

# COMREC PROGRESS REPORT FORM

COMREC Use Only  
Type of Review: \_\_\_\_\_

## The College of Medicine Research and Ethics Committee College of Medicine, Private Bag 360, Chichiri

### Progress Report

1. Title of Study

Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperazine administered as dihydroartemisinin-piperazine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study.

2. COMREC #

P.07/19/2746

3. Start Date

2	3	S	E	P	2	0	1	9
D	D	M	M	M	Y	Y	Y	Y

4. COMREC Expiration Date

2	2	S	E	P	2	0	2	0
D	D	M	M	M	Y	Y	Y	Y

5. Anticipated End Date

3	1	J	U	L	2	0	2	0
D	D	M	M	M	Y	Y	Y	Y

6. Principal Investigator

DR. CLIFFFORD GEORGE BANDA

7. Co-Investigator(s)

1. Prof Gary Maartens, MBChB, MMed, FCP, Professor of Clinical Pharmacology,
2. Prof Victor Mwapasa, MBBS, MPH, PhD, Professor of Epidemiology and Public Health
3. Dr Mwayiwawo Madanitsa, MD, PhD,

8. Host Department

Public Health Department, College of Medicine

9. Phone No:

+265 994717867

Email:

[cgbanda@mlw.mw](mailto:cgbanda@mlw.mw)

10. Student Investigator(s)

NOT APPLICABLE

11. Name of sponsor<sup>1</sup> Liverpool School of Tropical Medicine (LSTM); Pembroke Place,  
Liverpool L3 5QA, UK, Phone: +44 0151 7053794; Email:  
lstmgov@lstmed.ac.uk

12. Name of funder<sup>2</sup>: The European and Developing Countries Clinical Trials Partnership  
(EDCTP); Career Development Fellowship Scheme 2017

13. Amount of funding (*please indicate the currency*): 54, 279 €

14. Amount of CoM overhead fees CoM (10%) in the original  
approved budget: 10, 856 €

15. Amount of overhead fees paid to CoM (10%) 10, 856 €

16. Amount of CoM overhead fees outstanding (if any) 0

17. If CoM overhead fees are outstanding, provide an explanation why the fee is outstanding in the space below;

N/A. 25% overheads paid to COM as part of funder (EDCTP) requirement.

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<sup>1</sup> A Sponsor is either an individual, organization or other legal entity which takes responsibility for initiating, managing and/or financing a study.

<sup>2</sup> A funder is an institution, organization or company that simply provides funding, but does not take up the responsibility of initiating or managing the study.

## EXECUTIVE SUMMARY OF THE PROJECT

**In the space below, provide a brief summary of the progress and results obtained to date (Please explain any changes made or are being planned for approval as indicated in C4)**

### Recruitment:

- The study got approval from the local ethics committee (COMREC) on 23 September 2019.
- The study site was activated on 28 November 2019 and screening started on 30 November 2019. A total of 20 participants were screened and 16 were enrolled into the study. 2 participants were withdrawn (as described in section 3 above)
- The 17<sup>th</sup> participant was not enrolled into the as a COVID-19 precautionary measure to minimise putting potential participants at risk of COVID-19 exposure. This decision was arrived at a time when the pandemic was declared and there was emphasis from the local ethics committee to scale down research activities in Malawi, observe social distancing and limit study participant visits to essential safety visit.

### Follow-up and data collection:

- All enrolled 16 participants have completed follow up and exited the study. The last participant exited the study on 10<sup>th</sup> July 2020.
- There were no major protocol deviations/violations

### Analysis:

- Collected samples will be shipped to collaborating laboratories for drug assaying as soon this is possible (COVID-19 travel restriction permitting)

Data cleaning has been completed and the database has been locked from data entry, except with permission from the site-lead investigator, and where justified (e.g. query from external monitor).

There has been a total of 3 serious adverse events (SAE) since initiation of the study:

- Baby born to participant DDI02 had died (early neonatal death- on day 2 of life) due to birth asphyxia that was as a result of prolonged second stage of labour. The SAE, which was assessed to be unlikely related to the investigational product, was reported to regulatory body, and ethics committees including the pharmacovigilance team at LSTM
- Participant DDI03 had upper GI bleeding and was admitted to Zomba Central Hospital for one day. The SAE was sent to regulatory body as well as ethics committees and was assessed to be unlikely related to the investigation product.
- Participant DDI06 had premature rupture of membranes (at 33 weeks and 5 days) and delivered a premature infant with no complications. The baby did not need nursery admission and was followed up until 6 weeks postpartum. The SAE was reported to all regulatory body in Malawi and to all ethics committees. The SAE was assessed to be unlikely related to the investigation product.

No changes were made to the protocol or informed consent as a result of these SAEs.

There were no major protocol deviations but 4 minor protocol deviations.

**A. Project Status: (Since last approval, check one category only.)**

- |  |                                     |
|--|-------------------------------------|
| 1. Enrollment Has Not *  | <input type="checkbox"/>            |
| 2. Actively Enrolling Participants*  | <input type="checkbox"/>            |
| 3. Enrollment Completed, Contact with Participants Ongoing   | <input type="checkbox"/>            |
| 4. Contact with Participants Completed, Analyzing Identifiable Data<br>Analysis Only   | <input checked="" type="checkbox"/> |
| 5. Analyzing Identifiable Data (Samples or Data) Only  | <input type="checkbox"/>            |
| 6. Analyzing Unidentifiable Data; Data Do Not Contain Identifiers or<br>Linkage to the Data if this is a Program Project, check here | <input type="checkbox"/>            |
| 7. complete Section E., sign the Progress Report and attach a  | <input type="checkbox"/>            |
| 8. completed List of Associated Projects   | <input type="checkbox"/>            |

***\*If enrollment has not begun or you are actively enrolling participants, attach a copy of the consent document used or to be used.***

**B. Number of Participants enrolled, Records Reviewed or Samples Analyzed:**

What is the total sample size?

1. Since last renewal:

# of males

NOT  
APPLICABLE

# of females

0

# of adults

0

# of children

NOT  
APPLICABLE

2. Since original approval:

# of males

NOT  
APPLICABLE

# of females

16

# of adults

16

# of children

NOT  
APPLICABLE

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**C. (Answer Questions 1 through 7 based on information since last review. Attach a memo explaining "Yes" answers to questions 1 through 6.)**

**Yes No N/A**

1. Have any participants withdrawn voluntarily or been withdrawn from the study?

✓		
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2. Have any unexpected side effects, complications, or findings been noted that have not been reported to the Committee?

