ATTACHMENT: COUNTRY-SPECIFIC INFORMATION CLINICAL STUDY PROTOCOL MDGH-MOX-3002 DRC - VERSION 02, 30 JUNE 2020

1 TABLE OF CONTENTS

LIST OF FIGURES

Table 1: Abbreviations and Acronyms

Abbreviation	Term
CECA/20	20e Communauté Evangélique au Centre de l'Afrique
CRMT	Centre de Recherche en Maladies Tropicales
DPS	Division Provinciale de Santé
DRC	Democratic Republic of Congo
EDCTP	European & Developing Countries Clinical Trials Partnership
GCP	Good clinical practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
PICF	participant information and informed consent and assent forms
USH	Ugandan Shilling
ZSR	Zone de Santé Rurale

2 Introduction

In the Democratic Republic of the Congo (DRC), the study will be conducted in Ituri Province and may be conducted in an additional area to be identified.

3 Ituri Province

3.1 Investigator Organization

The study will be coordinated by the research team at the Centre de Recherche en Maladies Tropicales (CRMT).

CRMT was one of the research centers established for the moxidectin Phase III study (protocol ONCBL60801). It is located at the Referral Hospital (Hôpital de Réference) in Rethy, Ituri Province, and managed by the 20th Communauté Evangélique au Centre de l'Afrique (CECA20), Bunia, member of the Église du Christ au Congo, in DRC.

3.2 Study Team

The study will be led by Dr. T. Ukety, who is an ophthalmologist from Ituri, has conducted onchocerciasis-related studies in northeastern DRC (Ituri) prior to joining WHO and was involved in the Phase III study as a technical advisor.

The co-investigator, Dr. M. Mandro, is also from Ituri, has conducted onchocerciasis-related studies in Ituri and was a clinical monitor of the moxidectin Phase III study, in particular the site in Ituri. He has been seconded to this study from the DPS Ituri.

Some staff who conducted the Phase III study in Ituri will be involved in this study as well.

These staff, as well as additional staff hired for this study, will undergo (re)training on the ethical requirements for study conduct, the requirements for study conduct as outlined in the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH-GCP), the protocol, protocol required procedures and protocol required documentation.

The Standard Operating Procedures established for the Phase III study will be adapted or complemented for the study procedures required in this study.

3.3 Site Capacity

Establishment of the CRMT in preparation for the Phase III study included renovation of buildings not used by the Hôpital de Réference to provide rooms and facilities required for that study. These facilities, including laboratories, locked storage facilities for study documentation, locked and temperature controlled room for the storage and preparation of investigational product, a meeting room and staff offices will be used for this study.

Clinical, ophthalmological and laboratory equipment and material and other infrastructure elements such as cars, motorcycles, back-up generators, fuel reservoirs and communication means (satellite dish for internet connectivity) were also provided for the Phase III study and will be utilized for this study as needed. Additional and/or replacement equipment and material needed for this study will be purchased by CECA20 from the grant obtained from the European and Developing Countries Clinical Trials Partnership (EDCTP) by the Sponsor, the Investigator (Dr. T. Ukety, CECA20) and Co-Investigator (Dr. M. Mandro, DPS Ituri) and other co-applicants.

3.4 Recruitment areas

In Ituri (Figure 1) the study will be conducted principally in the Zone de Santé Rurale (ZSR) Logo, with possible extension of the recruitment area into the ZSR of Nyarambe (primary recruitment area) (Figure 2).

In view of civil unrest in these areas or the Ebola outbreak possibly preventing implementation or completion of the study in that area, the ZSR of Aru is planned as the backup recruitment area (Figure 3).

