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Post ExpOsure Prophylaxis for LEprosy in the Comoros and Madagascar

PEOPLE

Initial Protocol
Version 1.7, 18-Mar-2022

Sponsor: Institute of Tropical Medicine
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STATEMENT OF COMPLIANCE

By signing this protocol, the Investigator(s) acknowledge(s) and agree(s):

This protocol contains the necessary information for conducting this clinical study. The Principal Investigator will conduct this study as detailed herein and will make every reasonable effort to complete the study within the time designated. The Principal Investigator commits to carry out the study in compliance with the protocol, amendments, applicable procedures and other study-related documents provided by the Sponsor, and in compliance with the Declaration of Helsinki, Good Clinical [Laboratory] Practice (GC[L]P), the ESF/ALLEA Code of Conduct for Research Integrity, and applicable regulatory requirements.

The protocol and all relevant study information, which is provided by the Sponsor, will be made available to the physicians, nurses and other personnel who participate in conducting this study. The Investigator will use this material for their training so that they are fully informed regarding the drugs and the conduct of the study.

The Sponsor of this study – the Institute of Tropical Medicine in Antwerp, Belgium (ITM) – will at any time have access to the source documents from which Case Report Form information may have been generated and will be permitted to perform trial-related monitoring and audits. All study material will be maintained according to regulatory requirements and until the Sponsor advises that retention is no longer necessary.

DIRECTOR OF THE INSTITUTE OF TROPICAL MEDICINE:

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Signing this document, I commit to carry out the trial in accordance with the protocol, Good Clinical Practice and applicable ethical and regulatory requirements. I also acknowledge the paragraph relevant to study confidentiality and authorize the Institute of Tropical Medicine, Antwerp, Belgium to record my data on a computerized system containing all the data pertinent to the study.

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SYNOPSIS

This study will evaluate different modalities of post exposure prophylaxis (PEP) for leprosy on Madagascar and the Comoros. The islands of Anjouan and Mohéli on the Comoros are hyperendemic for leprosy with annual incidence rates of close to 10 per 10,000.[1] On Madagascar the disease is less endemic but still on an annual basis around 1,500 new cases are detected, while there are reasons to believe that the actual incidence may be substantially higher. One of the interventions currently advocated to curb transmission of leprosy is post exposure prophylaxis (PEP). However, in its 2016-2020 global leprosy strategy, WHO calls for more research into optimal implementation modalities.[2] Building on the results of the COLEP study that was conducted in Bangladesh, we will identify optimal target populations for PEP.[3] The COLEP study was a large cluster randomized trial in which the intervention arm was a single dose of Rifampicin (SDR) that was provided to close contacts of leprosy patients. In intervention clusters, there was a 57% reduction in leprosy incidence over a two-year period when compared to a placebo group. The highest protective efficacy was found in non-blood related contacts. Another trial on PEP for leprosy, the LPEP trial, is currently ongoing in India, Indonesia, Myanmar, Nepal, Sri Lanka, Tanzania, Brazil and Cambodia and is designed to evaluate effectiveness, impact and feasibility of contact tracing and SDR-PEP for leprosy under routine program conditions.[4, 5] The LPEP trial addresses aspects of feasibility of PEP under program conditions but does not address the issue of which contacts to target. An earlier study in Indonesia has shown that in hyperendemic contexts SDR-PEP given to household contacts alone may not be sufficiently effective.[6]
Therefore, the planned PEOPLE trial will be a cluster randomized trial aiming to:

1. Identify which approach to the selection of contacts for post exposure prophylaxis is most effective to reduce incident leprosy
2. Interrupt ongoing transmission from asymptomatic persons in the process of developing multibacillary leprosy.

Studies by Boeree et al. in tuberculosis treatment have shown that the early bactericidal effect of rifampicin is proportional to the dose used, and that safety is excellent and not dose related.[7] Even weight banding does not appear to be necessary. A recent study performed by our own group (ClinicalTrials.gov Identifier: NCT02153528) has provided extensive safety data for daily use of high rifampicin doses in adults for weeks, up to 6 months. This study too showed no increase in the risk of adverse events. We therefore opted for doubling the dose of Rifampicin in SDR-PEP from 10 mg per kg to 20 mg per kg and will refer to this regimen as 'single double dose rifampicin post exposure prophylaxis' or SDDR-PEP.

There will be four study arms to which villages on three islands (Anjouan, Mohéli and Madagascar) will be randomly allocated. These villages have been preselected based on leprosy incidence over the period 2013-2017. In all four study arms, annual door-to-door surveys will be conducted covering entire villages. All permanent residents will be invited for screening for leprosy.. Leprosy patients (further referred to as 'index patients') detected will be offered free treatment according to the international and country guidelines. In arm 1 no PEP will be provided, which is the current routine care on Madagascar and the Comoros. In arms 2, 3 and 4 SDDR-PEP will be offered to all eligible participants who have not received PEP in the preceding 2-year period. In arm 2 only household contacts of an index patient will be provided with SDDR-PEP, which target group is considered the standard approach when PEP is provided for leprosy. In arms 3 and 4 SDDR-PEP will also be provided to neighborhood contacts living within a radius of 100 meter of an index patient. In arm 3 all such contacts (including household contacts) will be provided SDDR-PEP, in arm 4 SDDR-PEP will be provided to all household contacts and to all those within the 100-meter perimeter testing positive to a serological screening test. Detailed costing will be performed of all study procedures.

In a second part of the study all incident leprosy patients identified during the trial period will be recruited and samples will be collected, in particular skin biopsies, slit skin smears, tongue swabs (only in Comoros) and nasal swabs. These samples will be used for DNA extraction and genotyping of the bacilli, which will allow us to assess at which level leprosy is clustered in the study villages/ islands.

The primary outcome measure will be the incidence rate of leprosy by study arm measured between the first and the fourth survey round. Incidence rate ratios will be calculated using the rate observed in arm 1 (no PEP) as reference category. As secondary outcomes we will calculate risk ratios for leprosy based on physical distance from the nearest index household, proportions of phylogenetically clustered patients, proportions of patients belonging to the social network of another patient, and cost per person treated with SDDR-PEP for each study arm.

1. INTRODUCTION

1.1 Background

Leprosy is an ancient infectious disease transmitted from man to man, probably via the airborne route. After contact with the causative microorganism (*M. leprae*) and before the onset of skin and nerve lesions, an infected person may be asymptomatic for years. Delayed treatment can lead to visible deformities, causing stigma. In 1991, the World Health Assembly decided on a leprosy elimination strategy aiming at reducing the prevalence to below 1 per 10,000 worldwide, assuming that at such levels transmission will eventually cease.[8] Leprosy prevalence has since then been greatly reduced, from almost 5 million in the 1980s to approximately 172,000 by early 2017. However much of the reduction in prevalence has been due to changes in case definition and in treatment duration, the latter having been reduced from lifelong to maximum two years and then again to maximum one year. The decline in leprosy incidence has been less impressive. After a steep decline between 2000 and 2005, reported worldwide leprosy incidence has now plateaued above 200,000 annually, showing continued transmission of the *M. Leprae*.[9]

The islands of Anjouan and Mohéli of the Comoros have been highly endemic for leprosy since decades, despite good adherence to WHO leprosy control guidelines. Yearly 300-400 new leprosy cases are detected on a population of approximately 450,000. Patients are generally detected at an early stage though, reflected in the fact that less than 3% of newly diagnosed patients present with visible deformities.[10] Madagascar has a much larger population (approximately 26 million) and has been reporting approximately 1,500 new leprosy patients per year over the last decade, without any apparent trend towards decline. In comparison to the Comoros, a much higher proportion (19% in 2016) present with visible deformities at time of diagnosis. In both countries, a substantial proportion of patients are children below 15 years of age (8% on Madagascar, 27% on the Comoros), indicative of ongoing active transmission.[10]

The WHO Global Leprosy Strategy 2016-2020 mentions post exposure prophylaxis (PEP) as one of the strategies requiring further research to overcome the current stalemate.[2] Studies in Indonesia and Bangladesh have shown that substantial reductions in leprosy incidence can be achieved when Rifampicin is provided to contacts of leprosy patients. In Bangladesh 57% reduction in incidence was achieved when comparing intervention clusters to placebo clusters, over a two-year period. [3] A single dose of Rifampicin had been provided to household contacts as well as close social contacts of leprosy patients. In Indonesia a three-fold reduction in incidence was achieved when treating an entire island population with two doses of Rifampicin given in an interval of one month.[6] On the contrary, in this hyperendemic setting, treating only household and social contacts showed no effect. Though a trial on a more potent regimen (PEP++ trial, including three doses of Rifampicin plus Moxifloxacin) is in the planning stages, the current standard of care when it comes to PEP is Rifampicin in a single dose (SDR-PEP). The aim of the trial described in this protocol (PEOPLE) is to document effectiveness of three alternative ways of implementing SDR-PEP at village level, by comparing to villages in which no PEP is provided.

