RESEARCH STUDY PROTOCOL

Community-level AntiBiotic Use in Nanoro district, Burkina Faso

(CABU-Burkina)

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Coordinating Investigator	Marianne van der Sande (ITM)
Principal investigators	Valia Daniel (CRUN) Brecht Ingelbeen (ITM)
Funder	InBev-Baillet Latour Fund (ITM Pump Priming Projects)

Title	Community-level AntiBiotic use in Nanoro district Burkina Faso
Version	V1.2 (26/05/2020)
Partnering institutions	Institute of Tropical Medicine, Antwerp, Belgium Clinical Research Unit of Nanoro, Burkina Faso

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Statement of Compliance

This protocol contains the necessary information for conducting this research study. By signing this document, the Investigator commits to carry out the study in compliance with the protocol, the applicable ethical guidelines like the Declaration of Helsinki, the European General Data Protection Regulation (GDPR), the ESF/ALLEA Code of Conduct for Research Integrity, and consistent with international scientific standards as well as all applicable regulatory requirements. The Investigator will also make every reasonable effort to complete the study within the timelines designated.

Once the final protocol has been issued and signed by the Investigator(s) and the authorized signatories, it cannot be informally altered. Protocol amendments have the same legal status and must pass through the mandatory steps of review and approval before being implemented.

Principal Investigator (CRUN):

Title, Name: Dr Daniel VALIA Date: 04/05/2020

Signed:

Principal Investigator (ITM):

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Coordinating Investigator:

Title, Name: Pr Marianne VAN DER SANDE Date: 05/05/2020

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Synopsis

The emergence and spread of antibiotic resistance are fuelled by the (incorrect) use of antibiotics in humans and animals, including wrong treatment choice, dose or duration, poor adherence and poor-quality antibiotics. Limited access to official healthcare facilities in low-resource countries results in widespread, potentially incorrect antibiotic use through self-medication, pharmacies or informal healthcare providers. Our objectives are (i) to quantify community-level antibiotic use and (ii) to assess the level of underdosed use in communities in Burkina Faso and other low-resource countries, in order to evaluate the relationship between incorrect community-level antibiotic use and the development and spread of antibiotic resistance. We will combine a qualitative and cross-sectional study to identify any (formal or informal) healthcare provider, and quantify antibiotic use at community-level. A similar study has been completed in the DRC, and the study will be repeated in two more low- and middle-income countries, when additional funding is secured. After an initial exploratory qualitative study to identify the (range of) health providers and how to appropriately sample them, we will conduct a population health seeking survey to determine the weight of each health provider in overall healthcare utilization, and patient healthcare visit exit interviews to measure antibiotic use by healthcare provider, in 2 health areas of Nanoro health district in Burkina Faso. We will quantify antibiotic use by healthcare provider, determine the proportion underdosed treatment courses, and explore reasons to seek medication from informal providers. Subsequent similar assessments/measurements of community-level antibiotic use in multiple low-income neighbourhoods in other countries will allow carrying out a multi-country ecologic analysis to assess to what extent community-level antibiotic use is associated with increased antibiotic resistance. From the findings, interventions to improve community-level antibiotic use can be developed.

1 INTRODUCTION

1.1 background

Increasing antibiotic resistance (ABR) is one of the main emerging health threats globally, and is strongly driven by excessive and underdosed use of antibiotics (1). Optimizing the use of antimicrobial agents is a key objective of WHO's Global Action Plan on antimicrobial resistance (2). This includes reducing antibiotic use where considered not useful, and promoting correct use when indicated. Excessive use of antibiotics increases the exposure to antibiotics of commensal bacteria and, through urinary and faecal excretion of antibiotics, also increases exposure of bacteria in the environment or sewage. This contributes to preferentially resistant bacteria to prevail and adds to selection pressure towards more ABR (1). At the same time, suboptimal dosage of antibiotics is known to put almost any bacterium at risk of developing resistance to antibiotics (3). Furthermore, the risk of acquiring antibiotic-resistant bacteria is not only dependent on personal antibiotic use, but as well on antibiotic use by the entire community (4).

In industrialised countries, human and animal antibiotic use are monitored through estimations from either sales data or hospital point prevalence surveys (5–7). Meanwhile, in low-resource countries a significant part of antibiotic use happens outside official health care facilities, through informal health seeking or self-medication, in many cases unregulated (8–10). As a result, antibiotic use cannot be accurately estimated in these settings.

In Burkina Faso, in contrast to the industrialised world, many pathogens underlying severe infections are typically community-acquired. The prevalence of antibiotic resistance among community-acquired bacterial infections has been increasing, reaching a proportion which may render treatment ineffective for many patients (11,12) (Valia, 2019, master thesis, publication in preparation). Therefore, it is imperative to identify strategies to measure and optimize antibiotics use, as key driver of ABR.

A recent WHO report estimated nationwide antibiotic consumption in Burkina Faso, based on wholesale drug sales during 2016-2018, at 13.8 Defined Daily Doses (DDD) per 1000 inhabitants per day (13). However, these estimates are based on official healthcare facilities, and do not account for informal healthcare providers, who play an important role in the health system and probably also in antibiotics use (14). No study has yet accurately recorded community-level healthcare provider based antibiotic prescribing, dispensing or use, which is essential baseline information to enable development of targeted interventions at community-level.

1.2 Hypothesis and study question

Since many pathogens underlying severe infections in Burkina are typically community-acquired, community-level antibiotic use likely affects the ABR prevalence of these pathogens. We hypothesize that, while antibiotic stewardship currently focuses on the hospital setting, the majority of antibiotics, including those at higher risk of stimulating ABR are used at community-level.

The purpose of our study is to measure use of antibiotics at community level in order to inform the development and implementation of interventions to optimize antibiotic use. We will assess (i) where, by whom and how much antibiotics are prescribed and dispensed from formal and informal providers, and (ii) to what extent their prescription can be considered appropriate and correct. We anticipate that insight in the quantity and appropriateness of the use of specific antibiotics, by different formal and informal providers, enables us to initiate/focus/strengthen antibiotic awareness and antibiotic stewardship programmes at the appropriate levels.

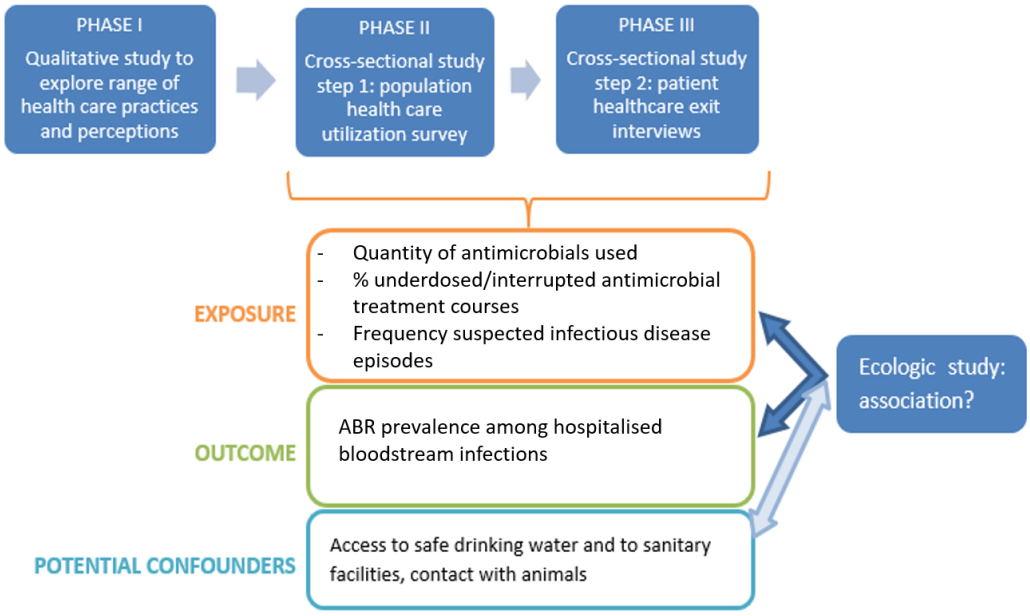
2 OBJECTIVES

1. Quantify overall and community-level antibiotic use (in defined daily doses by group of antibiotics and the percentage of underdosed treatment courses) by type of healthcare provider, in a rural and in a peri-urban community;
2. Assess appropriateness of quantity (including dose, duration, adherence) and indication of antibiotic use according to symptoms presented by patients and by type of health care provider;
3. When antibiotic use has been measured in multiple sites in four low- and middle-income countries, we aim to determine to what extent community-level antibiotic use is associated with the increase of ABR community-acquired BSI.

The proposed study will provide insight in the level, choices and appropriateness of antibiotic use at community-level. From a public health perspective, it should guide the development of interventions to optimize or regulate antibiotic use at community-level, and inform updates of the treatment guidelines at primary healthcare level, ensuring guidance is provided to primary healthcare providers on treatment for the main symptoms and clinical presentations for which healthcare is sought.

If important (incorrect) antibiotic use at community-level is shown, the findings should raise awareness and inform policy makers and the local health district staff to not only focus on hospitals when undertaking efforts to optimize antibiotic use (antibiotic stewardship) or to improve medical practice. The findings should support efforts to improve access to good quality diagnosis and treatment options, and potentially nationwide efforts to restrict unregulated and incorrect antibiotic use (by drug regulators and authorities).