Figure 1: Map of the Democratic Republic of Congo with its 26 Provinces

Figure 2: Map of the Zone de Santé Rurale (ZSR) Logo with adjacent ZSR Nyarambe in Ituri Province (primary recruitment area)

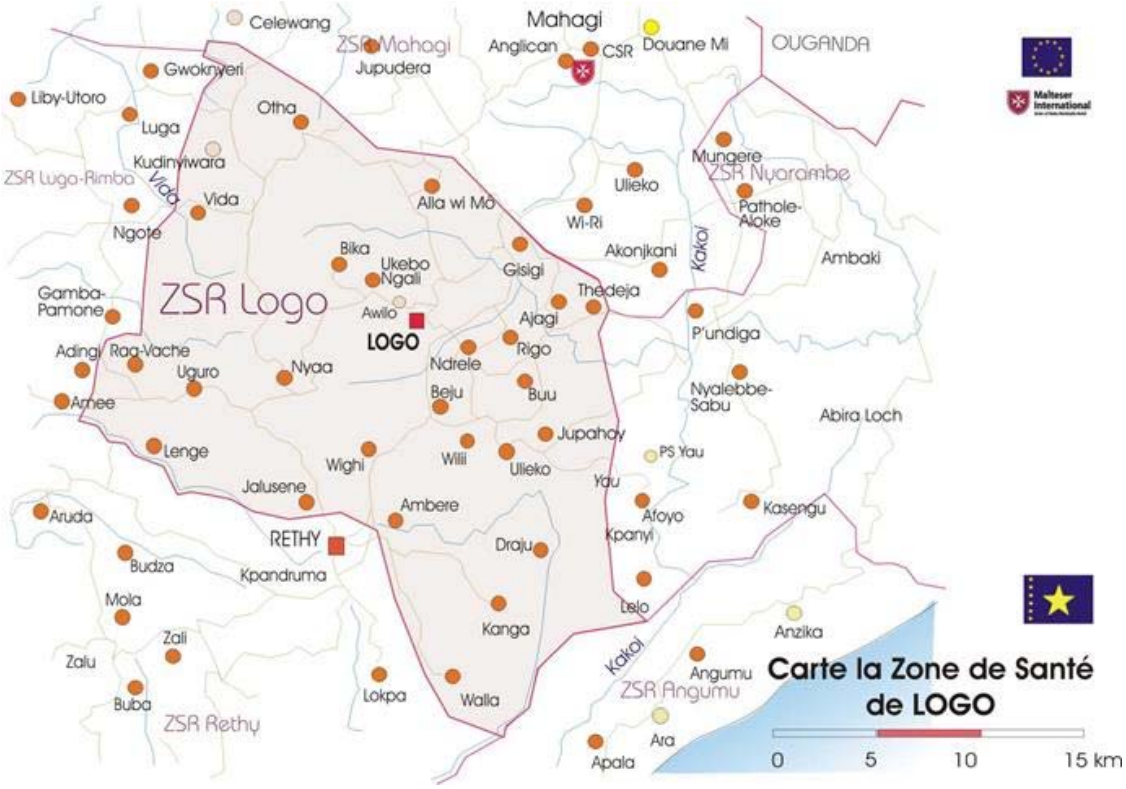
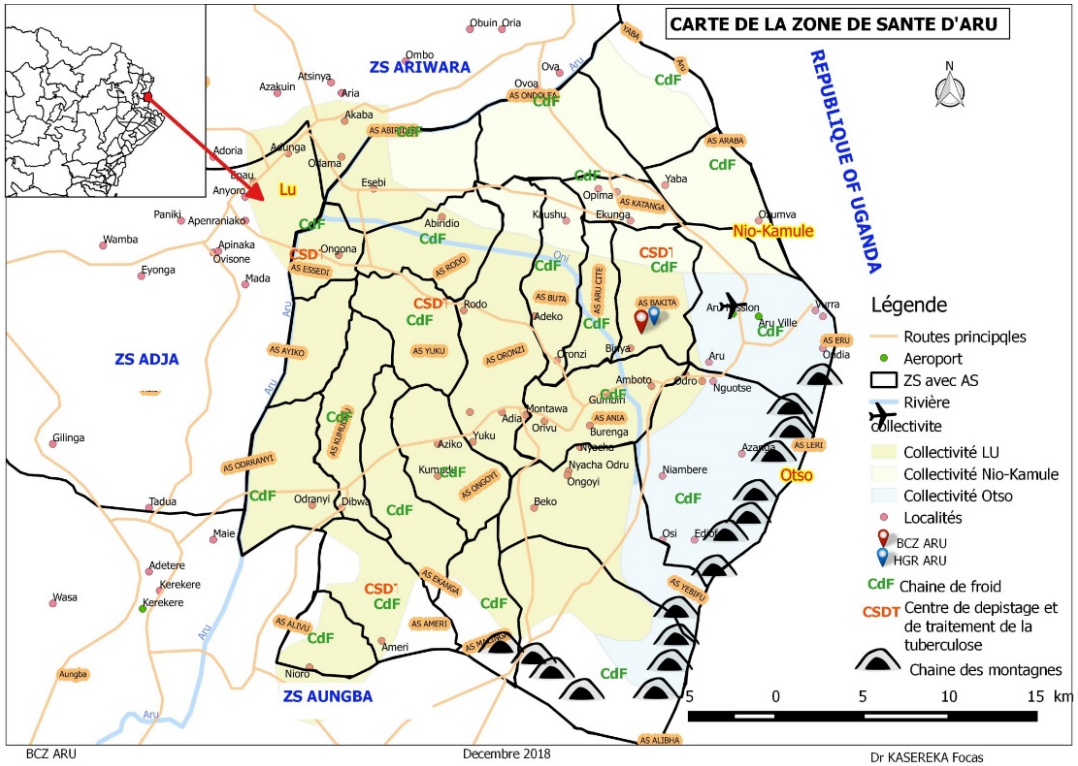