We will also enroll all leprosy patients diagnosed during the trial and collect samples (skin biopsy, slit skin smear, tongue swabs (only in Comoros) and nasal swab) with the aim of genotyping the causative bacilli to establish chains of transmission. With this study, we are in the search for less invasive samples to confirm microbiologically a leprosy diagnosis. A recent study on tuberculosis confirmed that *Mycobacterium tuberculosis* (transmitted via the upper respiratory tracts) is present on the papillae of the tongue of TB patients, and can be collected and confirmed with qPCR. The main transmission route for *Mycobacterium leprae* is also via the upper respiratory tract and thus we hope that *M. leprae* is also present on the tongue of clinically diagnosed leprosy patients, so that in the future we could replace invasive sampling by minimally invasive sampling like a tongue swab.

1.2 Rationale

Though SDR-PEP has been shown to be effective in reducing leprosy incidence, uncertainty exists about the optimal implementation modalities, particularly in environments of high incidence. In the PEOPLE trial we will compare different modalities of SDR-PEP and we will also perform DNA finger printing of strains of all incident cases in the study areas.

We will compare a study arm without PEP, which is the current standard of care in leprosy, to three intervention arms in which SDR-PEP is provided in different modalities. The first arm is the comparator arm in which door to door screening will be conducted but no PEP will be provided. In the second arm only household contacts of an incident case will be provided SDR-PEP, in the third arm SDR-PEP will be provided to all those residing within 100 meter of an incident case. In the fourth arm we will first conduct a rapid screening test for antibodies against *M. leprae* (anti-phenolic glycolipid-I or anti-PGL1) and treat all household contacts plus those residing within 100 meters that test positive to anti-PGL1. If in the third or fourth arm more than 50% (arm 3) or 75% (arm 4) of the village population need to be covered (with anti-PGL1 testing and/or provision of SDR-PEP), we will cover the entire village. The effect will be measured by comparing incidence in each of the intervention arms (arms two, three and four) to incidence in the comparator arm (arm one).

Including the study arm with the serological test (arm 4) will serve two purposes. The assumption is that transmission of leprosy is maintained by clinically apparent multi-bacillary patients. It has however been hypothesized that clinical multi-bacillary patients may just be the tip of the iceberg and that asymptomatic persons at the multibacillary side of the spectrum may be more important as sources of transmission because of their higher numbers. Such persons are expected to test positive to anti-PGL1 and can therefore be identified by a screening test. If this can be demonstrated, this would not only be important because of its effect on transmission but it would also seriously reduce the number needed to treat with PEP.

The results of DNA finger printing of incident leprosy patients will allow us to identify chains of transmission and levels of clustering (i.e. households, neighborhoods or entire villages), which will allow us to further rationalize the decisions on which groups of contacts to target with PEP.

In the COLEP study in Bangladesh there was a clear and statistically significant reduction of leprosy incidence in the two years following SDR-PEP implementation using Rifampicin in a dose of 10 mg/kg however the effect was only 50-60%.[3] The PEP++ trial, which is currently still in the planning stage, will use a reinforced PEP regimen consisting of three doses of Rifampicin plus Moxifloxacin for adults or Rifampicin plus Clarithromycin for children. The three doses will be administered with intervals of one month in between. This combination is expected to have higher efficacy (90% instead of 50-60%) but this still needs to be verified. Moreover administering three doses over a two-months period is logistically much more complex than administering a single dose. For reasons explained below we opt for a single dose of Rifampicin, but at a higher dosage than usual.

Rifampicin is also one of the cornerstones of tuberculosis treatment. When the drug was introduced in the 1970s, a dose of 10 mg/kg was chosen based on cost considerations and fears for toxicity.[7] This dose is probably at the lower limit of optimal efficacy.[11] Diacon *et al*. (2007) studied early bactericidal activity of Rifampicin in tuberculosis, comparing the regular dose (10 mg/kg) to a double dose (20 mg/kg). They observed a doubling of early bactericidal activity when the dose is doubled. More recently Boeree *et al*. tested even higher doses of Rifampicin, up to 35 mg/kg.[7] . They concluded that two weeks Rifampicin up to 35 mg/kg was safe and well tolerated, and that there was a non-linear increase in exposure to Rifampicin due to saturation of first-pass excretory capacity of the liver. In our very recent study 'Optimization of the TB Treatment Regimen Cascade (OneRIF, ClinicalTrials.gov Identifier: NCT02153528) no increase in toxicity was observed among 475 adult

patients who received Rifampicin in a dosage of 20mg/kg daily for six months as part of their treatment for tuberculosis, compared to 468 control patients receiving the regular dosage of 10 mg/kg. In leprosy too, higher doses of Rifampicin have been used both as post exposure prophylaxis and as treatment. Cartel *et al*. used a dosage of 25 mg/kg in a trial in French Polynesia.[12-14] Pattyn *et al.* treated leprosy patients with a single dose Rifampicin of 40 mg/kg, a regimen that proved effective in PB patients with a negative bacillary index. [15] Importantly the regimen was well tolerated and no side effects were observed among 240 patients evaluated. We therefore opted for a Single Double Dose Rifampicin Post Exposure Prophylaxis, or SDDR-PEP, of 20 mg/kg in the PEOPLE trial.

Since we will be conducting door-to-door surveys and pulmonary tuberculosis (PTB) is a major public health problem on the Comoros as well as on Madagascar, we will seize the opportunity to also enquire about chronic cough (of longer than two weeks' duration) and collect sputum samples from the individuals concerned. In both countries the leprosy and TB control programs are fully integrated at district level, allowing for easy referral of PTB suspects and/or patients identified.

2. STUDY OBJECTIVES AND OUTCOMES

2.1 Primary

To compare effectiveness in curbing transmission of leprosy of three different approaches of post exposure prophylaxis

Outcome: Three incidence rate ratios between the comparator arm and each of the intervention arms. These ratios will be based on incidence rates measured between the first and fourth household survey in each of the intervention arms, divided by that of the comparator arm.

2.2 Secondary

1. To assess cost and feasibility of SDDR-PEP under program conditions

   Outcome: Costs will be calculated per person screened, per person treated with SDDR-PEP and per leprosy case averted.

2. To identify patterns of clustering in transmission of leprosy, allowing better targeting of control measures

   Outcome: We will quantify the degree of clustering as the average proportion of leprosy cases belonging to a same phylogenetic cluster by village. Geographic clustering will also be assessed by calculating risk ratios for being diagnosed with leprosy as a function of geographic distance from incident cases diagnosed earlier in each of the four arms

3. To monitor rifampicin resistance among leprosy patients

   Outcome: We will quantify prevalence of Rifampicin resistant strains of *M. leprae* on each of the study islands making use of molecular markers.

3. STUDY DESIGN

3.1 General study design

The PEOPLE study is a phase 3-4 cluster randomized trial on effectiveness of different modalities of SDDR-PEP, i.e. PEP in the form of a single dose of 20 mg per kg bodyweight of Rifampicin. There are

four study arms to which villages on three islands (Anjouan, Mohéli and Madagascar) will be randomly allocated.

In all four study arms, four annual door-to-door surveys will be conducted covering entire villages. All permanent residents will be invited for screening, All leprosy patients detected will be offered free treatment according to the international and country guidelines.