3 STUDY DESIGN



Mixed methods study in 2 health areas of Nanoro health district, consisting of three stages:

- An exploratory **qualitative study** to identify informal and formal healthcare providers, healthcare utilization behaviour, illness and medicine perceptions and terminologies, and to inform the development of a contextualized healthcare utilization and patient exit survey;
- A **population healthcare utilization survey** to survey individuals in the population on their healthcare utilization and other population parameters and determine the weight of each healthcare provider in healthcare utilization;
- **Patient healthcare visit exit surveys** to quantify antibiotic use per healthcare visit, by type of health care provider.

After completing similar studies to measure community-level antibiotic use in ten more neighbourhoods in three other study countries (DRC, Mozambique, South Africa), we will carry out a **multi-country ecologic analysis** to determine the association between community-level antibiotic use (by neighbourhood) and the increase in ABR prevalence of BSI in patients from those neighbourhoods.

4 METHODS

4.1 Study population and setting

While we intend to carry out this study to measure antibiotic use in twelve neighbourhoods in four countries (DRC, Burkina Faso, Mozambique, Cambodia), we provide details here below for Burkina

Faso only, the second study site (DRC completed). The selection of neighbourhoods in other countries follows the same principles stated below.

The study will be carried out in two health areas, Nanoro and Nazoanga, included in the Health and Demographic Surveillance System (HDSS), established by the Clinical Research Unit of Nanoro (CRUN), in the Nanoro health district since 2009. Each year, the Nanoro HDSS carries out at least two rounds of four months each to record assets, housing characteristics and the demographic, socio-cultural, socio-economic characteristics of each household member in the health district (15). In Nanoro, the dry season is from December to June, the wet season from July to November. HDSS rounds are carried out all year round, and do not need to be interrupted due to seasonal rainfall. Bloodstream infection surveillance, including monitoring of AMR prevalence, is established at the Nanoro referral hospital (CMA), for all patients referred from health centres in health areas in the district.

Health area	Nanoro	Nazoanga
Context	peri urban	rural village at 15 Km from Nanoro
Population (2018)	17,334	8,828
Nombre de ménages dans le HDSS (round 18 ; 2019)	2,351	1,131
Public healthcare facilities (n)	2: primary health care centre and Nanoro reference healthcare facility	1: primary health care centre (referring patients to the reference healthcare facility in Nanoro if indicated)
Number of consultations at the primary healthcare facility (2018)	27,963 56% children <5y (15,744/27,963)	7,591 64% children <5y (4,890/7,591)

4.2 Sampling strategy and data collection

Interviews, household visits and informal conversations will only take place when no SARS-CoV-2 local transmission is ongoing in Nanoro health district. If data collection is postponed or interrupted, it will only be started (again) when during 3 consecutive weeks no new locally transmitted COVID19 cases have been reported in the Nanoro health district. General preventive measures in place in Burkina Faso will be complied to at any time during data collection: any study staff member will be wearing a mask, keep 1,5 m physical distance, regularly wash hands, or rub hands using hydro-alcoholic solution, avoid any physical contact. Interviews and household surveys will take place in the open air, while respecting confidentiality and at the same time respecting physical distance from patients waiting for consultations or other community members. Re-usable masks and hydro-alcoholic solution bottles will be provided to staff involved in data collection. Before and after every

interview, household survey, or verification of medical documents (during the healthcare visit exit survey), staff will rub their hands using hydro-alcoholic solution. During data collection, the CRUN principal investigator will monitor the COVID19 situation in Nanoro health district on a daily basis and has access to the latest daily epidemiological reports. No data collection activities involving more than one interviewer, (maximal) two interviewees (belonging to the same household) and potentially one witness (ideally again from the same household) will be conducted.

4.2.1 Qualitative study (Phase I)

An anthropologist from CRUN will conduct semi-structured interviews and participant observation including informal conversations or group discussions, to (1) identify the (range of) healthcare providers, (2) explore how pathogens, illnesses, symptoms and treatments are conceived, perceived and described by local communities and their (range of) healthcare providers, (3) context-specific reasons to seek provider-specific care, (4) potential local drivers of underdosed antibiotic use.

A range of informal and formal healthcare providers, community members of targeted neighbourhoods, and additional key informants (e.g. health district staff) will be approached face-to-face. Sampling will be theoretical (including new participants based on emerging results following a flexible and iterative approach), while also making use of snowball sampling techniques (the researcher is introduced to new potential participants by previous participants). Participants will be selected on purpose and not randomly (purposiveness), in accordance with emerging findings (gradual selection). The flexible sampling process requires continuous redefinition of inclusion/exclusion criteria. Critical cases, i.e. informants providing controversial or contradictory information, will be systematically included (maximum variation). Sample size will be determined by saturation of information, rather than a pre-defined number of interviews. We expect to sample a minimum of 20 informants per site. Only adult participants will be interviewed. Sampling will start from the healthcare workers, health district staff and patients admitted at the CMA.

In-depth semi-structured interviewing. In-depth interviews, mainly with different (formal and informal) healthcare providers, following continuously evolving semi-structured topic guides, will be conducted and will be held in a place where the respondents feel at ease to talk privately. Interviews will be recorded and transcribed.

Participant observation including informal conversations or group discussions. As per definition of the term “informal”, the informal degree of conversations held with participants in public settings in everyday life settings allows for the discussion of sensitive topics and/or reduced stress for participants as compared to a formal interview, hence a higher quality of data collection. This will involve having conversations with various participants in their own “natural” setting that will not be

recorded but documented in notes immediately after the conversation. Informal group discussions entail informal conversations in public spaces, for example in a pharmacy, where likely several people are present and it is not feasible to have a 'private' conversation with clients or providers. People around listen to the informal conversation, and often try to contribute to the discussion. This fosters informal debates about a topic, although not in any organized or structured way.

Informal conversations and interviews will follow topic guides, which will be continuously adapted.

Interviewees' verbal informed consent will be obtained before starting the interview or note taking. Informed consent is verbal for interviewed healthcare providers due to the sensitive nature of selecting informal/non legal prescribers or vendors of medicines, and for interviewed patients because the sensitive nature of the information/data provided, i.e. contact details of informal/non legal vendors of medicines. As further described, verbal consent will be documented by the signature of the person who obtains the consent.

Through these methods, the local health care providers will be identified and local terminology for medicines and antibiotics in particular will be explored, as well as community members' knowledge of different medicines and pathogens. This in order to prevent a non-sensical patient healthcare visit exit survey (phase III) or population healthcare utilization survey (phase II) from the patient's or healthy individuals' viewpoint, and thus optimize data quality throughout the rest of the study. As part of the phase III data collection training, the anthropologist will use phase I findings to train/raise awareness among phase III interviewers about how to approach healthcare providers and their patients, how to formulate the interview questions, e.g. on vocabulary used when talking about antibiotic treatment, and possibly more relevant findings from the phase I study.

4.2.2 Population healthcare utilization survey (phase II)

A healthcare utilisation questionnaire will be conducted in a random sample of households of the two study health areas, in addition to the routine HDSS rounds. CRUN field workers will survey household heads on each household member's (i) frequency of illness episodes during the past three (and six) months, with symptoms presented, (ii) frequency of healthcare use during that time, (iii) the type of healthcare provider visited (including traditional healers, dispenser at market, drug store or private pharmacy, self-employed provider or private clinic, first line health centre, referral hospital) or whether they self-medicated with antibiotics stored at home, (iv) hygiene conditions: access to a drinking water source protected from outside contamination, access to improved sanitation services that are not shared with other households, housing conditions, (observation of) handwashing practices, (v) contact with animals and antibiotics used for animals in the household, and (vi) consumption of industrially produced meat (potential confounders in an ecologic study), and (vii) ask

individuals who report self-medication additional questions on their antibiotic use (see phase 3). Other socio-economic factors are collected as part of HDSS rounds, and will be linked to the survey-specific database for included households.

The questionnaire will be administered to the household head, following the procedure of a routine HDSS round, and to the selected individual household member (if adult, the latter should consent; if minor, the household head should consent, with assent of the minor household member if he/she is between 14 and 18 years old). Household heads are asked to consent to interviewing each household member >14 years after informed consent of each member (assent by those <18y with informed consent by the household head) and to answer for household members <14 years of age. A household member is defined as any person living under the same roof in the same housing unit (unité d'habitation), who recognises the authority or legitimacy of a household head (parental link or not; male or female), who shares the same household facilities as other household members, belongs to a group of people who provide for their needs in terms of food and other essentials for living.

Using the HDSS households as sampling frame, a simple random sample of households for each of both health areas will be selected for the survey. The minimum sample size (number of households) per health area was calculated assuming a proportion of the population having sought healthcare of 0.2, a design effect (adjusting for intra household clustering) of 2 (16), an average household size of 7 (based on HDSS data), 95% confidence intervals, confidence limits of +/- 4% and a source population of respectively 17300 and 8800 in Nanoro and Nazoanga health areas respectively, 800 and 780 households should be interviewed.