	✓	
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**Yes No N/A**

3. Have there been any changes to the protocol (participant population, recruitment, study procedures, sample size or consent process) that have not been reviewed and approved by the Committee? ☒ ☐ ☐
4. Are you requesting any changes to the project (change in investigators, subject population, recruitment, study procedures, sample size or consent process)? ☐ ☒ ☐
5. Have there been any significant new findings which may relate to the participants' willingness to continue participation in the study? ☐ ☒ ☐
6. Has any new information appeared in the literature or been discovered from the study results that would affect the risk-benefit assessment of the project? ☐ ☒ ☐
7. Has a Data Safety and Monitoring Board been established for this project? If yes, provide a status report from the DSMB. ☐ ☐ ☒
8. Do any of the participating faculty (or their immediate family, staff or students) have a financial interest (royalty, equity or consulting) in the sponsor and/or products used in this project? ☐ ☒ ☐
- Has this been reported to the COMREC previously? ☐ ☐
-

**D. As Investigators indicate your assessment of the progress of this study**

As expected ☒

Not as expected ☐

Above expectation ☐

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**E. Funding Status: (select one)**

Awarded ☒

Pending ☐

Project **not** funded ☐

If awarded or pending, provide the following information:



Signature of Principal Investigator

3	0	J	U	L	2	0	2	0
D	D	M	M	M	Y	Y	Y	Y

Date

**\*\*\*SEE BELOW FOR INVESTIGATOR RESPONSIBILITIES\*\*\***



## **Investigator Responsibilities**

- Changes, amendments, or addenda made to the protocol or the informed consent process must be submitted to the COMREC for review and approval prior to initiating the change. This includes changes in investigator(s), sample size, population, research site, subject compensation, etc.
- Incarcerated individuals may not be included in the study unless the study has been approved by the COMREC for inclusion of prisoners.
- The COMREC protocol number should be cited in all correspondence.
- Adverse events should be reported promptly to the COMREC.
- Significant new information that may affect the risk: benefit ratio must be submitted promptly to the COMREC.
- Only consent/assent documents with a valid approval date may be presented to the participants.
- Signed consent forms for all participants enrolled in the study must be retained on file.
- All active research projects must be reviewed and re-approved by the COMREC prior to the project's expiration date.
- The Principal Investigator is responsible for submitting progress reports by the project's current submission date.
- The Principal Investigator is responsible for keeping the Co-Investigator(s) and Student Investigator(s) informed of the status of the project.

## **RETURN THIS FORM AND SUPPORTING DOCUMENT(S) TO:**

**College of Medicine Research and Ethics Committee, Mahatma Gandhi Road**

### **COMREC USE ONLY:**

Project Re-approved for Period \_\_\_\_\_ to \_\_\_\_\_

Project Reclassified as Exempt Status; Continuing Review No Longer Required

\_\_\_\_\_  
**Chair/Administrator, COMREC**

\_\_\_\_\_  
**Date and Stamp**



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## PROGRESS REPORT TO PHARMACY, MEDICINES AND POISONS BOARD

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*To be completed in typescript and submitted by the Principal Investigator. For questions with Yes/No options please indicate answer in bold type.*

### 1. Details of Principal Investigator

Name:	Dr Clifford George Banda
Address:	Training and Research Unit of Excellence, College of Medicine, University of Malawi, Private Bag 360, Blantyre-Malawi.
Telephone:	+265 (0) 994717867
E-mail:	<a href="mailto:cgbanda@mlw.mw">cgbanda@mlw.mw</a>
Fax:	

### 2. Details of study

Full title of study:	Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study.
Name of EC which approved the trial:	COMREC LSTM REC UCT REC
EC reference number:	COMREC: <b>P.07/19/2746</b> LSTM REC: <b>19-039</b> UCT REC: <b>266/2019</b>
Date of favourable (latest approval, attach certificate) ethical opinion:	24 March, 2020
Sponsor:	Liverpool School of Tropical Medicine (LSTM); Pembroke Place, Liverpool L3 5QA, UK.
PMPB Number:	PMPB/CTRC/IV/30072019115

### 3. Commencement and termination dates

Has the study finished? <i>If yes, submit "Declaration of end of trial"</i>	Yes / <b>No</b>
If no, what is the expected completion date? <i>If you expect the study to overrun the planned completion date this should be stated</i>	31 July 2021.  Study site activities will be completed on 31 July 2020.  However, sample and data analyses will be on-going until 2021
If you do not expect the study to be completed, give reason(s)	NA
Has the study started in Malawi?	<b>Yes</b> / No
If yes, what was the actual start date?	23 September, 2019.
If no, what are the reasons for the study not commencing?  What is the expected start date?	NA

#### 4. Site information

Number of Malawi sites proposed in original application:	- 1
Number of Malawi research sites recruited to date:	- 1
Do you plan to increase the total number of sites proposed for the study?	Yes / <b>No</b>

#### 5. Recruitment of participants

Number of participants recruited:	<p><i>Proposed in original application:</i></p> <ul style="list-style-type: none"> <li>• <b>17</b> (in protocol v4.0_24Mar2020)</li> </ul> <p><i>Actual number recruited to date:</i><b>16</b></p> <ul style="list-style-type: none"> <li>• The 17<sup>th</sup> participant was not enrolled into the as a COVID-19 precautionary measure to minimise putting potential participants at risk of COVID-19 exposure. This decision was arrived at a time when the pandemic was declared and there was emphasis from the local ethics committee to scale down research activities in Malawi, observe social distancing and limit study participant visits to essential safety visit.</li> </ul>
Number of participants completing trial:	<i>Actual number completed to date:</i> <b>16</b>
<p>Number of withdrawals from trial to date due to:</p> <p>(a) withdrawal of consent (b) loss to follow-up (c) death (where not the primary outcome)</p> <p>Total study withdrawals: 2- as follows:</p> <ol style="list-style-type: none"> <li>1. Participant DDI15 was withdrawn after completing the first treatment course, as a COVID-19 precautionary measure, in response to national and local ethics guidance to limit participant visits and only continue essential safety visits.</li> <li>2. Participant DDI16 was withdrawn from the study due to non- compliance to study procedures.</li> </ol>	

<p>Number of treatment failures to date (prior to reaching primary outcome) due to:</p> <p>(a) adverse events (b) lack of efficacy</p> <p>Total treatment failures: 0</p>
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Have there been any serious difficulties in recruiting participants?	Yes / <b>No</b>
If yes, give details:	
<p>Do you plan to increase the planned recruitment of participants into the study?</p> <p><i>Any increase in planned recruitment should first be notified to the local IEC that issued the ethics approval (COMREC or NHSRC) as a substantial amendment for ethical review.</i></p>	Yes / <b>No</b>

## 6. Safety/Product quality reports

Have there been any Suspected Unexpected Serious Adverse Reactions (SUSARs) in this trial?	<b>Yes</b> / No
<p>Have these SUSARs been notified to PMPB</p> <p><i>If no, please arrange urgently and give reasons for late notification.</i></p>	<b>Yes</b> / No
Has there been a time when Investigational Products were suspected to have been of poor quality?	Yes / <b>No</b>
Has there been time when there was cold chain breakage in the storage areas of medicines or times when temperatures fall out the normal storage conditions of medicines?	Yes / <b>No</b>
Has there been a time when Investigational Products were suspected to be ineffective?	Yes / <b>No</b>