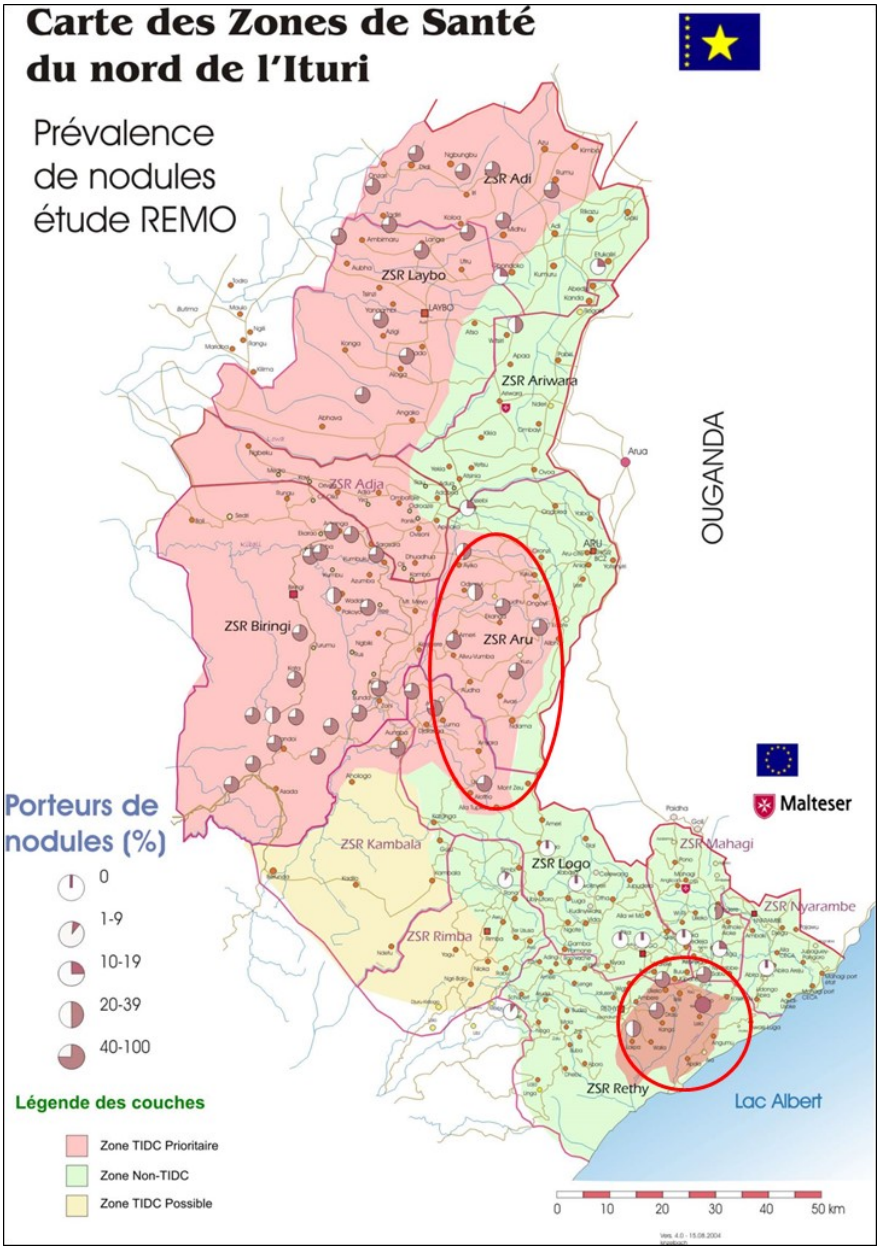
Figure 3: Map of the Zone de Santé Rurale (ZSR) Aru in Ituri Province (backup recruitment area)