On a weekly basis the data recorded and stored on a mobile device is synchronised to the central database (at CRUN). After survey completion in both health areas, healthcare utilization data will be extracted from the central database, without direct identifiers (pseudonymised), and merged with HDSS demographic/socio-economic data, and saved in a password locked csv file on the study laptop.

A single population survey during the wet season is budgeted, but a second survey during the dry season will be added if funding can be secured, to adjust healthcare utilization for seasonal variation, related to disease seasonality and season-related access to healthcare (8).

4.2.3 Patient healthcare visit exit surveys to quantify antibiotic use (phase III)

The health care providers of the health areas were identified in phase I and II. Their relative frequency (number of visits) was measured in the first survey round of phase II. In phase III, for each category (further referred to as 'type') of health care providers in the health areas (traditional healers, private pharmacy, self-employed provider or private clinic, informal drug vendor, first line

health centre, referral hospital), three providers will be randomly selected. Note that the de facto functioning of each health care facility will be considered when categorising a provider to a health care provider type. E.g. some so-called 'postes de santé' may be theoretically public but could function unregulated, organise supplies and staff totally autonomous, as if they were private clinics. In such instance such 'poste de santé' will be labelled as private clinic rather than first line health centre.

Patients completing a healthcare visit at these providers will be approached and requested to participate in a healthcare exit interview. Patients of any age (or caretakers if aged below 18 years of age) and with any indication, will be asked to be interviewed. A convenience sample of patients will be taken, by picking the next patient exiting the healthcare provider when the interview of the previous participant is finished. We will interview at least 50 patients who have received an antibiotic, per type of healthcare provider per health area (to provide +/- 2% confidence limits on the percentage of watch antibiotics[1] (fluoroquinolones and 3rd/4th generation cephalosporins) used/prescribed even if 50% are watch antibiotics; 95% confidence level). If less than three providers of a provider type exist or agree to participate (e.g. Health centres), the patients to be interviewed will be equally distributed between the available providers. In the referral hospital, 150 patients will be interviewed and these will be distributed between the different services of the healthcare facility, according to the frequency of admissions/consultations in each service. The same rule will be applied to other facilities with multiple services. Assuming 30% of patients received/used an antibiotic, overall 1800 patients completing a healthcare visit will be interviewed, during 21 days.

After completing a healthcare visit (provider or outlet), patients and caretakers of paediatric patients who consent to the interview will be asked about the following aspects, using a structured questionnaire: symptoms, the antibiotics for systemic use dispensed/purchased (if any; generic name), number of units (tablet, cap, vial, bottle) per treatment course, dose, route of administration, intake frequency, duration of treatment (including potential up/downscaling), number of antibiotics and antimalarials used concomitantly, reasons for using antibiotics and for health seeking choices (options developed following phase I), and whether the choice, number, dose of dispensed/purchased antibiotics differed from the prescribed antibiotics. If the antibiotics have already been purchased at the facility itself, also the following information can be obtained at this

[1] Watch antibiotics are the highest priority agents on the list of critically important antimicrobial drugs for human medicines. Monitoring their use is encouraged by WHO, to assist the development of tools for stewardship at local, national, and global levels. (Sharland M, Pulcini C, Harbarth S, *et al.* Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. *Lancet Infect Dis* 2018; **18**: 18–20.)

step, about the purchased product: price per unit, brand name, stated manufacturer, expiry date. A photo of the antibiotic and of its packaging (box, blister, bag or a combination of these) will be taken using the data collection mobile devices (stored as part of the data collection form).

In a follow-up phone call by the same interviewer, self-reported treatment uptake until day 7 will be assessed (number of days until treatment interruption; missed doses). If the prescription had not yet been dispensed/purchased at the time of the interview, the (incomplete) data from the interview will be updated by collecting missing information, such as the quantity actually purchased; if applicable, reasons for buying a different quantity than prescribed; where the product was purchased; price per unit, generic name brand name, stated manufacturer, expiry date.

Questionnaires will be immediately entered on a mobile device, which is uploaded on a daily basis to the study database. Data collection teams will consist of CRUN field workers who have great experience in this type of survey. They will be trained on this data collection and informed consent during a one-day training session.

4.2.4 Multi-country ecologic analysis

Parameters (AMR, antibiotic use and potential confounders) will be compared between communities/populations. For each parameter, there will be one observation per health area (12 in total over 4 countries). Population exposures will be antibiotic use, analysing three indicators

a. Quantity penicillins, fluoroquinolones or cephalosporins used at community-level (DDD/1000 pop./day)
b. Quantity penicillins, fluoroquinolones or cephalosporins used overall (out- and in-patient; DDD/1000 pop./day)
c. Percentage of underdosed community-level antibiotic use

As population outcomes we will select several antibiotic-pathogen combinations (i) that were clinically relevant; (ii) underlying most confirmed BSI in Africa; (iii) that are supposedly community-acquired; and (iv) part of the WHO priority list of AMR bacteria. AMR prevalence is available as part of existing routine BSI hospital surveillance at CMA Nanoro. The criteria to take a sample for blood culture, i.e. patients with suspected BSI, the laboratory set-up, standard operating procedures, reporting, quality assurance and control are harmonized across the multi-country study sites. Only one blood culture per patient, within 24 hours of admission, is included there. Hospital-acquired BSI, defined as diagnosed in a blood culture collected 48 hours or more after admission, will be excluded. Although estimating AMR among all community-acquired infections will not be feasible, AMR prevalence of BSI hospital surveillance is a reliable outcome measure to compare AMR between communities and universally recommended by WHO. Pathogen identification and antimicrobial susceptibility testing are done at the hospital, and repeated at the national reference laboratory.

Further quality control is undertaken on the samples after further analysis at ITM, as per surveillance protocol (Surveillance of antimicrobial resistance among consecutive blood culture isolates in tropical settings; Version 4.0, 2017; ITM IRB reference 613/08). The following will be used as outcome indicators (antibiotic-pathogen combinations depending on the antibiotic analysed): the prevalence of MDR, ceftriaxone-resistant and ciprofloxacin-resistant *E. coli, Salmonella enterica* serotype Typhi, and *Salmonella enterica* serotype Typhimurium BSI, and the relative change in these AMR prevalences over a five-year period, to account for potential selection bias of patients admitted with suspected BSI.

We will also collect data to adjust for potential confounding by differential prevalence of BSI and access to WaSH, by analysing a) BSI incidence (culture confirmed BSI surveillance, adjusted for healthcare utilization by neighbourhood), and b) a validated infrastructure indicator combining water, sanitation, and hygiene indicators (from the phase II population survey)(17).

4.3 Data analysis

4.3.1 Qualitative study (Phase I)

Qualitative data analysis will be a retroductive process, combining an emergent theory process with concurrent data collection. Preliminary data -collected through different techniques and at different moments in the process- will intermittently be analysed in the field (sequential analysis) after which further research, with question guides adapted to temporary findings, will be conducted confirming or refuting temporary results through constant validity checks until saturation is reached and the data could be theoretically supported. Raw data will be processed in their textual form and coded to generate and/or identify analytical categories or themes for further analysis.

Based on the preliminary qualitative data analysis, the questionnaire and instructions for phase II and III will be finalized. After data collection has finished, the final analysis of all qualitative data (interviews transcripts and observation notes) will be done by the CRUN anthropologist, in Nvivo 12 software for qualitative data analysis.

4.3.2 Quantifying community-level antibiotic use (Phase II and III)

We will assess patients' antibiotic treatment dose, dosage, duration, mode of administration and uptake courses to determine whether an antibiotic treatment course is underdosed: (i) dose, frequency (posologie) or duration too low, (ii) interrupted courses (non adherence or unavailable full course), based on the available local standardized treatment guidelines or the 2019 WHO Model List of Essential Medicines (for adults/adolescents and for children).

Antibiotic dosage, doses and duration will be recalculated to Defined Daily Doses (DDD) by Anatomical Therapeutic Chemical (ATC) group of antibiotics. For each ATC antibiotic group, we will calculate DDD per 1000 patients provided by each type of healthcare provider. By adjusting for the health utilization weight of each type of health provider, we will calculate DDD per 1000 inhabitants per day in each study area.

For each study area, we will determine the proportion of the study population visiting each type of healthcare provider. This proportion will be used to adjust the **quantity of antibiotics used by the community in the health area** (DDD, percentage watch and percentage underdosed antibiotic treatment courses), for provider-specific healthcare utilization. To determine a correction factor for potential season-related differences in healthcare utilization, we will utilise existing data of a 2015 healthcare utilization survey in Nanoro, Burkina Faso, during a study measuring the population incidence of bloodstream infections(18), unless funding can be secured to repeat the health care utilisation surveys during the dry season (see section 4.2.2).

We will undertake the same estimation of the quantity (DDD) of antibiotics used **by Access, Watch or Reserve classification** of antibiotics (AWaRe (19)), and relate this to available community antibiotic use estimates from high- and middle-income countries (20).

We will also calculate the quantity of antibiotics used and the percentage under-dosed antibiotic treatment courses by type of health provider.

4.3.3 Phase II and III: Patients' health seeking choices and reasons for using antibiotics

We will determine frequencies of patients' provider-specific reasons to seek healthcare, choose a specific provider, barriers to seek healthcare through official health facilities, financial or other barriers to access antibiotics, and to use antibiotics.