## 7. Amendments

Have any substantial amendments been made to the trial during the year?	<b>Yes</b> / No
If yes, please give the date and amendment number for each substantial amendment made.	Amendment details as shown below

Amendment date	Description
V4.0-24Mar20	<p>V4.0-24Mar20:</p> <ul style="list-style-type: none"> <li>• Description of risk mitigation strategies in natural disaster, epidemics or pandemics such as COVID-19</li> <li>• Removal of dosing in sequence 4 to minimise participant's number of visits in light of COVID-19 pandemic. This has resulted in dropping one secondary objective.</li> <li>• Removal of collection of PK samples at delivery as they are likely not to yield detectable blood concentrations of piperazine since sequence 4 dosing has been omitted; resulting in dropping of one secondary objective, as described above.</li> <li>• Modification of study / protocol title to align with the dropping of one secondary objective.</li> <li>• Minimising visits in sequence 4 (Table 2 of procedures) necessitating collection of one of the safety blood samples for viral load on day 28 of sequence 3 instead of before drug administration in sequence 4</li> <li>• Indication that the total sample size for study is 17, as previously calculated for primary and secondary objectives, and not 22 which was accounting for the dropped secondary objective as described above</li> </ul>
V3.0-29Dec19	<p>V3.0-29Dec19:</p> <ul style="list-style-type: none"> <li>• Clarification that a CD4 count sample will be collected as part of screening procedures</li> </ul>
V2.1-29Sep19	<p>V2.1-29Sep19:</p> <ul style="list-style-type: none"> <li>• Correction of inconsistencies within the protocol (between different sections, the text and tables) and between the approved informed consent form and the protocol.</li> </ul>

	<ul style="list-style-type: none"> <li>Clarification on implementation of the study in relation to HIV treatment guidelines in Malawi, particularly, implications of rapid scale up of use of dolutegravir-based ART and phasing out efavirenz-based ART.</li> </ul>
V2.0-23Aug19	V2.0-23Aug19: Clarification on risk mitigation when viral load >1000 copies/mL
V1.1-05Aug19	V1.1-05Aug19: Changes to lay summary

## 8. Breaches of the protocol or Good Clinical Practice


Have any breaches/deviations of the protocol or GCP occurred in relation to this trial during the year?	Yes / No
<p>If yes, please give the date of each notification to the PMPB.</p>	<p>The following deviations were assessed as minor and COMREC was informed on the following dates:</p> <ul style="list-style-type: none"> <li>• 05 March,2020: DDI03 was an illiterate participant whose consent form had initials which were written by the impartial witness (on 10 Dec 2019). The right designation would have been to use the participant's thumbprint.</li> <li>• 05 March,2020: DDI09 was an illiterate participant who had her initials written by the impartial witness. The correct designation would have been to use her thumbprint (on page 11 of the consent form).</li> </ul> <p>Additionally, on page 12 of the consent form, the name of the participant was missing. The right designation would have been that the witness should write the participant's name on page 12</p> <ul style="list-style-type: none"> <li>• 05 March 2020: A screened (potential) participant number S020 was illiterate but still had name initials on her consent form which were written by the impartial witness. The right designation would have been to use her thumbprint.</li> </ul> <p>Furthermore, the name of the participant was missing on the consent form. The right designation would have been that the witness should have write the participant's name on the form (on page 12)</p> <ul style="list-style-type: none"> <li>• 19 June 2020: The study participant opted to have another enrolled person act as her impartial witness</li> </ul> <p>Since all protocol deviations were minor (mostly clerical and did not affect participants safety or undermine the integrity of the study, they were all reported to local ethics committee (COMREC) and staff retrained on consenting</p>

## 9. Other issues



Are there any other developments in the trial that you wish to report to PMPB?	Yes / <b>No</b>
Are there any regulatory issues on which further advice is required?	Yes / <b>No</b>

#### 10. Declaration

Signature of Investigator:	
Name:	Dr Clifford George Banda
Date of submission:	31/07/2020

## FHS016: Annual Progress Report / Renewal

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
<b>This serves as notification of annual approval, including any documentation described below.</b>			
<input type="checkbox"/> Approved	Annual progress report	Approved until/next renewal date	
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	

**Note:** Please note that incomplete submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to [hrec-enquiries@uct.ac.za](mailto:hrec-enquiries@uct.ac.za).

Please clarify your plan for research-related activities during COVID-19 lockdown

Comments to PI from the HREC

### Principal Investigator to complete the following:

#### 1. Protocol information

Date (when submitting this form)	29 Jul 2020		
HREC REF Number	266/2019	Current Ethics Approval was granted until	30 Aug 2020
Protocol title	Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study		
Protocol number (if applicable)	N/A		
Are there any sub-studies linked to this study?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
If yes, could you please provide the HREC Ref's for all sub-studies? <b>Note:</b> A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Prof Karen I Barnes		
Department / Office Internal Mail Address	Division of Clinical Pharmacology, Department of Medicine, K45, Old Main Building, Groote Schuur Hospital		



1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?  <b>Note:</b> Any annual approvals for <b>Full Committee</b> review MUST be submitted on the monthly HREC submission dates.  (Please send electronic copy for full committee review to <a href="mailto:hrec-enquiries@uct.ac.za">hrec-enquiries@uct.ac.za</a> )	<input type="checkbox"/> Yes	N/A
<b>If yes in 1.2 please complete section 1.3 below for invoicing purposes</b>		
1.3 Annual Approval for <b>full committee</b> review	- R 3450 (inclusive of vat)	
For invoicing purposes, please provide:		
Sponsor's name		
Contact person		
Address		
Telephone number		
Email Address		

## 2. List of documentation for approval

In this notification, we highlight the progress of the study since it's initiation on 23 September 2019.

## 3. Protocol status (tick ✓)

<input type="checkbox"/>	Open to enrolment
<input checked="" type="checkbox"/>	Closed to enrolment (tick ✓)
<input type="checkbox"/>	Research-related activities are ongoing
<input type="checkbox"/>	Research-related activities are complete, long-term follow-up only
<input checked="" type="checkbox"/>	Research-related activities are complete, data analysis only
<input type="checkbox"/>	Main study is complete but sub-study research-related activities are ongoing
<input type="checkbox"/>	Study is closed → Please submit a Study Closure Form ( <a href="#">FHS010</a> )

## 4. Enrolment

Number of participants enrolled to date	16
Number of participants enrolled, since last HREC Progress report (continuing review)	16
Additional number of participants still required	0

## 5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	20
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## 6. Cumulative summary of participants

Total number of participants who provided consent	20
Number of participants determined to be ineligible (i.e. after screening)	4
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	14
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	2
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
N/A	
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0
N/A	

## 7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
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**Recruitment:**

- The study got approval from the local ethics committee (COMREC) on 23 September 2019, and from UCT HREC on 30 August 2019.
- The study site was activated on 28 November 2019 and screening started on 30 November 2019. A total of 20 participants were screened and 16 were enrolled into the study. 2 participants were withdrawn as described below:
  1. Participant DDI15 was withdrawn after completing the first treatment course, as a COVID-19 precautionary measure, in response to national and local ethics guidance to limit participant visits and only continue essential safety visits.
  2. Participant DDI16 was withdrawn from the study due to non-compliance to study procedures.
- 17 participants were planned to be recruited into the study. The 17<sup>th</sup> participant was not enrolled as part of a COVID-19 precautionary measure to minimise putting potential participants at risk of COVID-19 exposure. This decision was made at a time when the pandemic was declared and there was emphasis from the local ethics committee to scale down research activities in Malawi, observe social distancing and limit study participant visits (only conduct essential safety visits).