The primary as well as the backup recruitment areas were selected for the following reasons:

- Epidemiological surveys conducted by the national onchocerciasis control program in 2002 indicate that many villages are onchocerciasis meso- or hyper-endemic (Figure 4) and
- Data obtained during screening in the ZSR Logo for the Phase III moxidectin study found 66.7% were infected with *O. volvulus* (by skin snip); and
- The areas are not endemic for *Loa loa* infection.
- Ivermectin mass drug administration has not yet been implemented (ZSR Logo and Aru) or only relatively recently (since 2016 in the ZSR Nyarambe for lymphatic filariasis control).

Figure 4: Results of Rapid Epidemiological Mapping (REMO) of onchocerciasis conducted by the national onchocerciasis control program Ituri Nord in 2002 with the primary and backup recruitment areas encircled in red



Considerations for identifying the villages from which individuals will be recruited will include the following:

- Acceptability of the research to the village community;
- Prior information on onchocerciasis endemicity including, but not limited to, available endemicity data and/or proximity to known vector breeding sites;
- The number and timing of prior ivermectin treatment rounds;
- Accessibility of the village;
- Vicinity of the village to local health centers.

3.5 Cultural and Socio-economic Characteristics of the Population from which Participants will be Recruited

3.5.1 Primary Recruitment Area

In the rural areas of the ZSR of Logo and in the villages in the ZSR Nyarambe, 98% of population are from the Alur ethnic group. In the Aire de Santé targeted for recruitment, 100% of the population speak the Alur language (Dhu-Alur). The other languages spoken are Lingala (20% of the population) and French (60% of the literate population) and Kiswahili (5%).

Consequently, the information documents and the discussion about the studies will be in Dhu-Alur. The Principal Investigator is Alur.

The most practiced religion across the primary recruitment area is Catholicism (80%). There is a growing presence of traditional religions such as “Mungu lonycon” or “Karwo” who believe that God is all powerful and able to solve all problems in response to prayers and whose leaders are preaching against modern health care. Special advocacy work with these leaders is required to encourage participation in health programs, as well as to obtain their permission to approach the communities regarding research studies.

The belief in the effectiveness of traditional healers is also high.

The majority of the population is poor and lives off agricultural activities, including subsistence farming. The area is known for production of coffee, mostly sold in Uganda, which constitutes the main source of income and employment in this region.

The area is characterized by high fertility rates, poor nutrition and low educational attainment with high rates of illiteracy. Less than 20% of the girls come to complete the secondary school.

Children have a very high degree of respect for their parents and the elderly. Children and adolescents usually live with their parents until they get married. Orphans live with other family members. The head of the household is their ‘guardian’ and makes all decisions for these minors without there necessarily being an ‘official document’ attesting this. Minors may also be sent by their parents to live with other relatives.

The average daily earning is around 5 US Dollars. The currency most frequently used is the Ugandan Shilling (USH).

3.5.2 Backup Recruitment Area

The majority of the population in the ZSR Aru are from the Lugbara ethnic group (around 90%) and speak Lugbara-tii (75%) and Lingala (25%). However, Lingala speakers live in the urban areas, not the rural areas where recruitment would take place.

Consequently, to prepare for conduct of the study exclusively or partly in the rural areas of the ZSR Aru, the information documents have been translated into Lugbara-tii ~~and into Lingala~~ and the discussions about the studies will be in Lugbara-tii.

