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## The PEP4LEP study protocol: Integrated skin screening and SDR-PEP administration for leprosy prevention. Comparing the effectiveness and feasibility of a community-based intervention to a health center-based intervention in Ethiopia, Mozambique and Tanzania

Journal:	BMJ Open
Manuscript ID	bmjopen-2020-046125
Article Type:	Protocol
Date Submitted by the Author:	20-Oct-2020
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Keywords:	Public health < INFECTIOUS DISEASES, Infectious diseases & infestations < DERMATOLOGY, Tropical medicine < INFECTIOUS DISEASES

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3	1	The PEP4LEP study protocol: Integrated skin screening and SDR-PEP
4 5	2	administration for leprosy prevention. Comparing the effectiveness and
6 7	3	feasibility of a community-based intervention to a health center-based
8 9	4	intervention in Ethiopia, Mozambique and Tanzania
10 11	5	
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22 23	12	Tanzania, <sup>7</sup> Ministry of Health, Ethiopia; <sup>8</sup> Ministry of Health, Mozambique; <sup>9</sup> Ministry of Health,
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25 26	14	
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28 29	16	Correspondence: t.hambridge@erasmusmc.nl
30	17	
31 32	18	Abstract
33 34	19	Introduction
35	20	Leprosy, or Hansen's disease, remains a cause of preventable disability. Early detection,
36 37	21	treatment and prevention are key to reduce Mycobacterium leprae transmission. Post-exposure
38 39	22	prophylaxis with single-dose rifampicin (SDR-PEP) reduces the risk of developing leprosy when
40	23	administered to screened contacts of patients. This has been adopted in the World Health
41 42	24	Organization (WHO) guidelines on leprosy. The PEP4LEP study aims to determine the most
43	25	effective and feasible method of screening people at risk of developing leprosy and administering
44 45	26	chemoprophylaxis to contribute to interrupting transmission.
46 47	27	
48	28	Methods and analysis
49 50	29	PEP4LEP is a cluster-randomized implementation trial comparing two interventions of integrated
51	30	skin screening combined with SDR-PEP distribution to contacts of leprosy patients in Ethiopia,
52 53	31	Mozambique, and Tanzania. One intervention is community-based, using skin camps to screen
54 55	32	approximately 100 community contacts per leprosy patient and to administer SDR-PEP to eligible
56	33	contacts. The other intervention is health center-based, inviting household contacts of leprosy
57 58	34	patients to be screened in a local health center and subsequently receive SDR-PEP when
59	35	eligible. The mobile health (mHealth) tool SkinApp will support health workers' capacity in
60	36	integrated skin screening. The effectiveness of both interventions will be compared by assessing
		1

1 ว		
2 3	37	the rate of leprosy patients detected and the period of case detection delay, as well as feasibility
4 5	38	in terms of cost-effectiveness and acceptability.
6	39	
7 8	40	Ethics and dissemination
9	41	Ethical approval has been obtained in the project countries. Results from this study will be
10 11	42	published open access in peer-reviewed journals and provide evidence for the implementation of
12	43	novel leprosy screening methods and chemoprophylaxis to policymakers.
13 14	44	
15	45	Trial registration: The PEP4LEP project is registered at the Netherlands Trial Register (NTR),
16 17	46	receiving trial registration number NL7294 (NTR7503), registration date September 10, 2018.
18 19	47	
20	48	Keywords: leprosy, Hansen's disease, NTD, chemoprophylaxis, prevention, skin screening, case
21 22		
22	49 50	detection, single dose rifampicin, SDR-PEP, post-exposure prophylaxis, detection delay, skin
24 25	50	camps, Ethiopia, Mozambique, Tanzania, Africa, feasibility, acceptability, cost-effectiveness,
25 26	51	mHealth, eHealth
27 29	52	
28 29	53	
30 21	54	
31 32	55	Article Summary
33 34	56	
35	57	Strengths and Limitations
36 37	57	
38	58	In both interventions, newly diagnosed patients can be screened and treated for leprosy and other
39 40	59	skin diseases / skin NTDs, while SDR-PEP will be administered – according to the World Health
41	60	Organization's guidelines – to eligible contacts of leprosy patients to reduce their risk to develop
42 43	61	leprosy
44	62	<ul> <li>An integrated skin diseases approach will be used in which multiple diseases can be detected and</li> </ul>
45 46	63	treated at once, which may also overcome the frequently negative associations with leprosy that
47	64	can prevent people from participating in leprosy-related interventions; the included leprosy patients
48 49	65	do not need to share their disease status with their contacts in the community (skin camp)
50	66	intervention arm
51 52	67	The SkinApp will be used as a mHealth tool to support peripheral health workers in recognizing
53	68	and treating signs and symptoms of skin diseases
54	60	
55	69 70	Because of the long incubation period of leprosy as well as the delays in case detection, the     anidemiological impact of this study on the new sees detection rate will not became apparent within
55 56	70	epidemiological impact of this study on the new case detection rate will not become apparent within
56 57		
56	70	epidemiological impact of this study on the new case detection rate will not become apparent within