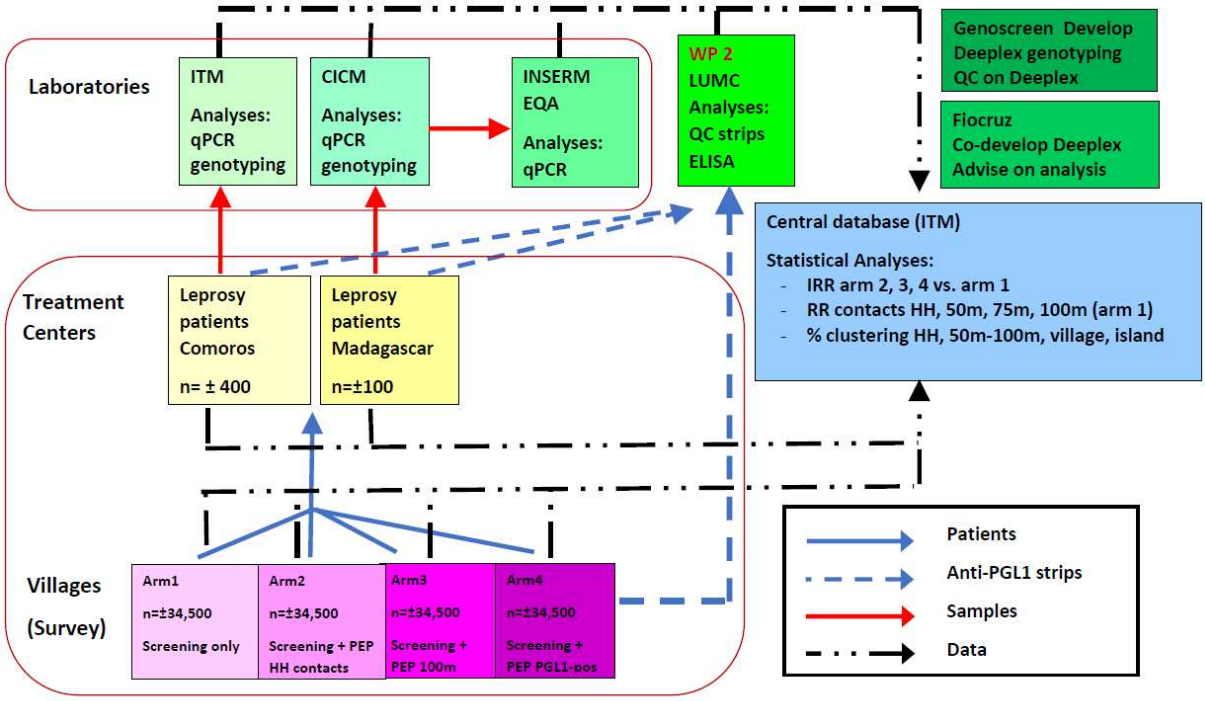
In arm 1 no SDDR-PEP will be provided, which is the current routine care on Madagascar and the Comoros. In arms 2, 3 and 4 SDDR-PEP will be offered to all eligible participants who have not received PEP in the preceding two-year period. In arm 2 only household contacts of an incident case will be provided with SDDR-PEP, which is the most common choice for PEP for leprosy. In arms 3 and 4 SDDR-PEP will also be provided to neighborhood contacts living within a radius of 100 meter of an index patient. In arm 3 all such contacts (including household contacts) will be provided SDDR-PEP, while in arm 4 all household contacts will be provided with SDDR-PEP, as well as other neighborhood contacts testing positive to a serological screening test. The test that will be used for this purpose is the anti-phenolic glycolipid-I (anti-PGL-I) test.(7) The test is in the format of a lateral flow test that can be read in the field, afterwards the test strips are sent to LUMC for quality assurance. The anti-PGL-I test identifies multi bacillary (MB) leprosy patients but also those who are still asymptomatic but progressing towards MB leprosy. Though passive case finding will continue throughout the year, anti-PGL-I testing and provision of PEP will only be done on a yearly basis, at the time of the screening rounds. However when deciding on risk zones and PEP provision, all leprosy patients identified will be taken into account, also those found in between surveys. In case in villages allocated to arm 3 more than 50% of the population would be included for SDDR-PEP, the entire village will be enrolled. In case in villages allocated to arm 4 more than 75% of the population would be included for SDDR-PEP and PGL1 screening, the entire village will be enrolled.

Before the start and during the first year of this clinical study there will be an anthropological study for which a separate protocol will be submitted. The main purpose of this sub-study will be to identify possible ways of improving acceptability. The anthropological study will also include a social network analysis. In case the anthropological study will reveal ways to improve acceptability, the PEOPLE protocol will be amended to include these.

Apart from the general population enrolled during door-to-door surveys, we will also enroll all leprosy patients detected during the study period. For this substudy a separate informed consent will be asked. This will be part of secondary objective number 2: 'To identify patterns of clustering in transmission of leprosy, allowing better targeting of control measures'. For this purpose several samples will be collected, i.e. nasal swab, tongue swabs (only in Comoros), slit skin smear and a 4mm punch biopsy of the lesion (except if the lesion is in the face). Samples to be collected include nasal swabs and tongue swabs (only in Comoros) for all patients and skin biopsies from non-facial lesions. Slit skin smears will be collected from all multi-bacillary patients. These samples will be tested with Ziehl-Neelsen (ZN) microscopy, with anti-PGL-I and with qPCR for *M. leprae* DNA. *M.leprae* DNA from qPCR positive samples will be used for DNA finger printing, which will in turn be used to establish phylogenetic clusters. Phylogenetic clustering will allow us to assess to which degree patients are infected by near neighborhood contacts or whether more remote contacts also play a role. In arm 4 in which all close neighborhood contacts will be tested with anti-PGL-I, in the second survey round we will also collect nasal swabs for qPCR from a subset of all contacts enrolled, to assess whether the presence of *M. leprae* DNA, indicating exposure/ "carrier state", is a risk factor for developing incident leprosy. The presence of DNA does not confirm that persons have colonization or disease with live *M. leprae*.

Figure 1: Flow chart of the PEOPLE trial (not including samples collected for tuberculosis screening)

Flow chart PEOPLE trial



In addition to the immunological and molecular studies, as part of the anthropological sub-study, social networks of patients will be mapped. For this study a separate protocol will be submitted for ethics approval. This again will help in corroborating whether or not observed reductions in incidence can be attributed to PEP having been provided to close neighborhood contacts.

While conducting the door-to-door surveys, staff will also ask whether or not each person screened for leprosy has been coughing for more than two weeks. Any person reporting cough of more than two weeks' duration will be asked for a sputum sample which will be tested for pulmonary tuberculosis by ZN smear microscopy and/or GeneXpert (according to the national TB program guidelines). Further management of tuberculosis patients and or suspects identified will be the responsibility of the national tuberculosis control programs. In both countries these programs provide free anti-tuberculosis treatment and care according to international standards.

The study is expected to start in the fourth quarter of 2018, and will end October 1st, 2022. A Gantt chart of the main project activities is presented below. The total study duration is estimated to be 42 months with a six months preparatory phase and three months for analysis.

Activity	2018		2019				2020				2021				2022		
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3
1. Obtaining ethics approval main study protocol																	
2. Finalizing survey procedures																	
3. Informing communities																	
4. First door-to-door survey																	
5. Outline risk areas arm 3 and 4																	
6. Baseline anti-PGL-1 testing (arm 4)																	
7. Baseline PEP (arm 2,3,4)																	
8. Second door-to-door survey																	
9. Redefine risk area																	
10. Anti-PGL-I testing + PEP																	
11. Third door to door survey																	
12. Redefine risk area																	
13. Anti-PGL-I testing + PEP																	
14. Fourth door-to-door survey																	
15. Data analysis																	

4. PARTICIPANTS, POPULATION & SELECTION

4.1 Study settings

The study takes place in two African countries, Comoros and Madagascar. On the Comoros we will include 56 villages distributed across two islands (Anjouan and Mohéli), on Madagascar 16 to 24 clusters of hamlets (fokontanys) from one district will be sampled. In both countries there are national leprosy and tuberculosis control programs (NLTCP) in place that provide free diagnostic and treatment services for both diseases, in accordance with international standards. Patients with skin conditions can present at public health centers where they are examined by general health services staff who have been trained in diagnosing and treating leprosy. They are supervised by staff from the national leprosy control programs, to whom they can also refer patients for consultation. In both countries the national leprosy control programs provide specific treatment free of charge, either directly or through the primary healthcare system. In addition outreach campaigns at village level are organized in which persons with skin conditions are invited to present themselves for screening. Free treatment is provided for minor skin conditions, any leprosy patient diagnosed receives full treatment. Such outreach campaigns, also called 'mini-campaigns' have been introduced on the Comoros since 2008 and were initiated more recently on Madagascar. For the PEOPLE trial, door-to-door screening activities will be carried out by mobile units under the direct supervision of the respective NLTCPs and under responsibility of the PI of each country. On the Comoros such surveys have already been successfully carried out by NLTCP staff in August/ September, 2017, covering four villages with an estimated population of 8,400. The mobile units will receive the necessary protocol and GCP training prior to the start of the study.

Any leprosy or tuberculosis patients identified will be treated according to the national guidelines of the countries, which are in accordance with WHO guidelines.

4.2 Study population and selection criteria

All those eligible for participation in the study will be screened yearly for leprosy and tuberculosis. As per study design, participants living in the surroundings of an index case may be given SDDR-PEP. Participants may choose to be screened for leprosy, but refuse to take PEP. Eligibility criteria only applicable for those receiving SDDR-PEP are marked below with (*).

All leprosy patients diagnosed during the study period will also be enrolled for addressing the second secondary objective: 'To identify patterns of clustering in transmission of leprosy, allowing better targeting of control measures'.

Inclusion criteria

1. Living in one of the study villages (32 on Anjouan, 16 on Mohéli and 16-24 on Madagascar)
2. Aged 2 years and above, as leprosy is very rare among infants and young toddlers
3. Able and willing to provide informed consent for leprosy and tuberculosis screening, and SDDR-PEP administration (as applicable in the different arms)
4. For leprosy index cases only: able and willing to provide informed consent for participation and sampling

Exclusion criteria

1. Signs of active leprosy (*)
2. Signs of active pulmonary tuberculosis (cough ≥2 weeks duration) (*)
3. Having received Rifampicin within the last 24 months (*)

4.3 Sample size

The sample size has been calculated based on the needs for the primary objective, using the methodology described by Hayes and Bennet for pair matched randomized controlled trials.(10) We will compare the arm with no PEP to each of the three intervention arms. At the start of the trial we assume an annual incidence rate of 1.5/1,000 based on data from the Comoros for 48 villages over the period of 2013-2017.

Our aim is to show a 50% reduction in incidence in any of the intervention arms in comparison to the comparator arm, over a 3-year period. Taking into account the fact that we will make 3 comparisons we opted to perform all tests at a significance level of 0.017. Based on the data from the Comoros we calculated a coefficient of variation between clusters (κ) of 0.29. To achieve a power of 80% with an average cluster size of 2,400, 13 clusters per study arm would be required, i.e. 4 * 31,200 participants. To account primarily for inaccuracies in the census data but also for absentees and non-responders, we opted for 36,000 participants per study arm, i.e. 15% extra.