The most practiced religions are Catholicism (40%) and Protestantism (35%) with other religions practiced by around 25% of the population. Aru territory is, like Logo, characterized by high levels of fetishism practice and belief in traditional healers.

The other cultural and socioeconomic characteristics are similar to the ones described for the primary recruitment area.

3.6 Concurrent recruitment into Study MDGH-MOX-3002 with recruitment into Study MDGH-MOX-3001

During the initial period of recruitment into study 3002, recruitment will be conducted concurrently with recruitment into study 3001. Details are provided in the protocol for study 3001 (submitted concurrently with the protocol for study 3002).

Briefly, volunteers not qualifying for study 3001 or deciding that they do not want to participate in study 3001 once they have been informed about the results of screening but who qualify for study 3002, will be provided the option to participate in study 3002.

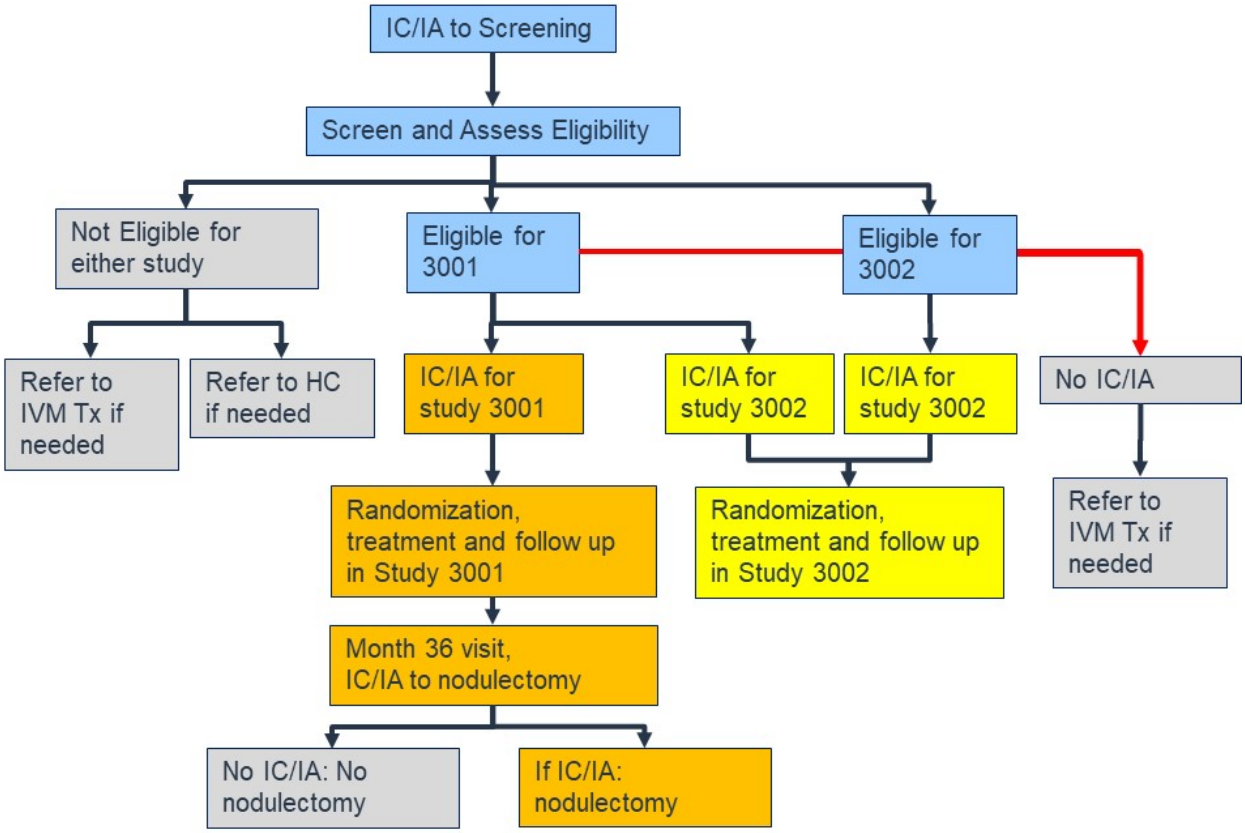
Concurrent conduct and recruitment into both this study and Study 3001 was decided upon to avoid having to tell people not eligible for study 3001 or not wanting to commit to study 3001 which lasts 3 years, but interested in participating in a study to come back later when individuals with their characteristics and interests 'are wanted'. Such an approach is considered disrespectful of their interests and their time, since they would have to be screened again and may at that time not be eligible for study 3002 anymore.