**Follow-up and data collection:**

- All enrolled participants (n=16) have completed follow up and exited the study. The last participant exited the study on 10<sup>th</sup> July 2020.
- There were no major protocol deviations/violations

**Analysis:**

- Collected samples will be shipped to collaborating laboratories for drug assaying as soon this is possible (COVID-19 travel restriction permitting)
- Data cleaning has been completed and the database has been locked from data entry, except with permission from the site-lead investigator, and where justified (e.g. query from external monitor).

**8. Protocol violations and exceptions (tick ✓ all that apply)**

<input type="checkbox"/>	No prior violations or exceptions have occurred since the original approval
<input type="checkbox"/>	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
<input checked="" type="checkbox"/>	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

**9. Amendments (tick ✓ all that apply)**

<input type="checkbox"/>	No prior amendments have been made since the original approval
<input checked="" type="checkbox"/>	Prior amendments have been reported since the last review and have already been approved
<input type="checkbox"/>	New protocol changes/ amendments are requested as part of this continuing review (See note below)

**Note:** If new protocol changes are being requested in this review, please complete an amendment form ([FHS006](#)).



Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

## 10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

There has been a total of 3 serious adverse events (SAE) since initiation of the study:

- Baby born to participant DDI02 had died (early neonatal death- on day 2 of life) due to birth asphyxia that was as a result of prolonged second stage of labour. The SAE, which was assessed to be unlikely related to the investigational product, was reported to regulatory body, and ethics committees including the pharmacovigilance team at LSTM
- Participant DDI03 had upper GI bleeding and was admitted to Zomba central hospital for one day. The SAE was sent to regulatory body as well as ethics committees and was assessed to be unlikely related to the investigation product.
- Participant DDI06 had premature rupture of membranes (at 33 weeks and 5 days) and delivered a premature infant with no complications. The baby did not need nursery admission and was followed up until 6 weeks postpartum. The SAE was reported to all regulatory body in Malawi and to all ethics committees. The SAE was assessed to be unlikely related to the investigation product.

No changes were made to the protocol or informed consent as a result of these SAEs.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable
If yes, please describe:		
All participants with SAEs were referred to the central hospital for management and the study team followed them up until discharge and recovery.		

## 11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?

<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable
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11.2 Did a Data and Safety Monitoring Board publish a report?

<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input type="checkbox"/> Not applicable
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11.3 If yes, please identify the agency and attach a summary of the findings.

Agency Name	1. COMREC Compliance Officer 2. John and John Clinical Research Services	Report attached	✓ Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable
			<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/> Not applicable



11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
If yes, please explain:	

## 12. Level of risk (tick ✓)

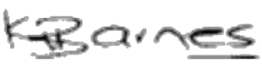
12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
<input type="checkbox"/>	Increased
<input type="checkbox"/>	Decreased
<input checked="" type="checkbox"/>	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.

## 13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form <a href="#">FHS013</a> ):	

## 14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	29/07/2020

## Form FHS011: Study deviation

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	

**Note:** Please note that incomplete submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to [hrec-enquiries@uct.ac.za](mailto:hrec-enquiries@uct.ac.za).

Please clarify your plan for research-related activities during COVID-19 lockdown

### Principal Investigator to complete the following:

#### 1. Protocol information

Date (when submitting this form)	31/07/2020
HREC REF Number	266/2019
Project Title	Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study
Protocol number (if applicable)	Version 4.0
Principal Investigator	Professor Karen I Barnes
Department / Office Internal Mail Address	Division of Clinical Pharmacology, Department of Medicine, K45, Old Main Building, Groote Schuur Hospital

#### 2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
<p><b>Inappropriate documentation of informed consent:</b></p> <p>DDI09 is an illiterate participant who had her initials written by the impartial witness. The correct designation would be her thumbprint should be used (on page 11 of the consent form).</p> <p>Additionally, on page 12 of the consent form, the name of the participant was missing. The right designation would be that the witness should have written the name on page 12</p> <p>Furthermore, the participant opted to have another enrolled person act as her impartial witness</p>

#### 3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
--



A note to file was written to explain this inappropriate designation as well as the missing name of the participant on page 12.

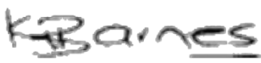
The participant was also reconsented with an appropriate impartial witness

3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.

Study staff were retrained on consenting and designation for both participant and impartial witness

#### **4. Principal Investigator's acknowledgement of responsibility**

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.

Signature of PI		Date	31/07/2020
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## Form FHS011: Study deviation

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	

**Note:** Please note that incomplete submissions will not be reviewed.  
 Please email this form and supporting documents (if applicable) in a combined pdf-file to  
[hrec-enquiries@uct.ac.za](mailto:hrec-enquiries@uct.ac.za).

Please clarify your plan for research-related activities during COVID-19 lockdown

### Principal Investigator to complete the following:

#### 1. Protocol information

Date (when submitting this form)	31/07/2020
HREC REF Number	266/2019
Project Title	Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study
Protocol number (if applicable)	Version 4.0
Principal Investigator	Professor Karen I Barnes
Department / Office Internal Mail Address	Division of Clinical Pharmacology, Department of Medicine, K45, Old Main Building, Groote Schuur Hospital

#### 2. Protocol deviation description

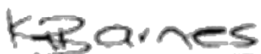
Please describe the deviation below, including the reason why the deviation occurred.
<b>Inappropriate documentation of informed consent:</b> DDI03 is an illiterate participant whose consent form had her initials which were written by the impartial witness on 10 Dec 2019. The right designation would have been to use the participant's thumbprint

#### 3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
A note to file was written to explain this inappropriate designation
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.
Study staff were retrained on consenting and designation for both participant and impartial witness

#### 4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.

Signature of PI		Date	31/07/2020
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## Form FHS011: Study deviation

<b>HREC office use only (FWA00001637; IRB00001938)</b>			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature/ Designee		Date	

**Note:** Please note that incomplete submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to [hrec-enquiries@uct.ac.za](mailto:hrec-enquiries@uct.ac.za).