4.3.4 Multi-country ecologic analysis: the association between community-level antibiotic use and the emergence or increase of ABR

The ecologic association between exposures, outcomes and confounding variables or effect modifiers, will be analysed by plotting antibiotic use against AMR prevalence and calculating two-tailed Spearman's coefficient (r) for non-parametric correlations. We will repeat this analysis for the different antibiotic use exposure variables (overall and community-level quantity by antibiotic group, % underdosed) and for each of the selected antibiotic-pathogen AMR prevalences. We will also explore other factors potentially associated with AMR, and the interaction between infectious disease incidence and antibiotic use on the association with AMR prevalence. Where necessary we will adjust the point estimates using multilevel (Bayesian) modelling (performing partial pooling).

5 ETHICAL ISSUES

5.1 Ethical Review

This study protocol and annexes will be submitted for formal review and approval to (i) the Institutional Review Board of the ITM in May 2020, and (ii) the Burkina Faso Ethic committee for Health Research in June 2020. We expect responses by the end of June, both in Burkina Faso and Belgium. A copy of the Ethical committees' approval letters will be filed in the investigator file. No participants will be enrolled or participant related activities performed before written approval from the appropriate bodies in each country is obtained, and the same will apply to any further substantial amendments.

The HDSS in Nanoro operates according to a study protocol approved by the ethic committee of health research in 2010 (Pharmacovigilance des combinaison thérapeutiques à base d'artémisinine en Afrique; ref 2010-27 - Version n°3 du 02 Mars 2010; Annex 8) and the local ethic committee of "Centre Muraz" (Pharmacovigilance des combinaison thérapeutiques à base d'artémisinine en Afrique; ref 03-2010/CE-CM).

The study will be carried out according to the principles stated in the Declaration of Helsinki (2013, and any further updates), all applicable international regulations and regulations in force in Burkina Faso, and according to established international scientific standards. The study will be compliant with the EU GDPR.

5.2 Obtaining Informed Consent

Informed consent will be in place for phase I and for phase III.

For phase II: a waiver of written consent is required for the use of data from the HDSS in Nanoro, considering that various conditions are simultaneously present: (a) the survey questions are part of the larger and regular HDSS survey, and the households in the HDDS have previously verbally consented to the periodical HDSS home visits; (b) data will be pseudo-anonymized, and will be treated confidentially, so that any risks related to privacy and confidentiality are acknowledged and minimized; (c) the study has a potential important social value for the concerned communities. The interviewers will inform the participants that a few more questions than usual will be requested for use in the study; he/she will inform them about the goal, topic, risk and benefit of the (additional) survey questions, provide an information sheet (Annex 4), and, if willing to participate, the interviewer will document a consent form (Annex 2) that the participants have verbally consented to these additional questions. Participants providing oral consent will be offered a copy of the participants' information leaflet. Information of household members of all ages will be included in

this part of the study. For individuals under 18 years of age, the responding parent or caretaker will be asked verbal consent, and adolescents >14 years of age will be asked verbal assent.

For phases I and III:

Participants in phase I interviews or informal conversations or discussions will be identified by the anthropology researcher, starting with the HDSS staff, health district staff and healthcare workers at CRUN, at the CMA and in the concerned health areas. Potential participants will be approached during working hours and proposed to participate to the semi-structured interviews and/or group discussions after working hours. Participants in phase III will be approached by the researchers in the health facility compound, when they are leaving it after a consultation.

All prospective interviewees will be informed before the start of the interview about project goals, the time requested for it, the topic and type of questions as well as their right to decline participation or to interrupt the conversation at any time, and that (non) participation or declining to participate will have no consequence for the access or quality of further healthcare. For health staff in licensed health facilities, it will be important to clearly state that this is not an evaluation, and that the contents of interviews will not be shared with their hierarchy/supervisors.

The informed consent interview will be conducted by an interviewer, who will have been trained in ethics requirements for informed consent, in a space allowing privacy of the interviewee and chosen or approved by them, and conducted in French or in Mooré, the most frequently spoken local language of the population in the Nanoro health district. Participants providing oral consent will be offered a copy of the participants' information leaflet.

The prospective participants information leaflets (Annexes 1, 4, 5 and 6) are adapted to each study phase and will be available in French, and translated in Mooré to illiterate particpants. The informed consent interview will be conducted in the language chosen by each prospective participant. The informed consent documents have been adapted to the study phase the person is participating in, and whether the interview concerns a child/adolescent or an adult. They will be paper-based, will be read to the patient or can be read by the patient.

For phase I, documented verbal consent (Annex 2) is proposed, because most interviewees will be informal healthcare providers, and requesting the subject's signature can have the potential of creating mistrust, leaving a trail for authorities to identify informal (sometimes not legal) vendors. If the prospective participant is willing to participate, the interviewer will declare and sign that the participant verbally consented. All participants will be above 18 years of age. The participant information leaflet (Annex 1) should be kept by the participant. The documented verbal consent

form signed by the data collector should be kept at a secure location, under the responsibility of the PI at CRUN.

For phase III, written informed consent will be obtained (Annex 5). For individuals under 18 years of age, the parent or caretaker will be asked to give the written consent (Annex 6), while adolescents >14 years of age will be asked a verbal assent (and their willingness not to participate should be respected). The participant information leaflet should be kept by the participant. The consent forms will on a daily basis be added to the investigator file, kept at a secure location, under the responsibility of the PI at CRUN.

5.3 Insurance

The Coordinator of this study, the Institute of Tropical Medicine has obtained an umbrella insurance to cover any injury, damage or loss to study participants and which is caused directly or indirectly by participation in low-risk studies (Annex 7).

5.4 Risk-benefit assessment

There is no direct health-related risk to this study. However, during the survey, interview or group discussion, it is possible that questions are asked about personal experiences, which might bring up bad memories, or that informal health providers might feel stigmatised, or that formal health providers may fear that their opinion could be shared with their superiors/used for evaluating them. In addition, there are risks related to privacy and confidentiality, and these are especially important for informal health providers. Last but not least, full confidentiality can never be assured in group discussions, because it depends also on other participants, and not only on the researchers; and if a follow-up call is needed (phase III), there might be risks related to the habit of sharing telephones. These risks will be mitigated in different ways. First, by de-identifying quantitative data and by protecting the confidentiality of qualitative data, as described in the section on Data Management; second, by choosing private locations for interviews (the questions and setting where these interviews are held, will be prepared in a way that makes the interviewee feel comfortable and secure, thus keeping this risk to a minimum); third, by explaining to participants in group discussion that they should commit to protect each other confidentiality, and by “segregating” group discussion by category of participants (as an example, no group discussion will be held involving at the same time informal healthcare providers and the official health authorities); forth, by discussing upfront in the informed consent interview the details of the follow-up phone call, to ensure that participants understand the possible risks before consenting to participate. How to deal with patients’ personal bad experiences, will be part of the interviewers’ skills and expertise, as documented by training and

experience records. When health providers need to move to participate in a group discussion, a transport reimbursement will be offered.

There are no direct benefits for interviewees participating in the study. However, interviewers will be trained on the subject, and additional pharmacological and medical support will be provided to them if needed, by referring specific questions related to antibiotic use, brought up during interviews, to the study PI. This will benefit the health providers' practices, leading to improved use of antibiotics. The study should allow setting up potential antibiotic stewardship interventions, which should benefit both the community's health, and provide support to healthcare providers.

It is possible that the qualitative interviews reveal bad medical practices, or even legally borderline behaviours. The qualitative researchers will be trained to identify major medical mistakes or bad medical practices. If such mistakes are identified, a feedback session with the study PI, a trained medical doctor, will be proposed to all the medical management team, to counsel them on good medical practice and educate on correct, evidence-based treatment. Direct corrective actions to the concerned health providers will be avoid in order to prevent them for stigmatization.

The patient healthcare exit interviews could reveal individual medical mistakes, such as prescription errors, e.g. contra-indicated antibiotics such as use of tetracyclines in children, wrong doses. The interviewer teams will be trained to detect potential severe and common treatment mistakes, and will refer/consult these with the study PI. If such mistakes are identified, these will be recorded, and after the interview of the patients addressed/discussed a.s.a.p. but in full confidentiality with the health provider, to allow the provider to rectify the treatment. If not (possible to) address the error with the concerned healthcare provider, the patient will be referred to the CMA in Nanoro. A clinician in the CMA will be informed when a patient is referred by the PI, and will follow up these referred patients, while ensuring discretion about the healthcare provider where the patient was referred from. The CMA staff will be informed on the possibility of such referrals from other healthcare facilities during the study. Each potential prescription, dispensing or usage mistake will be fully documented, at first by the interviewer, after a debriefing with the study PI, the study PI will further document the error (choice, dose, frequency, contra-indication, potential drug-druginteraction of the prescribed/dispensed/used medicine; mistake by whom), the corrective action undertaken (if so), feedback provided to the healthcare provider involved (if so), whether this has resulted in rectification, outstanding need to educate or create awareness about the practice involved, and follow-up of the patient in case the patient required referral. A file of each medication error with full documentation will be kept with the investigator file, and be de-identified as soon as corrective action has been undertaken. Throughout this process, the healthcare provider concerned

will not be identified, and full confidentiality will be retained, to avoid stigmatisation. Following data collection, structured feedback will be provided to the healthcare providers included in the study.