During concurrent recruitment informed consent/assent is divided into informed consent/assent for Screening for eligibility and informed consent/assent for participation in the study the participant is eligible for or chooses. Figure 5 provides an overview. For further information see Section 6 of the protocol for study 3001.

Provisions for Informed Consent/Assent to Study 3002 following completion of the period of concurrent recruitment are provided in the Main Protocol for study 3002.

The same principles for obtaining Informed Consent/Assent will be followed during both periods of recruitment (see Section 15.9 in both protocols)

Figure 5: Overview of Stepwise Informed Consent/Assent



Legend: C/IA = Informed Consent/Assent, Tx = Treatment, HC = Health Center, IVM = ivermectin

3.7 Compensation for Study Participants

As study participants will be recruited among villagers who are continuing to pursue their usual daily activities, the time participants spend on study activities will be time they are unable to pursue gainful work. To compensate study participants for the resulting loss of earnings, participants will be compensated for the time spent undergoing assessments based on the average daily earning of the population from which the study participants are being recruited, estimated by the Investigator at 5 US Dollars (US$). This is the equivalent of approximately 8500 Congolese francs (CDF) and approximately 20 000 USH, the currency commonly used in both the primary and back-up recruitment areas. The exchange rates vary over time and the local population is very familiar with the impact of these variations. To minimize participants suffering financially from exchange rates becoming unfavorable to them, the compensation is set based on the US$ and will be provided at the up-to-date exchange rate and in the currency the individual participant choses.

3.8 Considerations During the Development of the Participant Information Documents

In addition to the considerations during the Development of the Participant Information Documents (PICF) provided in Section 15.9.1 in the main protocol, the PICF were written to fit the notions in the population in the recruitment areas to ensure that they are familiar with specific concepts (e.g. currency exchange rates) or that unfamiliar concepts are explained (e.g.

blinding) or presented in terms meaningful to the potential participants (e.g. randomization as 'decided by chance', insurance as 'Sponsor having put money aside', password-protected as 'in a locked and secure area').

3.9 Preservation of Urine Left-over from Pregnancy Tests and Use for Improved Tools and Strategies for Control/Elimination of Onchocerciasis and other Neglected Tropical Diseases

Urine is a valuable resource for research into biomarkers as well as new drugs and vaccines. Therefore, CECA/20, the Sponsor and FR3, the repository that will receive the parasites obtained in this study (see Main Protocol Section 15.20.1), have agreed that urine samples left over from the pregnancy tests (see Main Protocol Section 7.4.5) should be provided to FR3. The extent to which this will be possible will depend on the funding that FR3 can raise for a freezer for short term storage at CRMT, provision of barcode-labeled storage vials, shipment on dry ice from DRC to FR3 and freezer space available at FR3.

The following special provisions are being put in place for minors.

After minors who have agreed to participate in the study become adults, they will be asked whether they continue to agree to study participation (see Main Protocol Section 15.9.3) and, if applicable, to the use of the left-over urine for future research. In case they change their mind, the Material Transfer Agreement between the Sponsor and CECA/20 and FR3 includes the following provisions:

- Samples identified as coming from minors will be put 'in quarantine' at FR3, i.e. will not be shipped to any requesters. They will be moved out of quarantine only after confirmation from the Sponsor or CECA/20 that the minor has confirmed agreement to future use of the left-over samples upon becoming an adult.
- Upon receipt of information from the Sponsor or CECA/20 that the minor has not maintained agreement to future use of left-over samples when becoming an adult or that further follow up of the minor for consent to future use of the left over samples is not possible, FR3 will retrieve and destroy the samples.

Retrieval of samples for 'moving them out of quarantine' or for destruction is made possible through the bar code system based sample management in place at FR3 and the fact that FR3 will provide bar-code labelled vials to CECA/20 for shipment of the samples.

For provisions for specimen anonymity and Material Transfer Agreement see Main Protocol Section 15.19.