Please clarify your plan for research-related activities during COVID-19 lockdown

### Principal Investigator to complete the following:

#### 1. Protocol information

Date (when submitting this form)	31/07/2020
HREC REF Number	266/2019
Project Title	Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study
Protocol number (if applicable)	Version 4.0
Principal Investigator	Professor Karen I Barnes
Department / Office Internal Mail Address	Division of Clinical Pharmacology, Department of Medicine, K45, Old Main Building, Groote Schuur Hospital

#### 2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
<p><b>Inappropriate documentation of informed consent:</b></p> <p>A screened potential participant number S020 was illiterate but her consent form had her initials which were written by the witness. The right designation would have been to use her thumbprint.</p> <p>Additionally, the name of the participant was missing on the consent form. The right designation would have been that the witness should have write the participant's name on the form (on page 12)</p>

#### 3. Follow-up actions


3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
A note to file was written to explain this inappropriate designation as well as the missing name of the participant on page 12.
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.



Study staff were retrained on consenting and designation for both participant and impartial witness

#### 4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.

Signature of PI		Date	31/07/2020
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## COLLEGE OF MEDICINE

The Principal College of Medicine  
Private Bag 360  
M. H. C. Mipando, MSc, PhD.  
Chichiri Blantyre 3 Malawi Our Ref.:  
Telephone: 01 871911

01 874107  
Your Ref.: P.07/19/2746  
Fax: 01 874 700

Email: comrec@medcol.mw

Date: 26<sup>th</sup> Mar, 2020

### **A REPORT ON COMREC INSPECTION FOR PROTOCOL # P.07/19/2746**

**STUDY TITLE:** Impact of dolutegravir –based ART on the pharmacokinetic profile and placental penetration of piperaquine administered as dihydroartemisinin –piperaquine for intermittent preventive treatment of malaria in pregnant women living with HIV virus in Malawi. A fixed sequence cohort study

**PRINCIPAL INVESTIGATOR:** Dr. Clifford Banda

Date of visit: Thursday, 5 March, 2020

Name of COMREC Inspector: Naomi Sibale

Date of study approval: December 29, 2019

#### **1. COMMENTS AND/OR ISSUES RAISED**

- 1.1. The consent forms do not have a number for a contact person who is always available on site. It has the PIs number who is not always available on site. For example, during the visit he was outside the country, making it difficult for participants to contact him in case they want to report something.
- 1.2. Chichewa Consent form page 4 there is a statement which says tidzatenga 'magazi okwana 8' which sounds vague, it has to be clarified



- 1.3. • Consent forms' pages 5 and 6 are not readable. Very dark, faint and small font.
- 1.4. Enrolled participants' numbers – 01, 05, 08 and 11 were consented by the study's PI who is not on the delegation log as such he has not been delegated any such duties.
- 1.5. • Participant number DDI-03 – This participant is illiterate and was supposed to thumbprint on the consent form. Instead the witness wrote the initials for the participant on the consent form
- 1.6. • Participant number DDI 09- This participant was supposed to thumbprint the consent form on Page 11 and not the witness putting the participant's initials. And on Page 12, the witness was supposed to write the name of the participant but it has been left blank.
- 1.7. Participant SC 5020 – Participant was supposed to thumbprint on page 11 and the witness was supposed to write the name of the participant on 12 but it has been left blank.

## **2. RECOMMENDATIONS:-**

- 2.1. We recommend that an amendment for the consent forms be submitted to correct all the errors that have been observed on the consent forms. Including adding a telephone number for a study member who is always available in the country so that participants can be contacting him/her when there is need to do so.
- 2.2. We recommend that all the staff that have expired GCP or do not have GCLP be trained and file the certificates in the ISF
- 2.3. We recommend that all the nurses that do not have their proof of registration in file, renew their registration and file the evidence in the ISF
- 2.4. We recommend that all the study staff that have not signed their CVs do so on each and every page of their CV.
- 2.5. We recommend that the Study PI be the first one on the delegation log with all the responsibilities delegated to him as per ICH-GCP.
- 2.6. We recommend that the PI submit a protocol violation and CAPA as he consented participants to join the study when he is not on the delegation log and neither was he assigned to conduct such duties as per the Delegation Log that is on file in the ISF
- 2.7. We recommend that a note to file be filed explaining that the 4 participants mentioned were consented by PI who was not on the delegation log at that time.
- 2.8. We recommend that Note to files be written to explain why participants were not thumb printing on the consent forms page 11 and file the Corrective Action Plan on how to avoid this in future. We also recommend a re-training for the study team on how to obtain informed consent and how to complete the ICDs to avoid such kind of mistakes in future and evidence be filed in the ISF.

3. **VERDICT:**

We recommend that the queries be addressed within a period of 4 weeks from the time of receiving the report as re-inspection will be done unannounced.

COMREC INSPECTOR: MS NAOMI SIBALE



COMREC IRB ADMINISTRATOR: MS. KHAMA MITA



COMREC CHAIRMAN: ASS. PROF. ERIC UMAR





## IMPROVE DDI STUDY

### RESPONSES TO ACTION POINTS IDENTIFIED DURING COMREC INSPECTION VISIT ON 5<sup>TH</sup> MARCH 2020

Issue	Comments	Action taken
1.1. The consent forms do not have a number for a contact person who is always available on site. It has the PIs number who is not always available on site. For example, during the visit he was outside the country, making it difficult for participants to contact him in-case they want to report something.	Site to submit an amendment for the consent to correct all the errors that have been observed on the consent forms	<ul style="list-style-type: none"> <li>The consent form was amended and was sent to COMREC for approval. More importantly, participants are also given an appointment card that has a study phone number. This provides an alternative option to communicate with the team in cases where the PI is away.</li> </ul>
1.2. Chichewa Consent form page 4 there is a statement which says tidzatenga 'magazi okwana 8' which sounds vague, it has to be clarified	Site to submit an amendment for the consent to correct all the errors that have been observed on the consent forms	<ul style="list-style-type: none"> <li>The consent form has been amended and was sent to COMREC for approval. The statement which says tidzatenga 'magazi okwana 8' in the Chichewa Consent form on page 4, has been changed to "tidzatenga magazi okwana ma teaspoon 8"</li> </ul>
1.3. Consent forms' pages 5 and 6 are not readable. Very dark, faint and small font.		<ul style="list-style-type: none"> <li>There is a printed readable copy for page 5 and 6 which is given to participants</li> </ul>
1.4. Enrolled participants' numbers – 01, 05,08 and 11 were consented by the study's PI who is not on the delegation log as such he has not been delegated any such duties.	<ul style="list-style-type: none"> <li>PI to submit a protocol violation and CAPA and to be in the Delegation Log that is on file in the ISF</li> <li>A note to file to be written and filed</li> </ul>	<ul style="list-style-type: none"> <li>A non- compliance report has been written and sent to COMREC</li> <li>The study PI has been included on the delegation</li> </ul>