4.4 Randomization

Randomization will be at the level of villages . These villages have been preselected based on leprosy incidence over the period 2013-2017. Per island they have been listed in order of decreasing incidence and then regrouped into blocks of four, so that an equal number of villages will be allocated to each of the four arms. Within these blocks we have used random numbers to allocate each village to one of the study arms (the highest random number to arm 1, the second highest to arm 2, etc.).

On Madagascar a slightly different allocation method will be used, taking into account the fact that there is a lack of reliable baseline data at village level. We have selected a highly endemic district and within this district we selected an area of 35,000 inhabitants that is made up of five sub-districts or communities. Communities are again subdivided in 'fokontanys', a 'fokontany' is a cluster of hamlets. During the first year of the study, door-to-door screening will take place in all 'fokontanys', at the end of which we will select 16 to 24 with the highest baseline leprosy prevalence, aiming at a total population of approximately 20,000. These fokontanys will then be listed in order of decreasing prevalence, divided into blocks of four, and within each block there will be a random allocation to the four study arms.

In each of the study arms we will measure the incidence rate of leprosy between the first and fourth door-to-door survey and calculate rate ratios using the non-intervention village (arm 1) as reference group. To ensure equal duration of follow-up between the study arms all villages/fokontanys within the same block of four will always be surveyed in parallel. On Madagascar for the incidence rate we will not consider the first year since PEP will only be provided after all villages have been surveyed once.

The nature of the trial, requiring anti-PGL-I testing on capillary blood samples in one of the study arms, makes blinding impossible. We will however use additional approaches to validate study results and detect possible observer bias, such as quantitative PCR (qPCR) testing of skin biopsy samples from leprosy patients diagnosed in all four study arms.

5. STUDY PROCEDURES

5.1 General Study Procedures

Each village will be screened door-to-door for four years in a row. Prior to the start of the study the village elders will be informed on procedures and purpose of the study. During the yearly screening rounds for leprosy, residents of the selected villages will be checked for eligibility, informed on all study procedures, and requested to provide informed consent. The health worker will then perform a physical examination to look for signs of leprosy. Note that for this study, the diagnosis of leprosy will be made based on the so-called cardinal signs, i.e. a patch with loss of sensation, enlarged peripheral nerves and/or a slit skin smear positive for acid fact bacilli. Results of qPCR and anti-PGLI testing will be not be used as diagnostic criteria. The health worker will also collect the necessary additional personal information from every individual.

In case the household is eligible for receiving PEP (i.e. an incident leprosy case is found in the household or in the surroundings – depending on the arm to which the village is assigned), the correct dose of Rifampicin will be distributed according to the schedule below:

- 10-20 kg: 300 mg
- >20-30 kg: 600 mg
- >30-45 kg: 900 mg
- >45 kg: 1200 mg

The health worker will witness the intake of the medication by the participant. In case the village is part of arm 4, the applicable households will first undergo an anti PGL-I test, and only those testing positive will be given PEP.

During the yearly screening for leprosy, the health workers will also collect a sputum sample from all participants who have been coughing for more than 2 weeks, to test for tuberculosis (according to the national TB program guidelines). Participants who are diagnosed with tuberculosis (based on the routine criteria of the national control program) will be referred to the national control program for treatment.

If a screened person is diagnosed with leprosy, he/she will be requested to sign an additional consent form for the collection of samples. This person will subsequently be treated as per the standards of the National Leprosy Control Program.

5.2 Laboratory procedures

5.2.1 Harmonizing protocols

APHP, CICM and ITM will exchange and harmonize protocols for DNA extraction from clinical samples and for *M. leprae* DNA detection through the RLEP qPCR and later on also the Deeplex-Myclep.

5.2.2 Sampling schedule

The local leprosy control teams on each island will be responsible for identifying new leprosy cases and collecting the samples. All samples will be identified by a patient-specific barcode only. Nasal swab, tongue swabs (only in Comoros) and skin biopsy sample from the lesion(s) (except from lesions in the face) are being collected from all newly diagnosed patients. In addition, for those patients who have MB leprosy, Skin Slit Smears are taken. During the second survey round nasal swabs will also be collected from a subset of close neighborhood contacts in arm 4. Fingerstick blood samples will be collected from all newly diagnosed patients and additionally in arm 4 from all close neighbourhood contacts.

Slit skin smears (SSS) will be collected from all consenting MB participants. The SSS will be taken from the two earlobes and one additional site presenting an active lesion. For this, skin will be pressurized and a small incision will be made in the skin and scraped, followed by spreading the smear over the surface of the glass slide. After drying the slides, they will be fixated by heating on site.

Skin biopsy (SB) samples will be obtained from all consenting leprosy cases by using a 4 mm punch and the removed tissue placed in a sterile 1.5 mL tube and stored in disolol for DNA extraction (not for histopathology). Local anaesthesia with 2% lidocaine will be administered subcutaneously prior to punching the biopsy.

Nasal swabs (NS) will be obtained from all consenting leprosy cases (and in arm 4 from a subset of all contacts during the second survey round) by gently rubbing a perinasal swab, in one side of each nostril over the lateral conchae. After collection, the swab containing cotton edge will be immersed (and broken off at the breakpoint) in a sterile and labelled tube containing disolol.

Blood samples (BS) blood drops are obtained from all consenting leprosy cases by finger prick. The blood is captured in a capillary and subsequently put in a tube containing buffer. In addition blood drops will be spotted on filter paper (Whatmann) and stored at room temperature.

Tongue swabs (TS) will be obtained from all consenting leprosy patients in the Comoros by rubbing the tongue with a swab for 15 seconds. After collection, the swab containing cotton edge will be immersed (and broken off at the breakpoint) in a sterile and labelled tube containing disolol.

5.2.3 Specific tests

For Madagascar and the Comoros the specific tests on all the samples (except for the fingerstick blood samples) will be executed by CICM and ITM respectively.
Analysis of the Anti-PGL1 LFA (fingerstick blood sample) will be done by the local leprosy controls team with a portable reader.

Slit skin smears

The SSSs will be coloured by the ZN staining in the local laboratories by the designated local leprosy control teams after a day of sampling. The subsequent microscopy reading of these slides will be done in the local laboratories.

Fingerstick blood

The fingerstick blood collected in a buffer, will be brought to the local laboratory after a day of sampling and run on the LFA strips (provided by the University of Leiden). The strips must dry up and are read by the portable reader (provided by the University of Leiden).

Nasal swabs, tongue swabs (only in Comoros), skin biopsies & SSS

a. DNA extraction:

DNA will be extracted with the slightly modified Maxwell LEV extraction procedure from biopsies, swabs and slit skin smears.

b. Diagnostic RLEP qPCR:

The RLEP qPCR is a highly sensitive and specific diagnostic qPCR, which targets the RLEP repetitive element, which is specific for *M. leprae*. This test targets 36 out of the 37 RLEP repetitive elements occurring in the genome of *M. leprae*.
After DNA extraction, all the samples will be processed by this RLEP qPCR. The presence of DNA in minimally-invasive samples (tongue, nose) may be due to colonization rather than leprosy disease.

c. Genotyping:

Genotyping will be performed on DNA extracts that are *M. leprae* positive as defined by a positive RLEP diagnostic test. We expect that samples from all MB patients and a subset of PB patients will have sufficient DNA for further genotyping.

Genotyping will be done by a novel sequencing technique called the Deeplex® MycLep assay, which consists of a single hi-plex amplification of 15 phylogenetic SNPs, 17 VNTR markers, and drug resistance conferring gene regions followed by next generation sequencing analysis. This assay is being validated in the ongoing COMLEP study. APHP, ITM, and potentially CICM, will perform amplification and targeted deep sequencing of the resulting amplicons, with quality control done at Genoscreen.

d. Clustering analyses:

We will establish transmission chains between newly diagnosed patients and the proportion of patients with genetically clustered bacteria.

All samples will be classified by SNP types and subtypes according to Sharma *et al.* 2015, with SNP type 1 expected to be predominant in Comoros and Madagascar based on genotyping results from Reibel *et al.* (2015). To fully explore the epidemiological relationships between isolates, VNTRs patterns will be analysed using Bionumerics, by constructing a similarity matrix using UPGMA and the Dice similarity coefficient. A Hunter-Gaston discriminatory index (HGDI) for each marker will be calculated, to determine how discriminatory these markers are in order to include/exclude them for further analysis. Transmission links will be defined as identical genotypes. The definition of clustering will be based on comparison of the copy number of the VNTRs using two different stringencies: either considering those that presented identical copy number for all 17 alleles, or considering those that had identical copy number excluding the most variable loci, according to the HGDI.

5.2 Shipment samples

The samples of Madagascar will be analysed at CICM. The samples of the Comoros will be shipped to the ITM for further analysis.