 As difficulties in recalling the first signs and symptoms are expected to increase over a longer duration of the disease, only recently diagnosed index patients will be included in this study to establish case detection delay

### 77 Introduction

Leprosy, or Hansen's disease, is a communicable disease caused by Mycobacterium leprae that is still a public health problem in many countries. It is formally recognized by the World Health Organization (WHO) as a neglected tropical disease (NTD).<sup>1</sup> The annual reported number of newly detected leprosy patients was 208,613 in 2018.<sup>2</sup> If left untreated, leprosy potentially results in disability, which can have severe consequences such as stigma and poverty.<sup>3</sup> Leprosy has a long and variable incubation time, ranging from 2 to 20 years, during which it is assumed that transmission can take place.<sup>4</sup> The risk of developing leprosy is higher in household contacts and neighbors of patients than it is in the general community.<sup>5</sup> Moet et al. demonstrated that physical and genetic distance were independently associated with the risk of a contact developing leprosy.<sup>6</sup> 

The WHO provides multidrug therapy (MDT) free of charge to all leprosy patients since 1995.7 However, to overcome ongoing transmission in high-endemic areas, innovative measures are needed. In 2008, a large randomized controlled trial in Bangladesh (Chemoprophylaxis of Leprosy study, COLEP) demonstrated that a single dose of rifampicin (SDR) given to contacts of newly diagnosed leprosy patients is effective in reducing the risk of leprosy by 57% (95% CI: 24–75%).<sup>8</sup> SDR-PEP was found to be cost-effective in Bangladesh.<sup>9</sup> In the Leprosy Post-Exposure Prophylaxis (LPEP) program, SDR-PEP was implemented in areas representing various health systems across three continents and eight countries, to evaluate the feasibility, effectiveness and impact (Richardus, et al. under publication).<sup>10</sup> The implementation of SDR-PEP within the routine leprosy control programs was proven to be safe and generally well accepted.<sup>11</sup> Based on the LPEP program and a microsimulation leprosy model (SIMCOLEP), SDR-PEP was also found to be cost-effective in India.<sup>12</sup> The concern that SDR-PEP could lead to increased rifampicin resistance in other diseases, such as tuberculosis (TB), was considered in an expert consultation that concluded that SDR-PEP given to contacts of leprosy patients, in the absence of symptoms of active TB, poses a negligible risk of generating resistance in *Mycobacterium* tuberculosis in individuals and in populations.<sup>13</sup> 

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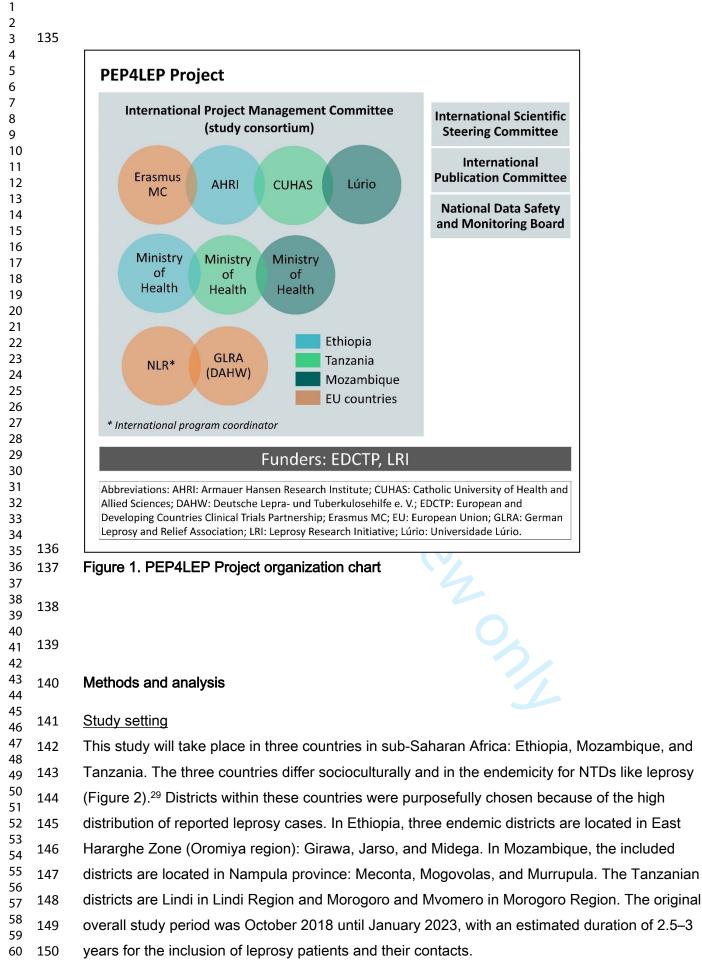
Skin screening is an important detection strategy for skin-NTDs like leprosy.<sup>1,14,15</sup> Screening for
 multiple skin diseases at once (integrated or common skin screening) is promoted by WHO.<sup>1,16,17</sup>
 Integration is considered to increase effectiveness and efficiency by minimizing costs and

