td>
</tr>
<tr>
<td>Internal audits</td>
<td>6</td>
<td>Lead mentor</td>
<td>8–11 August 2017</td>
</tr>
<tr>
<td>Basic GCLP training</td>
<td>30</td>
<td>Lead mentor</td>
<td>11–14 April 2017</td>
</tr>
</tbody>
</table>

KWTRP, KEMRI-Wellcome Trust Research Programme; SOP, standard operating practice; GCLP, good clinical and laboratory practice.

Figure 1. Comparison between baseline and mid-term assessments. KEMRI-CMR, Kenya Medical Research Institute – Centre for Microbiology Research.

quality assessment and equipment, reagents and materials elements. The laboratory performed less well in the reporting of results, conduct of the work, internal quality audits, corrective action, planning of the work and sub-contracting GCLP elements.

A total of 162 non-conformances arose from the baseline assessment (100 major findings and 62 minor findings); 62 non-conformances arose in the mid-term assessment (42 major findings & 20 minor findings); and 32 non-conformances arose in the final exit assessment (20 major findings & 12 minor findings). The decrease in major and minor non-conformities indicated progress in resolving queries and implementing corrective action (Figure 3).

KEMRI-CMR laboratory training

To build a competent and skilled laboratory workforce in the KEMRI-CMR laboratory, a total of 10 training sessions and workshops were conducted between April 2017 and September 2017. These trainings aimed to strengthen the quality
Figure 2. Kenya Medical Research Institute – Centre for Microbiology Research (KEMRI-CMR) performance comparison of the 12 good clinical and laboratory practice elements between the three assessments.

Figure 3. Non-conformance analysis at the baseline, midterm and exit assessments.

of services and systems in KEMRI-CMR. GCLP training was provided (Table 2) to twenty-five laboratory personnel. In total, 9 of the 10 conducted trainings were done onsite to allow more staff to attend and to reduce costs. All 25 (100%) laboratory personnel were trained in writing SOPs and analytical plans, microbiological techniques, and good documentation practice (Figure 4).

To decongest the laboratory and enhance efficient workflow for productivity management, principles of Kaizen 5S were adopted: equipment was rearranged for optimal workflow while removing obsolete and un-wanted materials from the laboratory. Equipment that was close to sinks was removed and placed separately as per the specimen workflow. The removal of obsolete equipment and old records that consumed considerable space...
enhanced the efficiency of the workflow. Documentation was done before and after the Kaizen 5S for comparison. KEMRI-CMR achieved a GCLP accreditation in May 2018 by Qualogy Ltd (UK).

Discussion

The results from the baseline to exit GCLP assessments showed the greatest improvements in facilities and safety element (21 points), followed by quality control and external quality assessment (15 points) and equipment, reagents and materials elements (14 points). The areas that were more challenging to improve were internal quality audits and corrective action (an improvement of 6 points), conduct of work (an improvement of 4 points) reporting of results and planning of the work (improvement of 3 points). The slower progress of these GCLP elements were attributed to unfamiliarity with the internal audit system by the laboratory staff, characterized by inadequate follow-up of the internal audit findings and insufficient documentation of corrective actions (management reviews as described by ISO 15189 standards) described by Maina et al. (2014) as Factor X. Despite the less strong performance in these three GCLP elements, the KEMRI-CMR laboratory QMS performance improved steadily from 10.7% at baseline assessment to successfully achieving 76.3% at the exit assessment.

The improvement of KEMRI-CMR’s laboratory QMS performance was in a large part due to staff’s positive attitude and commitment to work, and continued senior management support. Despite an initial opposition to change, there was a great enthusiasm to continue improving laboratory performance as observed in the final assessment results. Clearly identifying gaps and involving all staff in frank discussions about their solutions was key to achieving this. The foundation of best practice, and a ‘quality culture’ were established through the exchange visits, conducting trainings, mentors’ assistance coupled with managerial commitment. This reflects reports from other institutions implementing quality management process (Andiric & Massambu, 2014).

The implementation of Kaizen 5S greatly improved the laboratory’s workflow and space. The results indicate that there is a strong foundation for continuity of the quality management system at KEMRI-CMR (Khamis et al., 2009). The entire laboratory was physically re-organized by placing the equipment strategically to improve efficiency and enhance safety. The entire Kaizen 5S methodology for this study provided the best platform to accelerate the process of quality improvement process at KEMRI-CMR.

Engaging the management team of KEMRI-CMR through the leadership of the Centre Director was crucial in securing financial support for renovating the laboratory and providing adequate human resources for the quality implementation process. His open-door policy style of management and having frequent

Figure 4. Number of staff trained in the indicated area during the mentorship period. SOP, standard operating practice; GCLP, good clinical and laboratory practice.
discussions with the laboratory staff and the mentors made him clearly understand the significance of implementing a quality management system. Moreover, the formation of the fortnightly laboratory meetings to provide reports, feedback and recommendations accelerated the implementation of the quality management system using GCLP guidelines.

Conducting training on-site has also been shown to be an improvement factor during QMS implementation (Nkwawir et al., 2014). The trainings conducted at KEMRI-CMR laboratory coupled with a MN and institutional mentorship approach (Makokha et al., 2014) helped the mentor to more fully understand the operational functionality of the mentee laboratory by participating in the laboratory activities, providing hands-on trainings and guidance regarding what aspects of the quality management system to be implemented.