6. STUDY INVESTIGATIONAL PRODUCT

6.1 Purchasing

Rifampicin has been selected from the following WHO Prequalified manufacturer: Rifampicine - Eremfat® from Fatol Arzneimittel (registered in Germany). The product will be shipped by the supplier directly to the applicable national leprosy control programs.

No medication for treatment of skin diseases will be purchased for study purposes. All treatment is part of the routine leprosy control programs in the countries.

6.2 Participant compliance monitoring

All PEP treatment will be delivered by the health worker and intake will be directly observed. The health worker will indicate in the data collection tool that the participant has taken the medication.

The site staff will keep a study-specific inventory of all medication that is received for the study and all medication that has been distributed.

6.3 Prior and concomitant therapy

Due to the single dose administration of the drug, no specific precautions are needed regarding concomitant drugs.

The metabolism or activity of rifampicin is not known to be affected by concomitant drugs.

6.4 Packaging

The commercial formulation of rifampicin procured for the study will be used.

6.5 Reception, storage, dispensing and return

All study drugs will be stored in the central air-conditioned stock of the national leprosy control program. The mobile teams will be supplied with sufficient medication during their screening visits to the different villages. This medication will be kept in ambient temperatures. Medication that has been provided with a mobile team and that is returned to the central stock will no longer be used as the conditions in which it was stored cannot be guaranteed. An inventory will be kept of all incoming and outgoing medication.

7. SAFETY ASSESSMENT

The regimen used for prophylaxis, single dose Rifampicin, has been extensively tested in a number of leprosy PEP trials and is the current choice when PEP is implemented programmatically. Very recently (on 28 June, 2018) WHO have issued a guidelines for the diagnosis, treatment and prevention of leprosy which state that: 'Single-dose rifampicin (SDR) may be used as leprosy preventive treatment for contacts of leprosy patients (adults and children aged 2 years and above), after excluding leprosy and tuberculosis (TB) disease, and in the absence of other contraindications'.[16]

Rifampicin has been on the market for over 50 years and is the cornerstone of tuberculosis treatment as well as leprosy treatment. In tuberculosis treatment it is administered daily over a 6 months period, always in combination with other potentially hepatotoxic drugs. In this trial we will provide only one single dose of Rifampicin maximum once per two years, though the dosage will be higher (20 mg/kg) than that commonly used in treatment of tuberculosis and leprosy. As was mentioned in the 'trial design' section, Boeree *et al.* tested even higher doses of Rifampicin, up to 35 mg/kg and found that they were safe and well tolerated.[7] In the OneRIF study in Bangladesh (ClinicalTrials.gov Identifier: NCT02153528), results of which are yet to be published, a double dose of Rifampicin (20 mg/kg) was given daily for 6 months to 475 TB patients, without any apparent increase in toxicity when compared to 468 patients treated with the regular dose. Moreover this trial is not the first using a high dose of Rifampicin as post exposure prophylaxis, in an earlier trial in French Polynesia a dose of 25 mg per kg was used without any issues related to toxicity. [12-14]

Only passive collection of adverse events (AE) will be done in the study. An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this product. It can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. Participants who receive SDDR-PEP will be instructed to inform the study staff of any adverse events while the study teams are still in the village, or afterwards using the contact details in the information form of which each household will receive a copy. These reported adverse events will be recorded, together with their severity and relatedness to the SDDR-PEP.

Medical staff in health facilities in the districts concerned will also be informed about the trial in advance (and at the beginning of every yearly screening round) and will be asked to report any possible adverse reactions (AR) or serious adverse event (SAE) to the study team. An AR is an AE for which there is at least a reasonable possibility that it might be linked to the medicinal product under study. A SAE is an AE that 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or

prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect. ARs will be reported in the same manner as AEs. In case of a SAE however, the SAE report template will be completed by the study team and sent to the sponsor (pharmacovigilance@itg.be) within 24 hours following the notification of the SAE to the study team as per the SAE reporting instructions. Only events (AE, AR and SAE) that occur between the administration of the drug and three days after administration will be recorded for study purposes.

> *NOTE (1): In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is an SAE. When in doubt as to whether "hospitalization" occurred or was necessary, the event should be considered an SAE. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE, nor hospitalization for non-medical reasons (e.g., the participant stays at the hospital overnight because (s)he lives too far and/or there is not transport).*
> *NOTE (2): The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.*
> *NOTE (3): The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*

The risk of inducing Rifampicin resistance in (undiagnosed) tuberculosis or leprosy patients with one single dose of the drug is negligible.[17] As was described by Mitcheson for treatment of tuberculosis, resistance emerges as a result of selection of resistant mutants under conditions of monotherapy.[18] This requires high numbers of bacilli as observed in cavitary pulmonary tuberculosis, combined with prolonged exposure, as mycobacteria are slow to replicate. Repeated cycles of starting a treatment regimen, interrupting treatment, and restarting after some days can mimic monotherapy because of differential activity of drugs during the first days of treatment. However a single dose of Rifampicin, possibly repeated once every two years, will not result in drug resistance. To exclude any potential risk we will screen for signs and symptoms of pulmonary tuberculosis and exclude those participants from SDDR PEP. Also we will not provide SDDR PEP to anyone who has already received Rifampicin within the preceding 2 years. Lastly, we will also monitor molecular resistance on samples from all leprosy patients, as resistance conferring genes are included as targets in the molecular genotyping studies.

Rifampicin is also known to interact with other drugs, anti-retrovirals (ARV) in particular.[19] It is an inducer of various genes controlling drug metabolism and transport, such as cytochrome P450 isoenzymes and the drug efflux pump p-glycoprotein. As a result plasma concentrations of concomitantly administered drugs may be reduced. In this study only one single dose of Rifampicin will be provided. As Rifampicin has a serum half-life of less than 5 hours, the effect of such interactions would be expected to be negligible, regardless of the dosing. [20]

Other risks to the participants are minimal, no invasive diagnostic procedures will be undertaken. In study arm 4 a capillary blood sample will be taken by finger prick, and a swab of both anterior nasal vestibules, which may cause slight discomfort. Leprosy patients identified will also have a slit skin smear and a 4mm punch biopsy from the edge of the lesion taken (except if the lesion is in the face). The biopsy will be collected under local anesthesia. These procedures may cause slight pain, and carry a small risk of bleeding, which will be controlled by the person collecting these samples. The staff on the Comoros are already executing these procedures as part of the ongoing COMLEP study.

8. STUDY MANAGEMENT

A Trial Management Group (TMG) will be set-up for the purpose of the day-to-day management of the trial. The TMG will meet at regular basis to discuss the progress of the trial. The TMG will consist of representatives of the sponsor and the sites. Minutes will be written, distributed amongst the entire study team and filed in the Trial Master File.

A Scientific Advisory Committee (SAC) will be established for the purpose of providing independent advice on the quality of the data produced and the preliminary results that have been analyzed during the interim analyses. A charter detailing the modalities for this SAC will be made prior to the first meeting, which should take place as soon as possible after the start of the study.

9. DATA ANALYSIS

The main analysis will be based on incidence rates of leprosy in each of the four study arms, with interim analyses planned after the second and third survey round and final analysis after the fourth survey round. There will be four door-to-door surveys of which the first one will allow us to calculate a baseline leprosy prevalence per island. Based on results of the second, third and fourth surveys, we will calculate incidence rates per study arm. We will then fit a random effects Poisson model with study arm as explanatory variable, using the non-intervention group (arm 1) as baseline, and with 'island', 'block' (as described in sample size section, eight on Anjouan, four on Mohéli, four to six on Madagascar) and 'village' as nested random effects.

Two interim analyses will be conducted upon completing the second and third door-to-door surveys in which incidence rates of leprosy to date in study arms 2, 3 and 4 will be compared to the incidence rate in arm 1, just as in the final analysis. These analyses will allow us to assess whether the a priori assumptions on annual incidence made have been realistic or whether an extended study duration should be considered.

Results of DNA finger printing will be used to assess the degree of clustering at household and at village level. We will calculate proportions of patients belonging to a same cluster by household and by village. The space-time K-function will be used to assess clustering in time and space, to be triangulated with results of DNA finger printing. For this purpose we will use results of all leprosy patients identified, including those found at baseline.[21]

To establish the transmission networks in the Comoros islands and in the study area in Madagascar, we will overlay the molecular network with the spatial- and social networks. This will determine whether the 100m high risk zones around each index patient, applied in this study, capture most transmission events, or whether additional risk factors, beyond spatial, need to be taken into account in future PEP administration efforts in the study areas and elsewhere. Phylogenetic clustering of the *M. leprae* isolates allows us to identify risk factors for leprosy due to recent transmission. The findings of the spatial and social network analysis can be mapped onto a phylogenetic tree and molecular clusters based on the VNTRs, which can reveal risk factors for transmission of leprosy.

Prevalence of Rifampicin resistant strains will be calculated per island with in the numerator all leprosy patients with Rifampicin resistant isolates identified and in the numerator all patients tested.

For pulmonary tuberculosis we will calculate the baseline prevalence per island as well as annual incidence rates for the next three years.