6 MONITORING AND QUALITY CONTROL

During phase I data collection, constant qualitative process evaluation will complement comparative analysis of intermittent quantitative indicators, to identify areas to focus on which could not be foreseen at the study design and protocol development stage. This is an on-going research process focused on detecting emerging issues and providing an immediate response in close interaction with the stakeholders (i.e. healthcare providers, patients, researchers involved in phase II or III).

Phase II data collection will follow the HDSS survey procedure. Before data analysis, the completeness and accuracy of the data will be verified (the number of non-responders, missing data, compare results from different interviewer teams). If the data quality of specific variables or observations cannot be guaranteed, the PIs with the support of a statistician could jointly decide to exclude specific observations and/or variables, with a justification for each exclusion (to be kept in the investigator's file and to be described and justified in the study report).

During phase III data collection, both in person and by phone, the CRUN PI, will be present on-site and generate every two days a summary and quality report, identifying inconsistencies (including keypunching errors, ranges, antibiotic-related inconsistency checks) in the recorded data, which he will follow up on with the interviewers, and monitoring recruitment to adjust the planning of healthcare providers (if the intended number of surveys per provider has been attained). The report should allow rectification the following study day whenever still possible.

7 TIMELINE

Activities	2020			
	Q1	Q2	Q3	Q4
Develop and finalize protocol				
Ethical review				
Population HC survey				
Patient HC exit questionnaires				
Data analysis/writing				
Country feedback session				
Manuscript preparation				

The protocol will be submitted for ethics review by 5 May 2020 to the Institutional Review Board of the ITM and when approval obtained to the Burkina Faso Ethic committee for Health Research, in June 2020. Outcome is expected by end of June 2020.

Phase I should be conducted during July, 2020. Shortly after, following preliminary analysis of the qualitative data and an inventory of healthcare providers in the health areas, phase III patient healthcare exit surveys will be conducted, during maximum 21 working days in September2020.

The healthcare utilization survey (phase II) in the 2 health areas will be conducted during one month starting July 2020.

Data collection for all three phases should be completed by September 2020, with findings of the qualitative study and quantification of community antibiotic use submitted for publication by December 2020. The subsequent surveys in other countries will be carried out in 2021/2022 and final output of the multi-country ecologic study is expected by 2023.

8 DATA MANAGEMENT

8.1 Data Management

Following transcription, translation, processing and coding of the phase I interviews and observations, the recordings of interviews, kept in password-locked files on a password-locked CRUN laptop, with a backup on the CRUN PI laptop, will be deleted within one year from the end of the study (planned for December 2021). No names will be recorded during transcription of recorded interviews. All original recordings, transcripts and notes will be pseudo-anonymized (not carrying a name or direct identifying information), but they will contain narrative information and data that easily allows indirect identification, especially with a small sample size. Therefore, the access to the social science database is restricted to the concerned members of the research team. A list of identified health care providers in the community, by type, will be stored in a separate paper based file, securely held with the Investigator's File.

All phase II and III data (health utilisation and patient healthcare exit surveys) will be recorded without personal direct identifying information but with a unique identifier which will be noted on the informed consent form. Data collection happens electronically on mobile devices using ODK (Open Data Kit; https://opendatakit.org/). Upon completion of the interview, the database will be exported to a .csv file and stored on both the CRUN and ITM PI password-locked laptops, who will not copy the data elsewhere. Subsequent to the extraction, the data will be deleted from the Open Data Kit database.

For phase III, there will be follow-up phone conversation. Phone numbers will be noted, together with names and study ID code, on a dedicated "Identification Log", which will only be kept by the concerned research staff. Patient's data (names and telephone numbers) will be erased after completion of the follow-up telephone call and/or any other needed medical follow-up (if a patient had to be referred, if a potentially harmful prescribing error was found).

The signed Informed consent forms will be kept secured in a folder at the CRUN office in Nanoro, under the responsibility of the CRUN PI, separated from the study database, and held with the Investigator's File.

The data collection summary and quality reports, fully documented follow-up of corrections made following feedback and verification of potential data inconsistencies with the interviewers (see section 6. monitoring and quality assurance) will be kept in the Investigator's File.

Data security for the above stated data management will be augmented by automatic computer virus scanning at start-up of each data analysis session, and password protection for accessing data. Access to the electronic database and Informed consent forms will be restricted to the CRUN and ITM PIs and coordinating investigator.

8.2 Data sharing

The study database will be the joint property of CRUN and ITM. Access to (viewing or extracting) the database will be jointly restricted to the CRUN and ITM PIs in order to safeguard the privacy of the study participants and to protect confidential and proprietary data. Special considerations for shared access to deidentified study databases (i.e. with Ministry of Health and World Health Organization) may be made upon request. The healthcare utilization (phase II) data can be shared with the HDSS researchers at CRUN, providing there is a research protocol with ethics approval from the competent body to re-use these additional data.

After reporting the primary objectives of the study, aggregated antibiotic use data will be made available through an open data repository (see section open access to research data). Other study data may be shared with other interested users under restricted conditions, provided that patient data is de-identified (in which patient identity cannot be determined, neither directly nor indirectly). Any subsequent reporting of the shared data will require approval from CRUN and ITM.

8.3 Archiving

As required by international guidelines and national regulations, the electronic database with the pseudonymized source data will be stored on an encrypted and pass-word locked USB key by the CRUN and ITM PI for 5 years. The informed consent forms will be kept in the secured folder at the CRUN office for 5 years. This is beyond the study completion, to allow for audits and inspections even after the study completion.

The CRUN and ITM PI are responsible for ensuring a secure and appropriate location for storage of the Investigator's File and any other study related documentation, as well as for ensuring that only site staff that is competent and delegated to work for the study has got access to the files.

8.4 Open access to research data

At the time of publishing the related manuscript, aggregated antibiotic use data (quantity of each antibiotic group in DDD; % incorrectly used AB), by type of health provider, will be made available through Open Science Framework (https://osf.io/).

9 DISSEMINATION OF RESULTS

We plan to write manuscripts for submission to peer-reviewed journals on the following subjects and findings:

1) Healthcare and antibiotic utilization in Nanoro, Burkina Faso: a mixed-method study;
2) The association between community-level antibiotic use and ABR prevalence in low- and middle-income countries: an ecologic study.

Following the analysis of the results of the cross-sectional study, with a detailed overview of antibiotics used by healthcare provider in relation to the ABR prevalence reported in the surveillance system, we plan an on-site feed-back session involving Ministry of Health staff of the health district, clinical staff of the CMA and the involved healthcare providers (including non-official providers). Another session will be held with MoH staff at national level. These feedback sessions with the manuscripts should guide the set-up of potential antibiotic stewardship interventions and policies or regulations related to the community-use of antibiotics.

The findings, combined with those in the DRC (CABU-DRC), should provide a baseline assessment of community-level antibiotic use to inform the set-up antibiotic use monitoring, in line with the WHO Global Action Plan on AMR objectives (two of five objectives: Set up surveillance of antibiotic use; optimize antibiotic use). A workshop to develop this is planned for May 2021 (if funding applied for, is granted), on the initiative of researchers of Queens University in Belfast, who developed a similar effort in high- and middle-income countries.

When the community-level antibiotic use has been measured in 12 neighbourhoods all together, in four countries, the ecologic study will be to provide insight in how antibiotic use is related to AMR, in order to guide priority setting when addressing incorrect use: which providers to focus on, patient behaviour to address, how use can best be optimized.

Apart from the peer-reviewed journal articles, findings will be communicated with the scientific community through conferences, and with ITM and CRUN's global network through the ITM colloquia and newsletters.

10 BUDGET

Activities	Monthly cost in Euro	Number of staff required	Period (month)	Total in Euro

Field work (Fuel, car, motorbikes, communication, contribution to data management)	255	5	4	5,100
Administration (paperwork, copies etc.)	200	1	6	1,200
Study start-up (Ethics submission, interview for staff recruitment, Protocol, GCP training)	1000		3	1,000
Data analysis and reporting	400	1	3	1,200
Total in Euro				8,500

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12 ANNEXES

12.1 Participant information form for in-depth interviews (phase I)

INFORMATION POUR LE PARTICIPANT - ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES phase I

Vous êtes invités à participer volontairement à une étude de l'Unité de Recherche Clinique de Nanoro (CRUN) et de l'Institut de Médecine Tropicale (IMT, Belgique). L'étude est décrite dans cette fiche d'information. Si vous avez des questions au cours de l'étude, n'hésitez pas à les poser. De plus, vous êtes bien entendu libre d'interrompre votre participation à l'étude à tout moment.