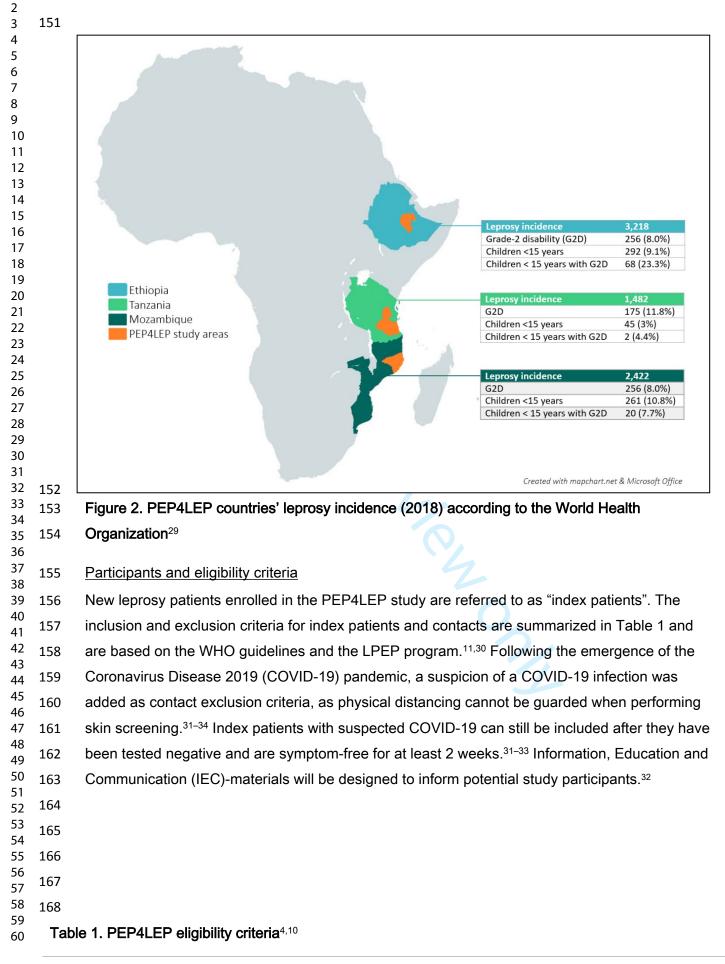
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3	109	expanding intervention coverage. <sup>16,18</sup> An important obstacle for integrated skin screening is the
4 5	110	scarcity of dermatologists in many areas with a high skin NTD endemicity. <sup>19</sup> In sub-Saharan
6	111	Africa, the situation is critical, with approximately 1 dermatologist per 500,000-1 million
7 8	112	inhabitants and even larger shortages in Mozambique and Tanzania according to field reports
9 10	113	from PEP4LEP consortium members. <sup>20,21</sup> According to the WHO, community health workers
11	114	(CHWs) and village volunteers can play a role in screening for skin diseases, but improved
12 13	115	knowledge, capacity, and motivation of health workers and community volunteers is
14	116	essential. <sup>14,16,22-26</sup>
15 16	117	As both integrated skin screening for NTDs and SDR-PEP against leprosy are promoted by the
17 18	118	WHO, additional implementation studies are necessary to establish whether a combined
19	119	intervention is acceptable, feasible, and cost-effective in leprosy endemic areas. <sup>1,4,16</sup>
20 21	120	
22	121	
23 24	122	Objectives
25		
26 27	123	The PEP4LEP project is a cross-functional collaboration among study consortium members in
28	124	five countries in sub-Saharan Africa and the European Union (EU) (Figure 1). The overall aim of
29 30	125	this cluster-randomized implementation trial is to contribute to interrupt the transmission of <i>M</i> .
31	126	leprae by identifying the most effective and feasible method of screening people at risk of
32 33	127	developing leprosy and by administering post-exposure chemoprophylaxis in Ethiopia,
34	128	Mozambique, and Tanzania. The primary study objectives are to compare the effectiveness and
35 36	129	feasibility of a community-based screening and prophylaxis (skin camp) intervention with a health
37	130	center-based screening and prophylaxis intervention solely for household contacts of a leprosy
38 39	131	patient. The case detection delay will be the primary outcome measure to assess effectiveness.
40 41	132	Additional objectives are to assess the cost-effectiveness, acceptability and health workers'
42	133	capacity regarding the integrated skin diseases approach and the use of the supportive mobile