Cost data will be gathered throughout the study and used to calculate the average cost per person screened for leprosy by island, average cost per case detected by island and average cost per case of leprosy averted by study arm and by island. Incremental costs will be calculated using the non-intervention arm as a baseline.

10. MONITORING AND QUALITY ASSURANCE

Regular study monitoring visits will be conducted by a representative of the sponsor, who is trained in GCP. This responsibility will be shared between the Coordinating Investigator (or representative) and the Clinical Research Scientist (CRS) of the Clinical Trials Unit (CTU) of ITM. The PI and involved site research staff will allocate adequate time and resources for such monitoring activities.

A report detailing the actions taken during the monitoring visit will be written and shared amongst the study team. The CRS will join the sponsor representative during at least one visit per year. The study monitoring plan will detail on the activities performed by the CRS.

The sponsor will inform the Investigators concerned immediately upon notification of a pending study centers inspection by any regulatory authority or funder. Likewise, the investigator will inform the sponsor of any pending inspection.

11. DATA MANAGEMENT

For data collection in the field sites we will make use of the informed consent forms and of two Android apps, to be adapted from apps already used in the framework of the COMLEP project on the Comoros. One app is used during door-to-door screening and allows recording village and date of survey, geographic coordinates of the households, and results of leprosy and tuberculosis screening for each individual. The other app is used to record data on leprosy patients diagnosed during the trial. We will first describe in detail the data collection procedures during the surveys. See Figure 5 for a complete study and survey data flow of the PEOPLE study.

11.1 Survey data collection (per island)

Upon arrival in the household the study team will explain the study, provide the information sheet and obtain informed consent. Consent will be obtained on the level of the individual.

If the head of the household agrees, the study team will write down on the ICF, name, age and gender of all permanent household members, starting with the head of the household, and ask those present to sign (or thumb print) for informed consent. Refusal to participate will be documented. The study team will return to the household in case of absent members while the study team is still in the village. The ICF (Figure 2) will consist of one A4 sheet per household. The study team will then put a check mark in column 'PR' to indicate those present.

Figure 2: ICF form

Informed Consent form survey: Post Exposure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE)
FSN 17

No	Nom	Age	Sexe	PR	EX	MH	BCG	CR	PEP	Consentement	Assentiment	Barcode
1			F □ M □	□	□	□	□	□	□			10193
2			F □ M □	□	□	□	□	□	□			10194
3			F □ M □	□	□	□	□	□	□			10195
4			F □ M □	□	□	□	□	□	□			10196
5			F □ M □	□	□	□	□	□	□			10197
6			F □ M □	□	□	□	□	□	□			10198
7			F □ M □	□	□	□	□	□	□			10199
8			F □ M □	□	□	□	□	□	□			10200
9			F □ M □	□	□	□	□	□	□			10201
10			F □ M □	□	□	□	□	□	□			10202
11			F □ M □	□	□	□	□	□	□			10203
12			F □ M □	□	□	□	□	□	□			10204

Next the study team will examine each consenting household member present and use the check boxes on the ICF to indicate whether or not a person was examined (column 'EX'), whether signs of leprosy were present (column 'MH'), whether or not a BCG scar was observed (column BCG), whether or not a sputum sample was collected (column 'CR'), and whether or not PEP was provided (column 'PEP'). This information is entered directly on the ICF to facilitate the data collection during the visit, questioning of present members, and physical and clinical interventions.

When the study team has examined all household members present, they will open the Open Data Kit (ODK) smartphone household app to record the serial number of the ICF form and the geographic coordinates of the household. Secondly, they will record in the app for each individual the following information:

- scan of corresponding barcode on the ICF form
- age and gender
- examination results
- whether or not a sputum sample was collected
- whether or not PEP was provided
- some additional questions on previous or current diagnosis/treatment for leprosy and presence of cough for last two weeks.

The empty ICF forms contain pre-printed unique barcodes for each individual in the last column. The decoded barcode is always shown below to allow a double check when the barcode is scanned into the ODK app. A small piece of cardboard with a cut-out rectangle will be used to cover adjacent barcodes and thereby minimize the risk of the wrong barcode being scanned.

In case a sputum sample is taken, the barcode corresponding number of the individual concerned will be written on the container.

Figure 3: The Android app used for screening

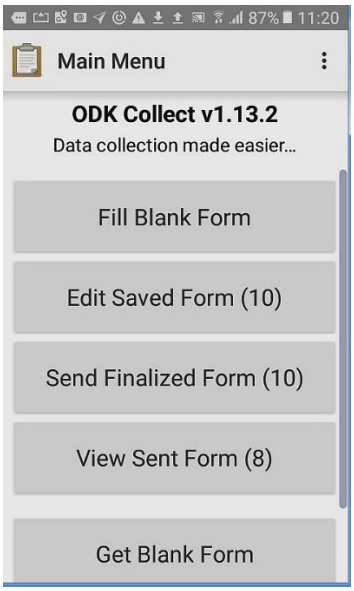
App:

<u>Per household:</u>

Island, district, village, form serial number, GPS coordinates, number of household members

<u>Per individual:</u>

Age, gender, present, history of leprosy, examined, signs of leprosy, cough > 2 weeks, sputum sample collected, barcode



Upon returning to their base, the study teams will hand over the ICF forms to the data entry clerks who will enter form serial number, name, age, gender and barcode of each individual in a secured MS Access database. This ICF database will be password protected and access will be restricted to the island study coordinator.

The ODK data from the smartphone will be sent to the secure ITM server using the 'Send Finalized Form' button of the app at least twice per week. The ODK data at ITM will only be accessible to the ITM CTU Data Manager and the ITM Coordinating Investigator. Once transferred to the ITM server, all data will automatically and permanently be deleted from the smartphone to reduce any risk of loss of confidentiality.

The ICF Access databases (1 per island) will be forwarded by the island study coordinator to the ITM CTU Data Manager by means of the encrypted Belnet Filesender protocol on a regular basis. The ITM CTU Data Manager will download the ODK data from the server (stored in the form of csv files) and merge with the Access databases through the barcodes. He will send back to the study coordinators on each of the islands their part of the complete database, again using encrypted Belnet Filesender.

The transfer of the ICF database, merging with the ODK dataset by the ITM CTU Data Manager and transfer back to the island study coordinators is performed to minimize the risk of any wrong manipulation or combining being done in any of the 3 sites. As soon as the complete datasets are sent back to the study coordinators, the received ICF databases are completely erased. The names in the merged ICF+ODK datasets at ITM will be completely deleted once it is confirmed that the study coordinators on the three islands have received a complete database for all their study subjects at the end of the study. Over the course of the study these responsibilities will gradually be shifted to the local study coordinators on the three islands.

11.2 Follow-up survey preparation and data collection

During the second, third and fourth survey rounds, each island study coordinator will print out from their ICF Access databases automatically generated survey forms per household that are identical to the ICF form but in which village name, the original form serial number, and name, age and gender of registered household members have already been preprinted, as well as the original barcode of each individual (Figure 4).

Figure 4: Example of pre-printed ICF for follow-up surveys

Informed Consent form survey: Post Exposure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE)

Date: __/__/____ **Village:** XXXX **Enquêteur:** YYYY **Numéro Formulaire : 1566**