But et description de l'étude

L'augmentation de la résistance aux antibiotiques rend des médicaments actuellement utilisés pour des infections bactérielles inefficaces. L'usage d'antibiotiques donne une exposition des pathogènes aux antibiotiques, ainsi permettant le développement de résistance chez ces pathogènes. Afin de développer et introduire des interventions qui permettraient un meilleur usage des antibiotiques dans la communauté, nous devrions d'abord comprendre où, quand, comment et quels antibiotiques sont utilisés. C'est pourquoi cette étude est proposée. Nous voudrions d'abord identifier l'ensemble des acteurs de soins où les antibiotiques sont utilisés dans une communauté. Cette première étape sera suivie par des entretiens avec des patients pour étudier quels antibiotiques sont utilisés e plus fréquemment, et comment.

Temps requis pour la participation

On vous demandera de réserver environ une heure pour un entretien.

Participation volontaire

Votre participation à cette étude est entièrement volontaire et ce choix n'est pas documenté ou rapporté dans les documents de l'étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment.

Si vous souhaitez participer, indiquez verbalement que vous acceptez de participer à l'étude.

Confidentialité

Toutes les informations recueillies à votre sujet au cours de l'étude resteront strictement confidentielles. Votre nom n'est pas enregistré et toutes les informations que vous fournissez resteront confidentielles. Seuls deux chercheurs de l'équipe de recherche auront accès aux données et informations collectées. Il est possible qu'un extrait de l'entretien ou discussion serve de «citation» pour appuyer notre étude / notre travail. Cependant, toute information qui vous identifie restera confidentiel.

Si vous êtes d'accord d'y participer, l'entretien ou discussion restera confidentiel. Votre identité ou contact ne sera dans aucun cas partagé avec les autorités, ou les autorités sanitaires. Nous garantissons que toutes les informations seront traitées de manière strictement confidentielle, et votre nom sera remplacé par un code dans tous les documents officiels de l'étude.

En cas de discussion en groupe, nous vous demandons de respecter les autres participants et de préserver la confidentialité des autres. Si vous êtes mal à l'aise de participer à une discussion, nous expliquerons / discuterons jusqu'à ce que tous les participants comprennent et se sentent à l'aise pour participer ou, si vous le souhaitez, vous pouvez retirer votre participation.

Une fois votre participation confirmée, nous aimerions enregistrer notre conversation uniquement à des fins de recherche. Vous êtes libre de le refuser, cependant, cela aidera notre analyse et notre travail. Toutes les informations enregistrées seront détruites après l'étude.

Avantages

Votre acceptation de participer à cet étude ne présente aucun avantage personnel direct. Néanmoins, en participant, vous pouvez nous fournir des informations précieuses qui pourraient le développement de futurs activités d'éducation ou support scientifique, et qui pourraient être utiles pour votre communauté.

Il n'y a pas de compensation pour participer à cette étude. Si vous avez dû vous déplacer, les frais de transport seront pris en compte (une somme forfaitaire).

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le Comité d'éthique en Recherche Clinique de Burkina Faso et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: Valia Daniel; Telephone: 70285553; Email: valiadaniel@yahoo.com

Ou le Comité d'éthique pour la Recherche en Santé du Burkina Faso.

Nom: XX; Telephone: XX; Email: XX

(le consentement verbal du participant sera documenté par l'interviewer – voir annexe 2)

12.2 Documentation of consent form for in depth interviews (phase I) and health utilization surveys (phase II)

(En italique des points spécifiques à l'étude stade II. Nous préparerons deux différentes fiches)

CONSENTEMENT VERBAL à remplir par l'interviewer – ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES phase I/*II*

Je confirme que la fiche d'information a été lue et expliquée au répondant interviewé*, et aux personnes (>14 ans) dont la fréquence l'utilisation des soins de santé va être documenté.*

Je me suis assuré que le répondant a bien compris qu'il/elle peut choisir librement de participer à l'étude, qu'il/elle n'a pas à répondre à une question dont il/elle préfère pas répondre, et qu'il/elle peut à tout moment mettre fin à l'entretien.

Le répondant a eu l'occasion de poser des questions sur l'étude et ses objectifs. Si le répondant avait des questions, moi ou un collègue de l'équipe de recherche a répondu correctement et clairement aux questions.

Le répondant a été expliqué que son nom n'est pas enregistré*, ni le nom des personnes dont la fréquence l'utilisation des soins de santé va être documenté*, que les informations fournies resteraient pseudonymisés (pas d'identification directe), et que les enregistrements de l'entretien seront détruit au plus tard un an après la fin de l'étude.

L'âge du répondant est 18 ans ou plus.

Le répondant a consenti de participer à l'étude/ *L'adulte (>18 ans) dont la fréquence l'utilisation des soins de santé va être documenté a consenti de participer à l'étude*. *Pour les personnes entre 14 et 18 ans dont la fréquence l'utilisation des soins de santé va être documenté, on a vérifié qu'il/elle est d'accord que son gardien (adulte) ou chef de ménage va répondre pour lui/elle, et le gardien (adulte) ou chef de ménage devra consentir de participer à l'étude.*

Nom du chercheur Date (dd/mm/yy)

Signature du chercheur

N° de participant: ___

12.3 (Draft) guides for in-depth interviews

- Neighbourhood/village:

Who lives in this neighbourhood/village?
Are services (including healthcare) sought within the neighbourhood/village? Or are people of this neighbourhood working/going to school/seeking healthcare/buying medicine elsewhere?
Are there any particular patterns related to mobility of people in this neighbourhood (eg. Seasonal work, transportation)?
Who are the healthcare providers, agents/acteurs de santé? What are their roles?

- Household healthcare seeking in the neighbourhood

What do people do when they have fever? What do they do to treat fever?
Which household member usually decides on whether and where to seek healthcare?
Are household members, adult and minors, usually accompanied by anyone? What is their role in care?
Is healthcare seeking different depending on the household? Reasons? Socio-economic? Other?

- Healthcare trajectories

At what point in their disease episode do people usually seek healthcare with you (the interviewed healthcare provider)?
Is any healthcare sought before coming here?
Which diseases do you treat?
Why do patients come to you as a healthcare provider?
Do you/Where do you refer patients? Reasons for referral?
Does the decision to seek healthcare depend on other factors that could change, eg. Season? Mobility?
What is the role of distance and mobility in the choice (where) to seek healthcare?

- Personal qualifications

What diploma/training do you have? Where were you trained?
Do you prescribe/dispense medication? Specific classes of medication?
Are different profiles of health agents working in this facility/outlet? Which?

- Medical decision making

What type of patient visits do you offer? (eg. Consultations, observation, hospitalisation, only delivery/selling)
How do you diagnose? What tools do you have available (eg. Rapid diagnostic tests, clinical algorithms, guidelines)
Do you use a guideline for medical decision making? Which?

- Medication prescribed/dispensed

What medication do you prescribe/dispense? Large families (e.g. antibiotics, antimalarials, antihypertensive, diabetes, antituberculosis, ART,…) and modes of administration (oral: tablets, caps or suspensions/syrups, injectables)
Do you prescribe/dispense antibiotic or antibacterial medication? Which? Classes, mode of administration, most frequent?
How do you decide which antibiotic to prescribe/dispense (specific symptoms, first exclude other infections?)? Indications to prescribe/dispense antibiotics?
If not dispensed, where do patients obtain prescribed antibiotics?
If dispensed, prescribed antibiotics only? For specific antibiotic classes/groups? Prescribed where?

Do patients obtain full antibiotic courses? For how many days? Duration is indication specific? If not obtaining full antibiotic courses, how is the antibiotic course completed, if so?

- Patient perceptions

Are patients aware they might be suffering from a bacterial infection?
Is taking medicines/drugs common? What kind of medicines?
Are patients aware they receive an antibiotic to treat a bacterial infection?
Do patients ask for antibiotics/expect to receive antibiotics?
What are patients' possible reasons to search for antibiotics?
What is the role of traditional medicine?

- Infection prevention and control

If patients are kept in observation or hospitalised in the facility, are the observed/hospitalised patients separated from other patients?
Gloves used/handwashing by agent? (when, frequency, between different patient consultations?, for specific interventions such as injections or fingerpricks?)
Frequency of cleaning/washing? With soap/disinfectant? Which?
Water/tap available? From? If not, where is water obtained from?
Latrines? Type of latrine? Shared between staff and patients? Shared between patients?
Food/drinks of patients and staff? Where? Who prepares?

12.4 Participant information form for additional questions during the HDSS round (phase II)

INFORMATION POUR LE PARTICIPANT - ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES phase II

Aujourd'hui, en plus des questions que vous sont normalement posés dans le cadre du système d'information sanitaire et démographique, on voudrait vous demander de répondre à quelques autres questions ; et ceci, pour nous aider à comprendre où vous, votre famille et vos voisins cherchez des soins de santé en cas de maladie. Ces questions sont posées dans le cadre d'une recherche de l'Unité de Recherche Clinique de Nanoro (CRUN) et de l'Institut de Médecine Tropicale (IMT, Belgique).

L'étude est décrite dans cette fiche d'information. Si vous avez des questions maintenant, ou plus tard , n'hésitez pas à les poser, y compris des questions sur les risques potentiels, les avantages et les inconvénients de la recherche.