In addition, the continued presence of the mentors at the KEMRI-CMR laboratory during the entire QMS implementation period helped to design specific activities tailored in their approach to assisting laboratory improvements, developing a working culture that emphasizes quality and a sustainable QMS as previously implemented by other organizations during their QMS journey (Nkwawir et al., 2014). Only one training (GCLP training) was attended by staff drawn from other departments. This was to enhance their understanding of the GCLP concept so that they could support the laboratory’s journey of implementing the quality management system. The experience at KEMRI-CMR during the quality implementation process clearly reveals what other laboratories that fully commit their concerted effort can achieve in implementing a quality improvement process.

Conclusions
Implementing an efficient and effective quality management system requires a system-wise approach and strong teamwork to ensure that set goals and objectives are realized. Compliance with GCLP standards, coupled with periodic audits/assessments, will help ensure that clinical research and trials performed at KEMRI-CMR meets international standards. Involving all laboratory personnel in the implementation of a QMS process is critical to its success. The use of an institutional mentorship (twinning) approach also shows the potential for future collaborations between accredited and non-accredited organizations and can be used to accelerate the implementation of a good QMS and continuous improvement.

Data availability
Data generated in the present study are available on figshare, DOI: https://doi.org/10.6084/m9.figshare.7200707 (Gumba, 2018).

Grant information
This study was funded by the Wellcome Trust (203077).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.


Open Peer Review

Current Peer Review Status: ✔️ ✔️

Version 1

Reviewer Report 19 December 2018

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 Paramesh Chetty
Human Immunology Laboratory (HIL), International AIDS Vaccine Initiative (IAVI), London, UK

1. The author mentions that GCLP is a standard when it is a guideline. Need to give some background as to why BARQA GCLP guideline was adopted.

2. Give more mention on resources as to implement the GCLP guidelines for GCLP compliance as mentioned it ensures all documentation are in place that must be followed to ensure GCLP compliance. This requires basic resources, unless the facility is relatively under-staffed.

3. Elaborate on the baseline assessment and disaggregate the non-conformances to the categories or topics of the training offered. This will give a clearer view of what non-conformances were resolved at exit visit and what was not.

4. There must be more background on why the Kaizen 5S approach was used and if this approach was also used at the KEMRI-Kilifi facility and proved to be successful.

5. Table 1: Give the details of the sections and the total points, but not more information on how the point scoring worked and was it related to findings. More information required on the types of findings (Differentiate between major and minor and advise what is acceptable to be GCLP compliant). Do a comparison between baseline, mid-term and exit audit against the findings to conclude if the facility is GCLP compliant as there are still higher major findings than minor at exit audit.

6. Need to be clearer in conclusion as to the outcome and impact and not only the output (e.g. Numbers only of those staff trained and non-conformances identified). Even though the non-compliances were reduced, did the non-conformances at the exit visit still impact the GCLP compliance of the site?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

**Competing Interests:** No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 18 December 2018

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Robert Njuguna
Kenya Accreditation Service (KENAS), Nairobi, Kenya

1. The problem statement (last paragraph under the background) needs to come out clearly to state how existing resources and quality systems impact GCLP implementation. Do we want others to learn from us how to implement QMS and better use of resources?

2. First paragraph under methods "This paper describes implementation of Good Clinical Laboratory Practice (GCLP) at the Kenya Medical Research Institute-Center for Microbiology Research (KEMRI-CMR) as part of a quality system to support medical research" fits well with background. I suggest it moves to the background in a summarized form.

3. There is no need to write GCLP in full since it’s already under the background. It’s enough to just abbreviate in all subsequent paragraphs.

4. "The aim was compliance and continuous monitoring to meet international GCLP standards in a way that could be replicated in other research organizations". I suggest the aims go
under the background.

5. The author needs to state what the outcome of the baseline assessment was so that this can be compared with the mid-term and exit assessment in terms of nonconformities etc. in the results section. Instead the author talks of what was done following the baseline assessment. This can be covered under the discussion section.

6. No need to mention the names/initials of mentors under Baseline, mid-term and exit assessments section. This may be included as roles for each author at the end of the manuscript.

7. Fig. 1 seems to be communicating information already covered in Fig. 2. I suggest removal of Fig. 1.

8. The first part of conclusion “involving staff in the implementation of QMS” is not very well supported by the results obtained in this study. Mentorship, trainings, active corrective actions following assessments are well supported by the results obtained.

9. “There was also slower progress in reporting of the results, planning of the work” this statement seems to be a repetition in the first paragraph of the discussion.

10. There seems to be minimal improvement in the QSC on ‘conduct of work’ yet this is not mentioned in the discussion.

11. In paragraph 4 of discussion the author seems to be focusing on personalities "His Open door" rather than position e.g. management/leadership.

12. In paragraph four of discussion fortnightly meetings are mentioned but this is not mentioned in methods. Consider having it in methods as part of the strategy that brought success. Also in the results in terms of how many meetings were held in this period compared to previously. This should support the conclusion that involvement of staff was instrumental in QMS implementation.

13. Paragraph five of the discussion need to specify which was mandatory training and which was supplemental training.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes
Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

*Competing Interests:* No competing interests were disclosed.

*Reviewer Expertise:* Quality management systems

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Comments on this article**

Version 1

Author Response 13 Jun 2019

**Horace Gumba,** KEMRI-Wellcome Trust Research Programe, Kilifi, Kenya

All the comments and suggestions from the reviewers have been implemented in the revised version of this paper.

*Competing Interests:* No