- <sup>43</sup><sup>43</sup> 134 health (mHealth) tool SkinApp.<sup>27,28</sup>

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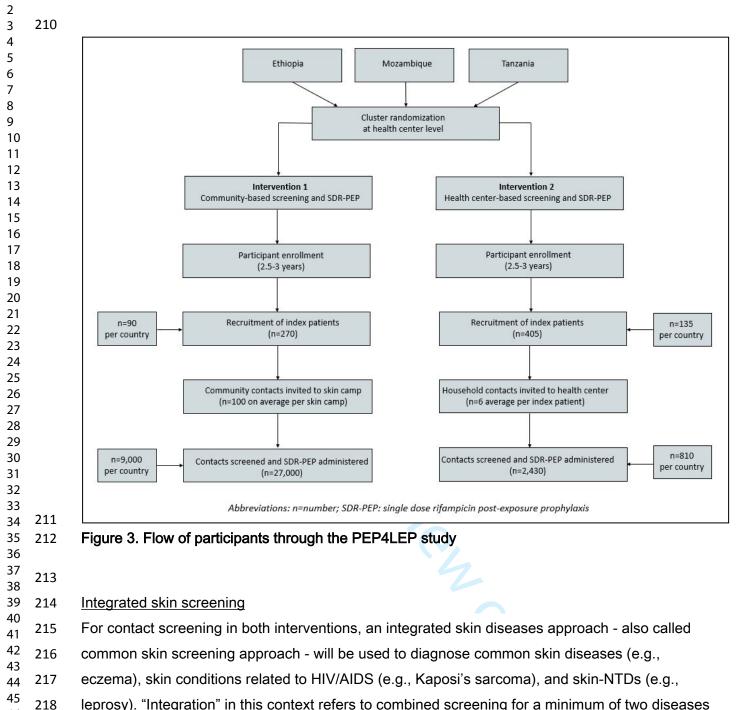
1 2			
2 3 4		Index patients	Contacts
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32	Inclusion criteria	<ul> <li>Consent to participate in the PEP4LEP project</li> <li>Diagnosed with leprosy (preferred maximum of 6 months prior to inclusion)</li> <li>Residence in the PEP4LEP districts for ≥3 months prior to the date of diagnosis</li> <li>Index patient has started MDT</li> <li>Community-based skin camp intervention: Leprosy patient gives permission for the set-up of a skin camp in his/her community (sharing their leprosy diagnosis with their contacts is not needed)</li> <li>Health center-based household screening intervention: Leprosy patient with household contacts, and who is willing to inform these contacts about PEP4LEP</li> </ul>	<ul> <li>Consent to participate in the PEP4LEP project</li> <li><u>Community-based skin camp</u> intervention: Community contact of the index patient for ≥3 months</li> <li><u>Health center-based household</u> <u>screening intervention</u>: Contact which is a household member of the index patient for ≥3 months, visiting the screening health center ≤3 months after the index patient was included</li> </ul>
33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 960	Exclusion criteria	<ul> <li>Index patient or parents/legal guardians unable to understand the purpose and risks of participating in the PEP4LEP study</li> </ul>	<ul> <li>Contact or parents/legal guardians unable to understand the purpose and risks of participating in the PEP4LEP study</li> <li>Age &lt;2 years and/or &lt;10 kg of weight*</li> <li>Pregnancy*</li> <li>Receiving or having received rifampicin for any reason in the last 2 years</li> <li>Known allergy to rifampicin</li> <li>History of liver or renal disorders</li> <li>Individuals with leprosy and those who have possible signs and/or symptoms of leprosy (e.g., leprosy- like skin lesions or nerve manifestations) until their disease status has been clarified<sup>35**</sup></li> </ul>