<u>But et description de l'étude</u>

Le but de cette étude est de comprendre l'utilisation des soins de santé et l'usage de médicaments, en particulier les antibiotiques, dans votre communauté (Nanoro). Les résultats de l'étude permettront de comprendre où et comment les médicaments sont utilisés, et où se trouvent des barrières pour accéder aux soins ou pour utiliser les médicaments. Cela, pourra permettre d'améliorer l'usage des médicaments, et en particulier des antibiotiques, dans votre communauté.

<u>Temps requis pour la participation</u>

Ces questions supplémentaires devraient prendre entre 5 et 20 minutes. En outre, on vous demande la permission de visiter votre ménage une deuxième fois pendant la saison sèche.

<u>Participation volontaire</u>

Votre participation à cette étude est entièrement volontaire, c'est-à-dire que vous avez le droit de refuser de participer, maintenant ou plus tard (au moment des visites à la maison), sans aucune conséquence. Ce choix ne sera pas documenté ou rapporté dans les documents de l'étude.

Vous, en tant que responsable principal pour la santé quotidienne et l'utilisation des soins de santé pour les membres de ce ménage, êtes invités à participer parce que vous vivez dans la localité où nous effectuons cette étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment. Vous êtes aussi libre de choisir les questions à répondre.

Si vous souhaitez participer, indiquez verbalement que vous acceptez de participer à l'étude.

Confidentialité

Toutes les informations recueillies sur vous ou votre ménage au cours de l'étude resteront strictement confidentielles. Votre nom n'est pas enregistré et toutes les informations que vous fournissez resteront confidentielles. Seulement l'équipe de recherche aura accès aux données et informations collectées.

Risques et avantages

Si des questions vous mettraient mal à l'aise, n'hésitez pas à tout moment de pas répondre à la question, de faire une pause, ou d'arrêter de participer à cette étude.

Il n'y a pas d'avantages directs à votre participation. Au cours des visites de votre ménage, notre équipe de recherche peut identifier les membres de votre ménage qui devraient chercher des soins de santé pour les maladies causant de la fièvre et autres. Par conséquent, l'équipe peut aider à fournir de l'information sur l'offre de soins établie dans votre communauté. Les avantages indirects sont que toutes les informations collectées contribueront à fournir des données importantes sur les problèmes de santé dans votre communauté. Ceci conduira à une meilleure compréhension du traitement de nombreux maladies, en particulier celles à traiter avec les antibiotiques, et de la façon d'améliorer l'accès aux soins de santé. Il n'y a pas de compensation pour participer à cette étude.

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le Comité d'éthique en Recherche Clinique de Burkina Faso et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

(le consentement verbal du participant sera documenté par l'interviewer – voir annexe 12.2)

12.5 Participant information + Informed consent form for the patient healthcare visit exit survey (adult participant)

INFORMATION POUR LE PARTICIPANT ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES phase III

Vous êtes invités à participer volontairement à une étude de l'Unité de Recherche Clinique de Nanoro (CRUN) et de l'Institut de Médecine Tropicale (IMT, Belgique), en répondant à quelques questions, principalement sur les traitements utilisés dans votre communauté. L'étude est décrite dans cette fiche d'information. Si vous avez des questions, maintenant ou plus tard, n'hésitez pas à les poser, incluant sur les avantages et les inconvénients de l'étude. De plus, vous êtes bien entendu libre d'interrompre votre participation à l'étude à tout moment.

But et description de l'étude

Le but de notre étude est de comprendre l'usage des certains médicaments pour traiter certaines maladies dans votre communauté, et en particulier de ce que les médecins appellent des *antibiotiques*: où ils sont prescrits ou distribués, et comment ces médicaments sont utilisés. Les résultats aideront à améliorer l'offre de santé, par exemple en développant d'outils adaptés pour les agents de santé, pour mieux utiliser ces médicaments. Ainsi, l'étude veut contribuer à l'usage correcte des antibiotiques, afin de garder ces traitements efficaces quand un malade en a besoin.

Nous allons vous poser quelques questions sur les médicaments qui vous ont été prescrits, donné, ou que vous avez acheté, par exemple le dosage, la fréquence avec laquelle vous allez prendre ces médicaments. On vous posera aussi quelques questions sur les raisons pour lesquelles vous avez cherché ces médicaments ici, chez cet agent de santé ou fournisseur de médicaments ; et on vous demandera de regarder les médicaments que vous venez d'obtenir. Finalement, nous vous demandons aussi la permission de vous appeler dans une semaine, pour une suivie sur l'achat et l'usage de ces médicaments.

Après la fin de l'étude, les données peuvent être partagés avec des autres chercheurs pour être utilisées dans des études ultérieures sur l'usage de médicaments. Avant de les partager, les donner seront « pseudo-anonymisées », ce qui veut dire que toute information qui permettrait de vous identifier, comme votre nom et numéro de téléphone, ne sera pas partagée.

Temps requis pour la participation

Répondre aux questions devrait prendre un maximum de 20 minutes. Le suivi après une semaine, par un appel téléphonique, ne devrait prendre que quelques minutes.

Participation volontaire

Votre participation à cette étude est entièrement volontaire, c'est-à-dire que vous avez le droit de refuser de participer, maintenant ou plus tard (au moment des visites à la maison), sans aucune conséquence. Le choix de ne pas participer ne sera pas documenté ou rapporté dans les documents de l'étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment. Vous êtes aussi libre de choisir les questions à répondre.

Si vous souhaitez participer, nous allons vous demander de confirmer par écrit que vous acceptez de participer à l'étude, et vous garderez une copie de ce document de « consentement », signé par nous deux.

Confidentialité

Toutes les informations recueillies au cours de l'étude resteront strictement confidentielles. Votre nom n'est pas enregistré et toutes les informations que vous fournissez resteront confidentielles. Seulement l'équipe de recherche aura accès aux données et informations collectées. Votre contact (n° de téléphone) sera gardé jusqu'à l'appel de suivi, et ne sera pas gardé après. Nous garantissons que toutes les informations seront traitées de manière strictement confidentielle, et votre nom sera remplacé par un code dans tous les documents de l'étude.

Risques et avantages

Il n'y a pas de risque direct associé à cette étude. Si des questions vous mettraient mal à l'aise, n'hésitez pas à tout moment de pas répondre à la question, de faire une pause, ou d'arrêter de participer à cette étude. Après avoir terminé les questions, l'équipe de recherche pourra fournir des informations sur les soins de santé communautaire, ou l'usage d'un médicament.

Au cours de l'entretien, notre équipe de recherche pourrait identifier des contre-indications ou des erreurs dans l'usage des médicaments, et ensemble avec le fournisseur de soins rectifier le traitement et vous aider à assurer une prise correcte du médicament. L'avantage indirect est que toutes les informations collectées contribueront à fournir des données exactes sur les traitements utilisés dans votre communauté, et peut ainsi conduire à une meilleure compréhension du traitement de nombreux maladies, et de la façon d'améliorer l'accès aux soins de santé. Il n'y a pas de compensation pour participer à cette étude.

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le Comité d'éthique en Recherche Clinique de Burkina Faso et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

PARTICIPANT

Nom du répondant (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

Si le répondant un témoin indépendant de l'équipe de recherche (par exemple membre du même ménage ou un voisin), doit être présente pendant l'entretien pour le consentement éclairé. Si à la fin de l'entretien, la personne accepte de participer, le témoin signera ce formulaire de consentement, et le/la participant/e enregistrera l'empreinte du pouce dans la boîte à côté.

Empreinte du pouce

TEMOIN

Nom du témoin (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

INTERVIEWER

Je confirme que la fiche d'information a été lue et expliquée au participant nommé ci-dessus dans une langue que le répondant comprend bien.

Je me suis assuré que le participant a bien compris qu'il/elle peut choisir librement de participer à l'étude, qu'il/elle n'a pas à répondre à une question dont il/elle préfère pas répondre, et qu'il/elle peut à tout moment mettre fin à l'entretien.

Le participant a eu l'occasion de poser des questions sur l'étude et ses objectifs. Si le répondant avait des questions, moi ou un collègue de l'équipe de recherche a répondu correctement et clairement aux questions.

Le participant a été expliqué que son nom n'est pas enregistré sauf sur le formulaire présent, qui sera gardé sécurisé, uniquement utilisé si le participant préfèrerait annuler sa participation à l'étude, et détruit un an après la fin de l'étude. Les informations fournies resteraient pseudo-anonymisés, c'est à dire que les identifiants directes tels que le nom seront remplacés par un code dans tous les documents officiels de l'étude .

Nom de l'interviewer (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

12.6 Participant information + Informed consent form for the patient healthcare visit exit survey (child or adolescent with caretaker)

INFORMATION POUR LE PARTICIPANT ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES phase III

Vous êtes invités à participer volontairement à une étude de l'Unité de Recherche Clinique de Nanoro (CRUN) et de l'Institut de Médecine Tropicale (IMT, Belgique), en répondant pour l'enfant pour lequel vous êtes parent ou gardien à quelques questions, principalement sur les traitements utilisés dans votre communauté. L'étude est décrite dans cette fiche d'information. Si vous, comme parent/gardien ou comme patient adolescent, avez des questions, maintenant ou plus tard, n'hésitez pas à les poser, incluant sur les avantages et les inconvénients de l'étude. De plus, vous êtes bien entendu libre d'interrompre votre participation à l'étude à tout moment.