1.5. Participant number DDI-03 – This participant is illiterate and was supposed to thumbprint on the consent form. Instead the witness wrote the initials for the participant on the consent form	<ul style="list-style-type: none"> <li>• Non- compliance report to be written and sent to COMREC</li> <li>• Note to file to be written and filed</li> <li>• Retraining of site team on proper filling of the consent form</li> </ul>	<ul style="list-style-type: none"> <li>• A non- compliance report was written and sent to COMREC</li> <li>• A note to file was appropriately written and filed</li> <li>• The study team was retrained on proper completion of the consent form, and training logs were signed</li> </ul>
1.6. Participant number DDI 09- This participant was supposed to thumbprint the consent form on Page 11 and not the witness putting the participant's initials. And on Page 12, the witness was supposed to write the name of the participant but it has been left blank.	<ul style="list-style-type: none"> <li>• Non- compliance report to be written and sent to COMREC</li> <li>• Note to file to be written and filed</li> <li>• Retraining of site team on proper filling of the consent form</li> </ul>	<ul style="list-style-type: none"> <li>• A non- compliance report was written and sent to COMREC</li> <li>• A note to file was written and filed</li> <li>• The study team was retrained on appropriate completion of the consent form and training logs were signed</li> </ul>
1.7. Participant SC 5020 – Participant was supposed to thumbprint on page 11 and the witness was supposed to write the name of the participant on 12 but it has been left blank.	<ul style="list-style-type: none"> <li>• Non- compliance report to be written and sent to COMREC</li> <li>• Note to file to be written and filed</li> <li>• Retraining of site team on proper filling of the consent form</li> </ul>	<ul style="list-style-type: none"> <li>• A non- compliance report was written and sent to COMREC</li> <li>• A note to file was written and filed</li> <li>• The study team was retrained on appropriate completion of the consent form and training logs were signed</li> </ul>
All the staff that have expired GCP or do not have GCLP be trained , and all nurses that do not have their proof of registration in file, renew their registration and file the evidence in the ISF		<ul style="list-style-type: none"> <li>• Staff with expired or missing GCP and GCLP, have been retrained and all nurses that do not have their proof of registration in file, have renewed their registration. The evidence has been filed in the ISF</li> </ul>

All the study staff that have not signed their CVs do so on each and every page of their CV.		<ul style="list-style-type: none"> <li>• All the study staff that did not sign their CVs, have signed each and every page of their CVs.</li> </ul>

Responses prepared by:



Dr Clifford George Banda- Site PI

16<sup>th</sup> April 2020



## Site Monitoring Visit Follow-Up Letter

10-January -2020

Dr Clifford Banda  
Department of Medicine  
University of Cape Town  
South Africa

**Re: Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile and placental penetration of piperaquine administered as dihydroartemisinin-piperaquine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study**

Dear Dr Clifford Banda,

Thank you for availability during the Interim Monitoring visit which was conducted at your site in Zomba, Malawi from 07 to 08/Jan/2020 for the above-mentioned protocol. It was a pleasure to meet with you and your key personnel. During the visit, we reviewed the following:

- Source documents and CRFs for 4 study participants including the first 2 participants to be enrolled.
- Source Data Verification
- AEs which had so far occurred in the study.
- Screening and enrolment logs.
- The investigator site file.
- Pharmacy, Laboratory and Clinic areas
- Follow up items from the site initiation visit

The communication below is a summary of the findings noted during the visit.

### **Attendees at the visit included:**

Attendees	Role
Dr Clifford Banda	Principal Investigator (PI)
Steve Munharo	Laboratory Technician
Sharon Muyaya	Data Entry Clerk
Mayamiko Kaphuka	Study Nurse
Marumbo Chirwa	Study Nurse
Nomsa Phiri	Site Study Coordinator

### **Subjects Reviewed:**

Subject	Reviewed From	Reviewed To
DDI01	D00_09/Dec/2019	D28_06/Jan/2020
DDI02	D00_17/Dec/2019	D14_31/Dec/2019
DDI03	D00_17/Dec/2019	D14_31/Dec/2019
DDI04	D00_18/Dec/2019	D14_31/Dec/2019

### **Action Items:**

Please ensure that the following findings are addressed as discussed during the debrief meeting on 08/Jan/2020:

Issue	Comments
001- Discrepancies were noted between source and EDC at the Screening visit for subject DDI01 (refer to question 12 for details).	Site to update EDC accordingly.
002- On the Medications Log, there was no response whether participant had ever taken Isoniazid preventive prophylaxis for subject DDI04.	Site to update source accordingly.
003- Subject DDI01: Sequence 1 Enrolment (Day 0) Form V1.0 dated 05/Sep/2019 does not have a section for recording participant's weight.	Clarification on the missing sections will be followed up at the next Site Monitoring Visit.
004- Sequence 1 Day 7 Form V1.0 dated 05/Sep/2019 did not have a section to note the visit date for subject DDI02.	
005 - COMREC approval for Protocol Amendment Version 2.1 dated 29/Sep/2019 is pending.	Site to follow up with COMREC
006 - PMPB Clinical Trial Authorization Certificate is pending.	Site to follow up with PMPB

Issue ( <i>continued</i> )	Comments
<p>007 - The following External Quality Assurance Laboratory Certifications are outdated, Site advised to obtain most recent certificates:</p> <ul style="list-style-type: none"> <li>• Laboratoire de Pharmacologie Clinique, Centre Hospitalier Universitaire Vaudois; EQA report for Anti-viral drugs is dated Dec/2017.</li> <li>• Zomba Central Hospital, EQA for HIV-1 Viral Load is dated 23/Dec/2018 for 2018 survey participation.</li> <li>• Johns Hopkins Project Laboratory, EQA certificate is for 2018 survey participation.</li> </ul>	<p>Site to follow up with affected Laboratories</p>
<p>008 - Locator Forms had the following omissions:</p> <ul style="list-style-type: none"> <li>• DDI02, DDI03: Usual Clinic name/address is missing.</li> <li>• DDI04: Participant's cellphone number is not indicated.</li> </ul>	<p>Site to ensure blank sections are completed or comment added to explain absence</p>
<p>009 - Calibration certificates for Hemocue (only one filed) and Pipettes are not filed in the ISF.</p>	<p>Site to file outstanding documents</p>

Please do not hesitate to contact us if you have any questions.