3.10 DEC-Patch Evaluation, Shipment, Dispensation and Accountability

The DEC-Patch will not be evaluated during screening for concurrent recruitment into Study MDGH-MOX-3002 and Study MDGH-MOX-3001 (see Section 3.6). Furthermore, beginning of evaluation of the DEC-Patch will depend on availability of all required documentation and thus arrival of the DEC-Patch at CRMT.

DEC-Patches will be shipped to the site from Germany only after

- the letter on DEC-Patch provision to be sent by WHO to the Ministry of Health has been returned to WHO signed by the Ministry of Health,
- relevant export and import permits into DRC have been obtained and

- the Sponsor has confirmed that all relevant authorizations and Sponsor documentation requirements for the study and DEC-Patch evaluation have been met.

Shipment to the site may occur before the Site Initiation Visit with secure storage at the site under quarantine, until the study has been initiated. DEC-Patches will be stored and transported at ≤25 ºC. For transport between the CRMT and the villages, CRMT will have been provided with cold storage boxes.

Evaluation of the DEC-Patch during screening does not require blinding. Consequently, the DEC-Patch can be dispensed (envelope opened) as well as administered by blinded study team members. Dispensation and administration will be recorded by these study team members in source documents.

The Investigator will be responsible for ensuring accurate records are maintained for all DEC-Patches received, dispensed, dispensed and not administered, administered, returned or destroyed. The inventory, dispensing and administration logs must be available for inspection by the ~~un~~blinded Study Monitor or the unblinded Study Monitor.

DEC-Patch supplies must be accounted for by the blinded Study Monitor or the unblinded Study Monitor, and DEC-Patches not dispensed returned to the Sponsor for destruction at the end of the study or provided to the Ministry of Health if the Ministry of Health requests it. Copies of the records of DEC-Patches returned to the Sponsor must be retained by the Investigator.

As required by national law and in consultation with the sponsor and the Ministry of Health, unused DEC-Patches may be destroyed locally consistent with the local regulations. Copies of records on the destroyed DEC-Patches shall be retained by the Investigator. These records must show the quantity of DEC-Patches disposed of, the method of destruction, and the person who disposed of the DEC-Patches. Copies of such records shall be submitted to the Sponsor.

3.11 Overview of Measures to Minimize Risk of Transmission of SARS-CoV-2 virus during study conduct based on national/local guidance as of 30 June 2020

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Across all	Across all		• All measures to minimize risk of transmission of COVID-19 will be implemented in coordination and collaboration with the DPS "Equipe d'Intervention Rapide COVID-19 & Maladie de Virus Ebola (MVE)" • All communication about and community engagement regarding COVID-19 (Communication des risques et engagement communautaire en réponse à la COVID-19) will occur in coordination and collaboration with the DPS "Equipe d'Intervention Rapide COVID-19 & MVE" and use their communication material.
Community mobilization (Sections **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**)	Government authorities; Provincial and national parliament members; Provincial and Territory and Health Zone authorities and staff	Yes	• By the time community mobilization is initiated, all members of this 'target population' will have already undergone education on COVID-19, and procedures for screening for COVID-19 symptoms before entering their buildings will have been put in place and everybody will wear masks. • Meetings will be arranged to include not more than a total of 20 participants (including study team members). • The offices/meeting rooms of the 'target population' will have already been set up for physical distancing and procedures will have been put in place to refer anybody with COVID-19 symptoms to the designated local health facility/COVID-19 team. • Documents distributed will be left with meeting participants.