But et description de l'étude

Le but de notre étude est de comprendre l'usage de certains médicaments pour traiter certaines maladies dans votre communauté, et en particulier de ce que les médecins appellent des *antibiotiques*: où ils sont prescrits ou distribués, et comment ces médicaments sont utilisés. Les résultats aideront à améliorer l'offre de santé, par exemple en développant d'outils adaptés pour les agents de santé, pour mieux utiliser ces médicaments. Ainsi, l'étude veut contribuer à l'usage correcte des antibiotiques, afin de garder ces traitements efficaces quand un malade en a besoin.

Nous allons vous poser quelques questions sur les médicaments que votre enfant (ou l'enfant pour lequel vous êtes gardien) ont été prescrits, donnés, ou que vous avez acheté pour votre enfant, par exemple le dosage, la fréquence avec laquelle l'enfant va prendre ces médicaments. On vous posera aussi quelques questions sur les raisons pour lesquelles vous avez cherché ces médicaments ici, chez cet agent de santé ou fournisseur de médicaments; et on vous demandera de regarder les médicaments que vous venez d'obtenir. Finalement, nous vous demandons aussi la permission de vous appeler dans une semaine, pour une suivie sur l'achat et l'usage de ces médicaments.

Après la fin de l'étude, les données peuvent être partagés avec des autres chercheurs pour être utilisées dans des études ultérieures sur l'usage de médicaments. Avant de les partager, les donner seront « pseudo-anonymisées », ce qui veut dire que toute information qui permettrait de vous identifier, comme votre nom et numéro de téléphone, ne sera pas partagée.

Temps requis pour la participation

Répondre aux questions devrait prendre un maximum de 20 minutes. Le suivi après une semaine, par un appel téléphonique, ne devrait prendre que quelques minutes.

Participation volontaire

Votre participation à cette étude est entièrement volontaire, c'est-à-dire que vous avez le droit de refuser de participer, maintenant ou plus tard (au moment des visites à la maison), sans aucune conséquence. Le choix de ne pas participer ne sera pas documenté ou rapporté dans les documents de l'étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment. Vous êtes aussi libre de choisir les questions à répondre.

Si vous souhaitez participer, nous allons vous demander de confirmer par écrit que vous acceptez de participer à l'étude, et vous garderez une copie de ce document de « consentement », signé par nous deux. Si l'enfant malade (la patient) a plus de 14 ans, nous demanderons s'il/elle est d'accord que son parent ou gardien répond pour lui/elle.

Confidentialité

Toutes les informations recueillies au cours de l'étude resteront strictement confidentielles. Votre nom et le nom de votre enfant ne sont pas enregistrés et toutes les informations que vous fournissez resteront confidentielles. Seulement l'équipe de recherche aura accès aux données et informations collectées. Votre contact (n° de téléphone) sera gardé jusqu'à l'appel de suivi, et pas gardé après. Nous garantissons que toutes les informations seront traitées de manière strictement confidentielle, et votre nom sera remplacé par un code dans tous les documents de l'étude.

Risques et avantages

Il n'y a pas de risque direct associé à cette étude. Si des questions vous mettraient mal à l'aise, n'hésitez pas à tout moment de pas répondre à la question, de faire une pause, ou d'arrêter de participer à cette étude. Après avoir terminé les questions, l'équipe de recherche pourra fournir des informations sur les soins de santé communautaire, ou l'usage d'un médicament.

Au cours de l'entretien, notre équipe de recherche pourrait identifier des contre-indications ou des erreurs dans l'usage des médicaments, et ensemble avec le fournisseur de soins rectifier le traitement et vous aider à assurer une prise correcte du médicament. L'avantage indirect est que toutes les informations collectées contribueront à fournir des données exactes sur les traitements utilisés dans votre communauté, et peut ainsi conduire à une meilleure compréhension du traitement de nombreux maladies, et de la façon d'améliorer l'accès aux soins de santé. Il n'y a pas de compensation pour participer à cette étude.

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le Comité d'éthique en Recherche Clinique de Burkina Faso et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

REPONDANT

Nom du répondant (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature :

_____

Empreinte du pouce

Si le répondant un témoin indépendant de l'équipe de recherche (par exemple membre du même ménage ou un voisin), doit être présente pendant l'entretien pour le consentement éclairé. Si à la fin de l'entretien, la personne accepte de participer, le témoin signera ce formulaire de consentement, et le/la participant/e enregistrera l'empreinte du pouce dans la boîte ci-dessus

TEMOIN

Nom du témoin (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

INTERVIEWER

Je confirme que la fiche d'information a été lue et expliquée au répondant nommé ci-dessus et (si le patient concerné est adolescent) au patient concerné dans une langue qu'ils comprennent bien.

Je me suis assuré que le répondant et (si le patient concerné est adolescent) l'enfant ont bien compris qu'il/elle/ils peut/peuvent choisir librement de participer à l'étude, que le répondant n'a pas à répondre à une question dont il/elle préfère pas répondre, et qu'il/elle peut à tout moment mettre fin à l'entretien.

Le répondant a eu l'occasion de poser des questions sur l'étude et ses objectifs. Si le répondant avait des questions, moi ou un collègue de l'équipe de recherche a répondu correctement et clairement aux questions.

Le répondant a été expliqué que son nom n'est pas enregistré sauf sur le formulaire présent, qui sera gardé sécurisé, uniquement utilisé si le répondant préfèrerait annuler sa participation à l'étude, et détruit un an après la fin de l'étude. Les informations fournies resteraient pseudo-anonymisés, c'est à dire que les identifiants directes tels que le nom seront remplacés par un code dans tous les documents officiels de l'étude.

Nom de l'interviewer (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

12.7 Proof of insurance for low-risk studies involving human participants

BIJ-336 v 1.3

Commissie Medische Ethiek
Prof. Dr. Peter Michielsen
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10
2650 Edegem

Concerns - No-fault liability insurance for the submitted protocol- Amlin Corporate public liability insurance agreement N° 99-002-067

Dear Chairperson

By means of this letter, I wish to inform you about the insurance agreement pertaining to this research study.

As required by the Belgian law on experiments involving human subjects of May 7th 2004, a no-fault liability insurance must be in place for this research study. As a research institute, we have negotiated an umbrella agreement with *Amlin Corporate Insurance* in which our minimal risk studies, in Belgium or abroad, are automatically no-fault insured. This umbrella agreement requires neither preceding notification to our insurer, nor a separate, study specific insurance agreement.

Since the herewith submitted study is a low-risk study which falls under this umbrella agreement, no separate insurance agreement has been drawn up.

Limits of indemnity are as follows:

Bodily injury: € 5.000.000,- per occurrence and per insured year
Material damage: € 1.000.000,- per occurrence and per insured year

I hope this arrangement and clarification is satisfying to you. In case of any additional questions, please do not hesitate to contact me.

Lastly, I wish to thank you for your genuine review and evaluation of the submitted study.

Sincerely,

Prof. Dr. Marc-Alain Widdowson
Director

T. 03 247 07 62 00
E. mawiddowson@itg.be

Institute of Tropical Medicine - Nationalestraat 155, 2000 Antwerp, Belgium
www.itg.be - Foundation of Public Utility 0410.057.701 - IBAN BE38 2200 5311 1172

MINISTERE DE LA SANTE

MINISTERE DES ENSEIGNEMENTS SECONDAIRE, SUPERIEUR ET DE LA RECHERCHE SCIENTIFIQUE

COMITE D'ETHIQUE POUR LA RECHERCHE EN SANTE

BURKINA FASO
Unité - Progrès - Justice

DELIBERATION N° 2010-27

1. TITRE DE LA RECHERCHE

Pharmacovigilance des combinaisons thérapeutiques à base d'artémisinine en Afrique

2. REFERENCE DU PROTOCOLE

Version n°3 du 02 mars 2010

3. DOCUMENTATION

- protocole de recherche ;
- budget de l'étude.

4. REFERENCE DU DEMANDEUR

Investigateur principal : Dr TINTO Halidou PharmD., Mcs, PhD, IRSS-DRO/Unité de Recherche Clinique de Nanoro (URCN), CMA Saint Camille de Nanoro

5. SITES DE LA RECHERCHE

Département de Nanoro

6. DATE DE LA DELIBERATION

14 avril 2010

7. ELEMENTS EXAMINES

- conception scientifique et conduite de la recherche ;
- soins et protection des participants à la recherche ;
- protection de la confidentialité des données du participant à la recherche ;
- processus de consentement éclairé ;
- budget de la recherche.

8. OBSERVATIONS (incomplet)

- relire les fiches d'information des participants à l'étude pour les adapter à une étude de pharmaco vigilance et non de recherche clinique ;
- retirer du formulaire de consentement éclairé (page 4), « représentant légal ou parent » pour la femme en grossesse.

9. AVIS DU COMITE

Avis favorable
Soumettre au Comité la version amendée du protocole qui prend en compte les observations ci-dessus.

10. RESERVES

RAS

11. RECOMMANDATIONS

Ouagadougou, le 14 avril 2010

Le Rapporteur

Scholastique M. D. TRAORE

Le Président

Dr Bocar A KOUYATE
Chevalier de l'Ordre national