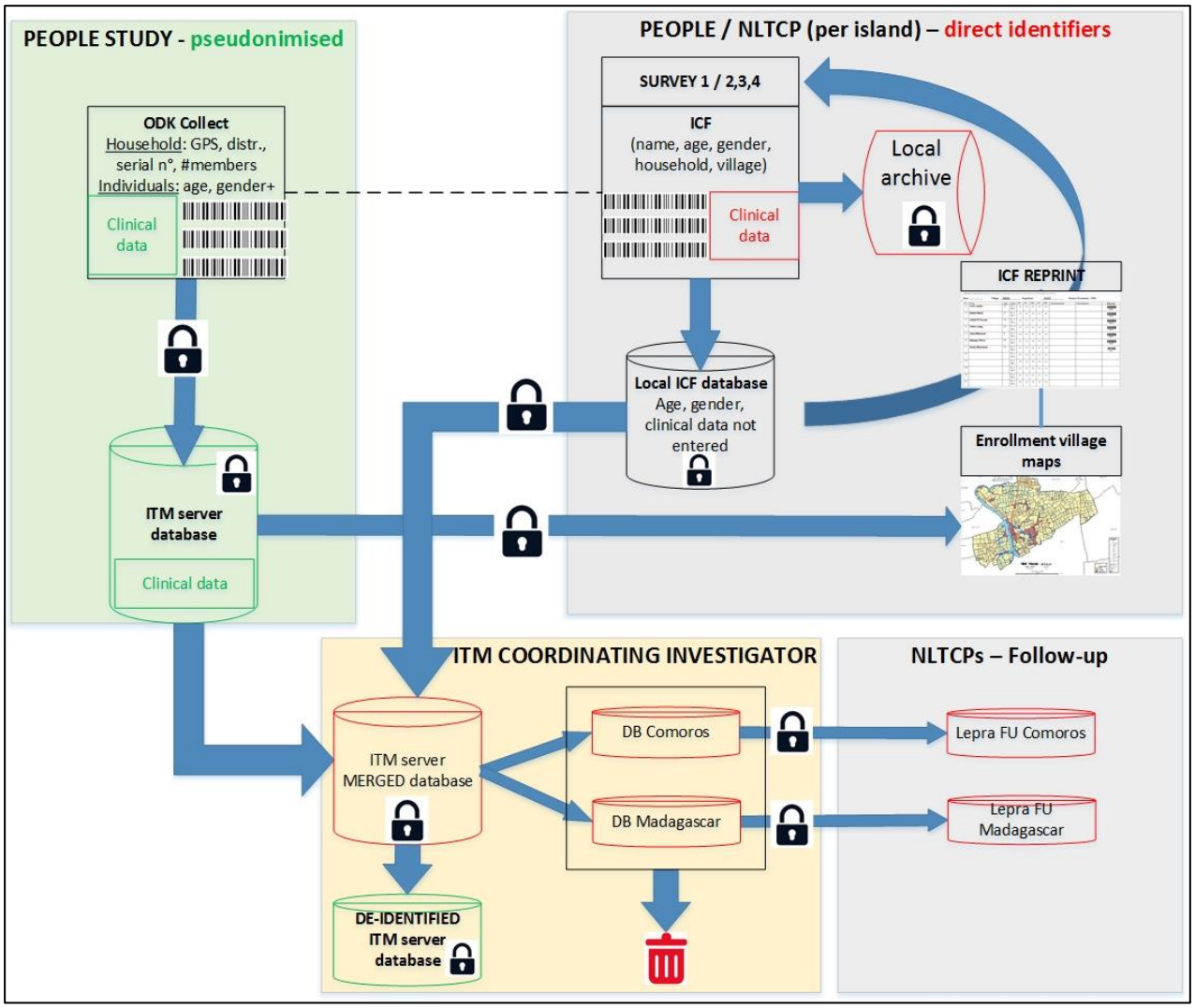
No	Nom	Age	Sexe	PR	EX	MH	CR	PEP	Consentement	Assentiment	Barcode
1	Soula Jziaka	55	F ☐ M ✓	☐	☐	☐	☐	☐			10001
2	Ahmed Binali	22	F ☐ M ✓	☐	☐	☐	☐	☐			10002
3	Suhati Ali Cussene	54	F ✓ M ☐	☐	☐	☐	☐	☐			10003
4	Fatima Ireka	12	F ✓ M ☐	☐	☐	☐	☐	☐			10004
5	Echat Athoumani	8	F ✓ M ☐	☐	☐	☐	☐	☐			10005
6	Aboudou Ahmed	19	F ☐ M ✓	☐	☐	☐	☐	☐			10006
7	Farda Abderemane	35	F ✓ M ☐	☐	☐	☐	☐	☐			10007
8			F ☐ M ☐	☐	☐	☐	☐	☐			
9			F ☐ M ☐	☐	☐	☐	☐	☐			
10			F ☐ M ☐	☐	☐	☐	☐	☐			
11			F ☐ M ☐	☐	☐	☐	☐	☐			
12			F ☐ M ☐	☐	☐	☐	☐	☐			

They will also receive a village level map showing all household enrolled with their serial numbers. The teams will then go to the village, locate each household and examine those present. They will check the boxes on the paper survey form and then record all data using the same app as in the first survey round, with exception of the geographic coordinates. Each paper survey form will have a few empty rows to record any new household members if applicable, in case an entire new household is enrolled the procedure will be the same as in the first survey round. Upon returning to their base the study teams will again upload the data from the smartphone to the ITM server and hand over the paper survey forms to the data entry clerks. Any new household member or any entirely new household enrolled will be added to the ICF Access data base which will again be sent to the ITM CTU Data Manager for merging with the data collected through the app. Again, all transfers will be done by using the encrypted Belnet Filesender system.

After the ICF forms have been entered in the ICF data base, the paper ICFs as well as later survey forms will be stored in a secure cabinet in the offices of the respective national control programs on the three islands. They will serve as source documents for monitoring, auditing and inspection purposes.

The CTU Data Manager will provide a de-identified and locked extract from the merged database to the CTU Study Statistician for analysis. The use of any data received from other partners/vendors that is not entered in ODK falls under the responsibility of the ITM Coordinating Investigator.

Figure 5: Data flow for the PEOPLE project



11.3 Registration of leprosy patients and follow-up

A second app is currently used to register leprosy patients enrolled in the COMLEP study and allows to record results of a short interview as well as barcodes of samples taken. We will continue to use this app for leprosy patients diagnosed during the PEOPLE trial and enrolled in the study, with a few minor adaptations. In particular we will remove the names of patients enrolled and instead scan a unique barcode from an individual ICF form. An identical barcode is printed on 6 different stickers, one is stuck on the ICF form, the others on each of the samples belonging to the patient concerned. As was done for the survey data, ICF forms will be collected and used to enter name and barcode of each subject in an Access database. As was the case with the survey data, upon uploading to the ITM server, data will automatically and permanently be deleted from the Android device. Access databases will be forwarded to the ITM CTU Data Manager via Belnet Filesender, who will download the data collected by Android devices from the ITM server and use the barcode to link to the Access files.

11.4 Filing and archiving

All essential documents for the trial will be kept in paper format in the Investigator Files at the study sites. Each Principal Investigator is responsible for completeness and ensuring a secure and appropriate location for storage of the Investigator Files and any other study related documentation present at sites, as well as for ensuring that only site staff that is competent and delegated to work for the study have got access to the files.

After study completion, all the relevant study documentation should be retained for a period of 20 years or in accordance with the local legislation. ITM should be informed prior to destruction of study files.

The Investigator Files should at all times remain available for internal audits and/or inspections of regulatory authorities, also after completion of the project.

The Trial Master File and any other sponsor related documentation will be archived at ITM at a secure and appropriate location and will only be accessible for competent and delegated sponsor staff. After completion of the study, the Trial Master File will remain available for internal audits and/or inspections of regulatory authorities for a period of 20 years or according to regulatory requirements.

12. ETHICAL ISSUES

12.1 Ethical and regulatory review

The study will be submitted for review and approval to the 'Comité d'Ethique de la Recherche Biomédicale' (CERBM) in Madagascar and the 'Comité National d'Ethique pour les Sciences de la Vie et de la Santé' (CNESS) in the Comoros. As ITM is the sponsor of this project, approval by the Institutional Review Board (IRB) of the ITM will also be requested. In addition, the study will be submitted for approval to the Ethics Committee (EC) of the University of Antwerp Hospital in Antwerp. Potential comments from all these review boards will be answered to, the same applies to comments from the selected collaborating partners. No participants will be enrolled or participant related activities performed before written approval from all these bodies in Belgium and in the study country concerned is obtained. Any substantial amendment to the study (documents) will also require approval from the above mentioned bodies. A yearly update on the status of the study will be provided as required. The study will be carried out according to the principles stated in the Declaration of Helsinki, all applicable regulations and according to established international scientific standards. Choice of treatment for the patient will not depend on the results of the PEOPLE study.

Prior to the start, this study will also be included in the Clinicaltrials.gov public registry.

12.2 Protocol amendments

Once the final clinical study protocol has been issued and signed by the authorized signatories, it cannot be informally altered. Protocol amendments have the same legal status and must pass through the appropriate steps before being implemented. Any substantial change must be approved by all the bodies and EC's that have approved the initial protocol, prior to being implemented, unless it is due to participant's safety concerns (in which case the immediate implementation can be necessary for the sake of participant's protection. In case modifications to the protocol or amendment are requested by any local EC/CA during the review process, these must be discussed and agreed upon with the Sponsor prior to any resubmission incorporating those changes.

12.3 Informed consent

Informed consent for participation in the trial (which includes yearly screening for leprosy and treatment with PEP, as applicable depending on the assigned study arm) will be sought from all residents in the study area.

As it will be practically and culturally not possible to perform the entire informed consent process for every individual in the study area, the procedure will take place per household. This will facilitate the study enrolment, while keeping any undue influence to a minimum.

Households will be provided with an approved Participant Information Sheet, detailing in lay language the purpose, content, risks and benefits, voluntariness, etc. of the trial. A delegated member of the study team will sign this Participant Information Sheet on the date that the information was given to the household, stating that all information has been given, that all questions have been answered satisfactorily and that consent was freely given by all participating household members.
On a separate approved Informed Consent Form, all participating household members, as well as the guardian and witness, as applicable, can separately sign for participation in the study. For practical purposes, this form will also include information on whether or not the participant was examined, was diagnosed with leprosy, has given a sputum sample, etc. (as detailed in chapter 11). No separate copy of this signature page will be given to the household members. The form will be stored by the study team in a secure manner.

Written informed consent will be obtained before any study specific procedure is performed. For the sample collection for incident leprosy cases identified during the yearly screening, a separate consent will be obtained. As these numbers are much lower, the standard signature process will be followed (i.e. one copy for the participant and one for the study; signed by the participant and the delegated site staff, and the guardian and/or witness as applicable).