Kind regards,

John and John Clinical Research Services.

cc:

Carl Henry – LSTM

John Chabuka – John and John Clinical Research Services

## IMPROVE DDI STUDY

### RESPONSES TO ACTION POINTS IDENTIFIED DURING INTERIM MONITORING VISIT BETWEEN 7-8 JANUARY 2020

Issue	Comments	Action taken
001- Discrepancies were noted between source and EDC at the Screening visit for subject DDI01 (refer to question 12 for details).	Site to update EDC accordingly.	The EDC was appropriately updated to correct these discrepancies
002- On the Medications Log, there was no response whether participant had ever taken Isoniazid preventive prophylaxis for subject DDI04.	Site to update source accordingly.	Record on whether participant took isoniazid or not has been updated on the medication log and appropriately reflected in the data base
003- Subject DDI01: Sequence 1 Enrolment (Day 0) Form V1.0 dated 05/Sep/2019 does not have a section for recording participant's weight.	Clarification on the missing sections will be followed up at the next Site Monitoring Visit.	A note to file has been made to clarify that an old draft copy of the CRF was used instead of the final version. Version control of all CRFs has now been updated to avoid a similar scenario.
004- Sequence 1 Day 7 Form V1.0 dated 05/Sep/2019 did not have a section to note the visit date for subject DDI02.		
005 - COMREC approval for Protocol Amendment Version 2.1 dated 29/Sep/2019 is pending.	Site to follow up with COMREC	COMREC acknowledgement of notification of changes in version 2.1 and approval of version 3.0 were made concurrently. The approval letter of COMREC for version 3.0 has been filed appropriately
006 - PMPB Clinical Trial Authorization Certificate is pending.	Site to follow up with PMPB	PMPB Clinical Trial Authorisation Certificate is now filed in the ISF
007 - The following External Quality Assurance Laboratory Certifications are outdated, Site advised to obtain most recent certificates: <ul style="list-style-type: none"> <li>Laboratoire de Pharmacologie Clinique, Centre Hospitalier Universitaire Vaudois; EQA report</li> </ul>	Site to follow up with affected Laboratories	<ul style="list-style-type: none"> <li>Updated EQA for CHUV laboratory for the assays they will work on antiretroviral and piperazine are now updated</li> </ul>

## IMPROVE DDI STUDY

### RESPONSES TO ACTION POINTS IDENTIFIED DURING INTERIM MONITORING VISIT BETWEEN 7-8 JANUARY 2020

<p>for Anti-viral drugs is dated Dec/2017.</p> <ul style="list-style-type: none"><li>• Zomba Central Hospital, EQA for HIV-1 Viral Load is dated 23/Dec/2018 for 2018 survey participation.</li><li>• Johns Hopkins Project Laboratory, EQA certificate is for 2018 survey participation.</li></ul>		<ul style="list-style-type: none"><li>• Zomba Central Hospital lab's EQA certificate for 2019 has been filed</li><li>• Johns Hopkins Project Laboratory has annual EQAs done at the end of the year and the certificate issued in March of the following year. 2019's certificate will be issued in March 2020. This will be made available to our team and filed appropriately</li></ul>
<p>008 - Locator Forms had the following omissions:</p> <ul style="list-style-type: none"><li>• DDI02, DDI03: Usual Clinic name/address is missing.</li><li>• DDI04: Participant's cellphone number is not indicated.</li></ul>	<p>Site to ensure blank sections are completed or comment added to explain absence</p>	<p>All blank sections on locator forms have been completed with "Not applicable" or as appropriate where information is not available.</p>
<p>009 - Calibration certificates for Hemocue (only one filed) and Pipettes are not filed in the ISF.</p>	<p>Site to file outstanding documents</p>	<p>Calibration certificates for HemoCue Pipettes have been appropriately filed in the ISF and laboratory folder</p>

Responses prepared by:



Dr Clifford George Banda- Site PI

29 February 2020



## Site Monitoring Visit Follow-Up Letter

26-June -2020

Dr Clifford Banda  
Department of Medicine  
University of Cape Town  
South Africa

**Re: Impact of dolutegravir-based antiretroviral therapy on the pharmacokinetic profile and placental penetration of piperazine administered as dihydroartemisinin-piperazine for intermittent preventive treatment of malaria in pregnant women living with human immunodeficiency virus in Malawi: a fixed sequence cohort study**

Dear Dr Clifford Banda,

Thank you for availability during the Interim Monitoring visit which was conducted at your site in Zomba, Malawi from 18 to 19/Jun/2020 for the above-mentioned protocol. It was a pleasure to meet with you and your key personnel. During the visit, we reviewed the following:

- Source documents and CRFs including the first 2 participants to be enrolled.
- Source Data Verification
- (S)AEs which had so far occurred in the study.
- Screening and enrolment logs.
- The investigator site file.
- Pharmacy, Laboratory and Clinic areas

The communication below is a summary of the findings noted during the visit.

### **Attendees at the visit included:**

Attendees	Role
Dr Clifford Banda	Principal Investigator (PI) (attended via teleconference)
Steve Munharo	Laboratory Technician
Sharon Muyaya	Data Entry Clerk
Mayamiko Kaphuka	Study Nurse
Marumbo Chirwa	Study Nurse
Dumisile Nkosi	Study Physician
Glory Mzembe	Study Physician

**Subjects Reviewed:**

Subject Records Reviewed at this Visit		
Subject	Reviewed From	Reviewed To
DDI01	D28_06/Jan/2020	Exit_27/Feb/2020
DDI02	D14_31/Dec/2019	Exit_15/May/2020
DDI03	D14_31/Dec/2019	Exit_15/Apr/2020
DDI04	D14_31/Dec/2019	Exit_02/Apr/2020
DDI05	D00_14/Jan/2020 (Screening Visit on 07/Jan/2020)	Exit_21/May/2020
DDI06	D00_18/Jan/2020 (Screening Visit on 16/Jan/2020)	D00_18/Jan/2020 (SAE reviewed at Delivery Visit_19/Feb/2020)
DDI07	D00_20/Jan/2020 (Screening Visit on 13/Jan/2020)	D00_20/Jan/2020
DDI08	D00_21/Jan/2020 (Screening Visit on 17/Jan/2020)	D00_21/Jan/2020
DDI09	D00_27/Jan/2020 (Screening Visit on 23/Jan/2020)	D00_27/Jan/2020
DDI10	D00_27/Jan/2020 (Screening Visit on 24/Jan/2020)	D00_27/Jan/2020
DDI11	D00_03/Feb/2020 (Screening Visit on 22/Jan/2020)	D00_03/Feb/2020
DDI12	D00_05/Feb/2020 (Screening Visit on 31/Jan/2020)	D00_05/Feb/2020
DDI13	D00_11/Feb/2020 (Screening Visit on 07/Feb/2020)	D00_11/Feb/2020
DDI14	D00_27/Jan/2020 (Screening Visit on 24/Jan/2020)	D00_27/Jan/2020
DDI15	D00_02/Mar/2020 (Screening Visit on 26/Feb/2020)	D00_02/Mar/2020
DDI16	D00_09/Mar/2020 (Screening Visit on 04/Mar/2020)	D00_09/Mar/2020

### **Action Items:**

Please ensure that the following findings are addressed as discussed during the debrief meeting on 19/Jun/2020:

Issue	Comments
001 - On 17/Mar/2020 There was a temperature excursion of -10°C recorded on the -20°C freezer temperature log. It was recorded at 08:00; however, at 16:00 the temperature was within range at -23°C. The freezer was holding samples at the time of the excursion. This excursion was not reported.	Laboratory is advised to document an incident report.
002 - On 11/Jan/2020 there was a temperature excursion of -2°C recorded on the -20°C freezer temperature log. It was recorded at 08:00 and the entry was not initialed. No entry was made at 16:00. There were no samples at the time of the excursion.	Laboratory advised to document a Note to File.
003 - On 12, 22, 24 and 30/Jan/2020 the temperatures of the -20°C freezer were not recorded. There were no samples in the freezer on these dates.	Laboratory advised to document a Note to File.
004 - The version date for the ICF Addendum was documented as 24/Mar/2019 on the approved ICF, yet in fact it was meant to be 24/Mar/2020.	As the ICF was already approved and was merely a typographical error, Site is advised to document a Note to File.
005 - DDI02: Per review of participant progress notes and SAE form on file, participant delivered on 13/May/2020. However, the baby died on 15/May/2020 due to birth asphyxia. The SAE was reported to the sponsor and to the IRBs on the same day. However, the SAE was unavailable in REDcap at the time of review.	SAE to be entered in REDcap.
006 - DDI03: Per review of the SAE Log, participant had SAEs for Excessive vomiting and upper GI bleeding. However, only one SAE Form (Upper GI bleeding) was completed and submitted to the sponsor and to the IRBs.	Site to clarify and/or make necessary corrections.
007 - DDI03: On the Adverse Event Information Form, SAE for Excessive Vomiting was changed to UTI on 24/Jan/2020 by staff with initials MP. However, the AE Log was not updated to reflect this change and participant chart notes were also not updated.	Site to clarify and/or make necessary corrections.

Issue ( <i>continued</i> )	Comments
008 - DDI03: Per review of AE Information form, an SAE for UTI was documented with start date 23/Jan/20 and end date of 24/Jan/2020. However, no corresponding SAE Form was been completed.	Site to clarify and/or make necessary corrections.
009 - DDI09 is illiterate and an Impartial Witness was present. However, the Impartial Witness was another participant already enrolled to the study. Therefore, does not meet the requirements of an Impartial Witness as prescribed in ICH GCP R2; "Section 1.26: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial..."	Site is advised to trace the participant if they are still active on the study and re-administer consent. The Site should also report the GCP violation to IRB.
010 - DDI15; Participant's name on ICF is spelt differently on Health Passport and on the Identification log.	Site advised to make a note that it was discussed and confirmed by the participant.

Please do not hesitate to contact us if you have any questions.

Kind regards,

John and John Clinical Research Services.

cc:

Carl Henry – LSTM

John Chabuka – John and John Clinical Research Services

**IMPROVE DDI STUDY**  
**RESPONSES TO ACTION POINTS IDENTIFIED DURING INTERIM MONITORING VISIT BETWEEN 18-19 JUNE 2020**

<b>Report Section</b>	<b>Issue</b>	<b>Comments</b>	<b>Action taken</b>
Non-Compliance, Question 3.	001- On 17/Mar/2020 There was a temperature excursion of -10°C recorded on the -20°C freezer temperature log. It was recorded at 08:00; however, at 16:00 the temperature was within range at -23°C. The freezer was holding samples at the time of the excursion. This excursion was not reported.	Laboratory is advised to document an incident report.	<i>An incident report explaining that this did not affect sample integrity was written and filed appropriately</i>
	002- On 11/Jan/2020 there was a temperature excursion of -2°C recorded on the -20°C freezer temperature log. It was recorded at 08:00 and the entry was not initialed. No entry was made at 16:00. There were no samples at the time of the excursion.	Laboratory advised to document a Note to File.	<i>A note to file was written and filed appropriately</i>
	003- On 12, 22, 24 and 30/Jan/2020 the temperatures of the -20°C freezer were not recorded. There were no samples in the freezer on these dates.	Laboratory advised to document a Note to File.	<i>A note to file was written and filed appropriately</i>
Non-Compliance, Question 5.	004- DDI02: Per review of participant progress notes and SAE form on file, participant delivered on 13/May/2020. The baby died on 15/May/2020 due to birth asphyxia. The SAE was reported to the sponsor and to the IRBs on the same day. However, the SAE was unavailable in REDcap at the time of review.	SAE to be entered in REDCap.	<i>This SAE has been entered on REDCap</i>

**IMPROVE DDI STUDY**  
**RESPONSES TO ACTION POINTS IDENTIFIED DURING INTERIM MONITORING VISIT BETWEEN 18-19 JUNE**

	005- DDI03: Per review of the SAE Log, participant had SAEs for Excessive vomiting and upper GI bleeding. However, only one SAE Form (Upper GI bleeding) was completed and submitted to the sponsor and to the IRBs.	Site to clarify and/or make necessary corrections.	<i>DDI03 has one SAE on upper GI bleeding and the AE log was corrected.</i>
	006- DDI03: On the Adverse Event Information Form, SAE for Excessive Vomiting was changed to UTI on 24/Jan/2020 by staff with initials MP. However, the AE Log was not updated to reflect this change and participant chart notes were also not updated.	Site to clarify and/or make necessary corrections.	<i>The AE log has been updated to reflect UTI the change that was made.</i>
Non-Compliance, Question 5. (continued)	007- DDI03: Per review of AE Information form, an SAE for UTI was documented with start date 23/Jan/20 and end date of 24/Jan/2020. However, no corresponding SAE Form was been completed.	Site to clarify and/or make necessary corrections.	<i>The adverse event on UTI was marked as serious: i.e. "was AE serious?" and the response was indicated "Yes" instead of "No". Additionally, "hospitalization" was incorrectly ticked. Note that this error has been corrected on the CRF and the database. A note has been filed to detail correction of this error</i>
Subject Data, Question10	008- The version date for the ICF Addendum was documented as 24/Mar/2019 on the approved ICF, yet in fact it was meant to be 24/Mar/2020.	As the ICF was already approved and was merely a typographical error, Site is advised to document a Note to File.	<i>A note explaining the error in dates has been written and filed appropriately</i>

**IMPROVE DDI STUDY**  
**RESPONSES TO ACTION POINTS IDENTIFIED DURING INTERIM MONITORING VISIT BETWEEN 18-19 JUNE**

	009- DDI09 is illiterate and an Impartial Witness was present. However, the Impartial Witness was another participant already enrolled to the study. Therefore, does not meet the requirements of an Impartial Witness as prescribed in ICH GCP R2; "Section 1.26: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial..."	Site is advised to trace the participant if they are still active on the study and re-administer consent. The Site should also report the GCP violation to IRB.	<i>The participant was reconsented with an impartial witness and a protocol deviation report has been written and reported to the research ethics committee. Additionally, staff were retrained and reminded of consenting procedures</i>
	010- DDI15; Participant's name on ICF is spelt differently on Health Passport and on the Identification log.	Site advised to make a note that it was discussed and confirmed by the participant.	<i>A note to file was written to clarify the spelling for the participant and it was filed in the informed consent folder.</i>

Responses prepared by:



Dr Clifford George Banda- Site PI  
13 July 2020