Principal objective (protocol section)	'Target Population'	Physical Distancing possible	Information on physical distancing or measures to be taken to reduce risk of transmission
	Civil society (e.g. associations of different professional, religious groups, non-governmental organizations), Local staff of Local media staff	Yes	• By the time community mobilization is initiated, all meeting participants will have undergone education on COVID-19. • Meetings will be arranged to include not more than a total of 20 participants (including study team members). • Study team will bring thermometers for temperature measurements and inform, as necessary, participants about COVID-19 related requirements. • Study team will ask all meeting participants about symptoms of suspected COVID-19 cases and advise those meeting suspected case definition to self-isolate and to call the responsible health /COVID-19 team. They will be excluded from the meeting. • Study team will ensure that all passing this screening will wash hands before entering the room and wear masks throughout the meeting. • Study team will ensure meeting space is set up to allow physical distancing. • The study team will initiate the meeting with a demonstration on how to properly use and clean cloth masks and an overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing. • Documents distributed will be left with meeting participants.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Community mobilization (Sections **Error! Reference source not found.**, **Error! Reference source not found.**)	Religious Leaders, Village/ Community Leaders, Elders, Relais Communautaires (RECOs)	Yes	• By the time community mobilization is initiated, all meeting participants will have undergone education on COVID-19. • Meetings will be arranged per village, and include not more than 20 participants, including not more than 10 chiefs and elders (typically 5), 5-7 RECOs and approximately 3 study team members. • Meetings will be set up in open spaces, a church or a school with study team ensuring seating is arranged for physical distancing. • Study team will bring thermometers for temperature measurements. • Study team will ask all meeting participants about symptoms of suspected COVID-19 cases and advise those meeting suspected case definition to self-isolate and to call the responsible health facility (or the study team will call the health facility/COVID-19 team on their behalf). They will be excluded from the meeting. • Study team will be bringing megaphones and cloth masks for all meeting participants, and ensure availability of soap and water (or hand sanitizers) for handwashing at the beginning and the end of the meeting. • Study team will ensure that all meeting participants wash hands before entering the meeting space, wear masks all along the meeting and wash hands at the end of the meeting. • The study team will initiate the meeting with a demonstration on how to properly use and clean cloth masks and an overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing. • Documents and cloth masks distributed will be left with meeting participants who will be advised to bring the mask to subsequent meetings.

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
Consultation with village communities and providing information required for village members to decide on participation in the study (Section **Error! Reference source not found.**)	Village inhabitants	Yes	• By the time community mobilization is initiated, the communities will have undergone education on COVID-19. • While the pandemic is ongoing, the community meetings as per protocol section **Error! Reference source not found.** will be preceded by a meeting with heads of families to provide them with a short overview of government guidance on minimizing the risk of SARS-CoV-2 transmission, early detection, self-isolation, COVID-19 designated health facilities and contact tracing, demonstration on proper use and cleaning of cloth masks and the arrangements for further meetings with their family members about the study. • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs. • The 1st and 2nd meeting as per Section **Error! Reference source not found.** will be arranged to take place with no more than 20 meeting participants including 1 RECO, 1 potential (or selected) literate witness, and up to 16 members of 3-4 families (and two or three study team members). • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs.
Provision of informed consent / assent (Sections **Error! Reference source not found.**, **Error! Reference source not found.**)	Village inhabitants interested in study participation	Yes	• Meetings between 1 study team member (or 1 study team member plus 1 translator) and an individual wanting to provide informed consent (or a minor with their parent(s)/guardian wanting to provide informed assent and consent) and the literate witness will take place in a setting that will allow physical distancing. • For further information, see provisions for meetings with religious, village, community leaders, elders and RECOs. • All will be asked to bring the cloth masks provided to them to the next meeting (study visits).

Principal objective (protocol section)	**'Target Population'**	**Physical Distancing possible**	**Information on physical distancing or measures to be taken to reduce risk of transmission**
All study visits (Section **Error! Reference source not found.**)	Screening/study participants	Yes/No	• All study team members will wear masks and gloves during all interactions with study participants. • (Potential) participants will be asked to bring and wear the cloth masks they were provided with during the meetings in which they were informed about the study. • Soap and water (or hand sanitizers) will be brought so that each visit can be initiated and end with hand washing/sanitizing. • Staff members will wash/sanitize hands and change gloves between interactions with different participants. • Areas where screening/study participants can wait will be set up with physical distancing. • At the beginning of each study visit a study team member will measure the temperature of all participants and ask them about COVID-19 symptoms, will advise them to self-isolate and either ask them to call the designated health facility/COVID-19 team or call that health facility/COVID-19 team on their behalf. If they are identified by the health facility/COVID-19 team as not COVID-19 infected, the relevant study visit will be rescheduled. If they are identified as COVID-19 infected, study visits will be arranged to take place after they have been confirmed as recovered by the designated public health staff. • All equipment will be sanitized between use on different participants.