Participants who provide samples (i.e. index cases and neighborhood contacts in arm 4) will be informed that their samples will be stored for 20 years and may be used for other research in the future. They will also be informed that these samples can be shipped abroad.

The legal age of consent in in the Comoros is 18 and in Madagascar 21. For participants, between 2 andand the legal age of consent in the particular countries, informed consent of the parents or guardian will be sought. However, as of the age of 12, additional signed assent from the minor is needed before he/she can participate in the study.

The informed consent interviews will be conducted in the preferred language of the patients by a qualified person formally delegated by the PI. Informed consents will be available in French, English, and Malagasy. Comorian is a rather spoken language and therefore the IFC will be orally translated by the interviewer on-site. Translations will be performed by a native speaker with thorough knowledge of the English or French language and checked for consistency by another native speaker.

In case participants are illiterate, an independent witness will be sought to ensure that the participants receive complete information. In such case, the participant will thumbprint the consent form and the witness will add his/her signature.

Because the first year of leprosy screening in Madagascar will be used to select 16 to 24 villages with the highest baseline leprosy prevalence, a separate informed consent has been created. The process will be similar to that of the main study (i.e. all consents of one household on a single page, etc.). The selected villages will then be re-consented in the second year based upon the arm their village has been assigned to.

12.4 Confidentiality

Incident leprosy cases will not be made publicly known outside the household to avoid stigmatization. Data for the study will be collected by the study team via an Open Data Kit Android application, in which participants will be identified by their geographical location and a barcode. The data will be uploaded regularly to a secure ITM server. Upon uploading to the ITM server, data will automatically be deleted from the Android device. Names will be recorded on the informed consent form, as is required for management purposes by the NTLCPs who are responsible for follow-up and treatment of all leprosy and TB suspects or cases identified. The names will be linked to the data collected in the Android app through a barcode. For the final analysis a dataset without names will be used.

The Informed Consent Forms with the participant names will be stored in a secured location in a lockable cabinet with access limited to country PI's only. The Access database with ICF data will be managed and secured by the NTLCP's.

Any other forms and reports needed for the study will be anonymous and can only be linked to the study participant by barcode.

Participant's study information will not be released to anybody outside the medical team, except as necessary (and under confidentiality agreement) for the purpose of monitoring, auditing and inspection by competent authorities.

During or after final publication of results, individual level participant data might be shared for secondary research purposes in an anonymized or coded manner and by means of a controlled data access procedure and after the signing of a data sharing agreement.

12.5 Potential Risks

The most important risk in this study is loss of confidentiality. This risk is minimized by targeting for screening entire villages/hamlets, thus presence of the team cannot be interpreted as presence of leprosy patients in a household. Screening will be for skin conditions in general and for signs of pulmonary tuberculosis. For household contacts anti PGL-I testing and nasal swabbing in study arm 4 and distribution of Rifampicin in study arms 2-4 will be done while the team is still in the household. Distribution of Rifampicin to neighborhood contacts (arms 3 and 4) and anti PGL-I testing and nasal swabbing (during the second survey round) of neighborhood contacts (arm 4) will be done upon completion of the door-to-door survey in the village. However since we are using a 100 meter common perimeter around all leprosy cases identified the numbers of households included will always be large. If more than 50% (arm 3) or 75% (arm 4) of households are to be included we will include the entire village. Unlike in an approach where PEP would be provided to neighbors, or neighbors of neighbors, in the approach used in this trial it will be almost impossible to deduce where the source case was located. In four villages on Anjouan screened in 2017, 84% of the population would reside within these 100-meter perimeters.

At a higher level there could be a risk of villages or neighborhoods being stigmatized because of being involved in the study. This risk is not very high because leprosy is widespread in the study countries. In the areas targeted most villages are known to be affected. On Anjouan since 2008 and more recently also on Madagascar and on Mohéli, villages are regularly visited by leprosy control program teams for active case finding activities. In these villages such problems have never occurred. The fact that in the PEOPLE trial even more villages will be included further reduces the risk of entire villages being stigmatized.

In this study, participants will (depending on the arm their village is randomized in) receive a single dose of 20mg/kg Rifampicin, which is double of the standard dose used so far as PEP and also double

the standard daily dose used in tuberculosis treatment. As mentioned in the introduction and in the safety section, studies have shown that with a daily double dose of Rifampicin during 6 months used in treatment of tuberculosis, there is no increase in toxicity compared to the standard dose in participants ages 15 years and above. Therefore, the potential risks of receiving a double dose of Rifampicin are similar to those of the standard dose and include: vomiting and anorexia, headache, tingling sensation in the extremities, insomnia, joint pain and rashes. Nevertheless, the current study will include children as of 2 years old. Single dose of Rifampicin has shown to be safe in children under 15 years of age and clear guidelines are available on the product leaflet. However, no studies have shown safety of double dose of Rifampicin in children under the age of 15.

Capillary blood sampling by finger-prick, tongue swabs (only in Comoros) and nasal swab collection will be performed on a subset of participants. No side effects apart from minor discomfort are to be expected from these tests.

Skin biopsy and slit skin smear require making a small incision in the skin and taking a superficial skin sample. Local anesthesia will be applied to reduce the discomfort for the participants to a minimum.

12.6 Benefits

The yearly door-to-door screening as part of the study yields the greatest advantage of the study for the people living in the study target area, as this will guarantee early detection of leprosy and consequently early treatment. Moreover, concomitant sputum collection will allow the study staff to refer participants with TB to treatment early on. So even for people living in the villages assigned to arm 1, there is a benefit of being part of the trial.

For people living in villages assigned to arms 2, 3 or 4 and living in close proximity of a leprosy case, the study is expected to reduce transmission of leprosy due to PEP being offered through the study. To increase efficacy, a double dose of Rifampicin (20mg/kg) will be used. As mentioned above, no increased safety concerns are to be expected from this higher dose.

There will be no compensation to the participants for their participation in the study. As study teams will perform door-to-door screening, also no travel reimbursement is foreseen. On the other hand, participants will not have to pay for any of the study procedures, nor for the PEP medication provided as part of the study.

12.7 Compensation for participation

All tests and procedures that are part of this study are free of charge for the participants. Also treatment for leprosy is offered free of charge by the national leprosy control programs, but are not part of this study. Participants will not receive any money, nor other form of compensation, for their participation.

12.8 Insurance

Prior to the start of the trial, ITM as sponsor of the trial will obtain a no-fault study insurance to cover any injury, damage or loss to study participants and which is caused directly or indirectly by their participation in the study. Participants will be informed of such insurance in the Participant Information Sheet.

13. DISSEMINATION OF RESULTS, INTELLECTUAL PROPERTY

All study documents are provided by the Sponsor to the Investigators and his/her appointed staff in confidence. None of this material may be disclosed to any party not directly involved with the study, without written permission from the Sponsor.

The results of this study will be presented in a scientific articles submitted to peer- reviewed journals. They will also be presented in other fora such as the Leprosy Research Initiative (LRI) meeting.

14. ARCHIVING

The sponsor and Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be verified. The relevant (essential) documents are those documents which individually and collectively permit to assess the conduct of the trial, the quality of the data produced and the compliance with GCP standards and applicable regulatory requirements.

All the relevant study documentation present at all partners involved should be retained for a minimum of twenty (20) years, unless differently requested by national authorities. The Sponsor should be informed prior to destruction of the files. After completion of the study, the IF will remain available for internal audits and/or inspections of regulatory authorities for a period of twenty years, unless differently requested by national authorities.

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16. LIST OF ABBREVIATIONS

AE	Adverse Event
ALLEA	All European Academies
Anti-PGL1	Anti-phenolic glycolipid-I
APHP	Assistance publique-Hopitaux de Paris
AR	Adverse Reaction
BCG	Bacille de Calmette Guérin
BS	Blood Samples
CICM	Centre d'Infectiologie Charles Mérieux
CRF	Case Report Form
CRS	Clinical Research Scientist
CTU	Clinical Trial Unit
DF	Damien Foundation
EC	Ethics Committee
EDCTP	European and Developing Countries Clinical Trial Partnership
ESF	European Science Foundation
FRF	Fondation Raoul Follereau
GC(L)P	Good Clinical (Laboratory) Practice
HGDI	Hunter-Gaston Discriminatory Index
HH	Household
IRB	Institutional Review Board
ITM	Institute of Tropical Medicine
LRI	Leprosy Research Initiative
LUMC	Leidsch Universitair Medisch Centrum
MB	Multi bacillary
NS	Nasal swabs
NTLCP	National Tuberculosis and Leprosy Control Program
ODK	Open Data Kit
PEOPLE	Post ExpOsure Prophylaxis for LEprosy in the Comoros and Madagascar
PEP	Post Exposure Prophylaxis
PI	Principal Investigator
PTB	Pulmonary Tuberculosis
qPCR	Quantitative Polymerase Chain Reaction
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SB	Skin Biopsy
SDDR-PEP	Single Double Dose Rifampicin Post-Exposure Prophylaxis
SDR	Single Dose Rifampicin
SSS	Slit skin smears
TMG	Trial Management Group
ZN	Ziehl-Neelsen