3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 22 33 34	affil ** If pro ***	voucher will be given for repeated skin screening and SDF liated health center when this person becomes eligible (e.g f referral was needed and no leprosy is detected, repeated wided in a PEP4LEP affiliated health center. Skin screening and SDR-PEP can only be provided in a P ntact is tested negative for COVID-19/TB (according to nati	g., after giving birth). skin screening and SDR-PEP can be EP4LEP affiliated health center after the
35 36 27		breviations: COVID-19: Coronavirus Disease 2019; MDT: i ampicin post-exposure prophylaxis; TB: tuberculosis	multidrug therapy; SDR-PEP: single-dose
		breviations: COVID-19: Coronavirus Disease 2019; MDT: i ampicin post-exposure prophylaxis; TB: tuberculosis	multidrug therapy; SDR-PEP: single-dose
36 37	rifa		multidrug therapy; SDR-PEP: single-dose
36 37 38 39 40 41	<i>rifa.</i> 169	ampicin post-exposure prophylaxis; TB: tuberculosis	
36 37 38 39 40	<i>rifa.</i> 169 170	mpicin post-exposure prophylaxis; TB: tuberculosis	ion trial (Figure 3). One intervention is
36 37 38 39 40 41 42 43 44	<i>rifa.</i> 169 170 171	<i>Study design</i> The study is a two-arm, cluster-randomized implementat	ion trial (Figure 3). One intervention is ately 100 community contacts
36 37 38 39 40 41 42 43 44 45 46	<i>rifa</i> 169 170 171 172	<u>Study design</u> The study is a two-arm, cluster-randomized implementat community-based, using skin camps to screen approxim	ion trial (Figure 3). One intervention is ately 100 community contacts patient and to provide them with SDR-
36 37 38 39 40 41 42 43 44 45	<i>rifa</i> 169 170 171 172 173	<u>Study design</u> The study is a two-arm, cluster-randomized implementat community-based, using skin camps to screen approxim (household members and neighbors) of a leprosy index	ion trial (Figure 3). One intervention is ately 100 community contacts patient and to provide them with SDR- inter-based, inviting the household
36 37 38 39 40 41 42 43 44 45 46 47 48 49	<i>rifa</i> 169 170 171 172 173 174	<u>Study design</u> The study is a two-arm, cluster-randomized implementat community-based, using skin camps to screen approxim (household members and neighbors) of a leprosy index p PEP when eligible. The second intervention is health cer	ion trial (Figure 3). One intervention is ately 100 community contacts patient and to provide them with SDR- inter-based, inviting the household
36 37 38 39 40 41 42 43 44 45 46 47 48	<i>rifa</i> . 169 170 171 172 173 174 175	<u>Study design</u> The study is a two-arm, cluster-randomized implementat community-based, using skin camps to screen approxim (household members and neighbors) of a leprosy index p PEP when eligible. The second intervention is health cer	ion trial (Figure 3). One intervention is ately 100 community contacts patient and to provide them with SDR- inter-based, inviting the household
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36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58	<i>rifa</i> . 169 170 171 172 173 174 175 176 177 178 179 180 181	Study design         The study is a two-arm, cluster-randomized implementate         community-based, using skin camps to screen approxime         (household members and neighbors) of a leprosy index p         PEP when eligible. The second intervention is health cere         contacts of an index patient to be screened and given SI         Community-based skin camp intervention         A skin camp will be organized when a leprosy patient is a         people living in the surrounding area (or inhabitants from         are designed to bring specialized care closer to the comp         Besides preventive and curative treatment, these camps	ion trial (Figure 3). One intervention is ately 100 community contacts batient and to provide them with SDR- inter-based, inviting the household DR-PEP when eligible. diagnosed by inviting approximately 100 the 20 closest houses). Health camps munity, thus expanding access. <sup>36</sup> often also play a significant role to re been proposed as an effective way to

close collaboration with community leaders and local organizations.<sup>36,39</sup> In a skin camp, health staff screen individuals for skin diseases and then treat or refer patients if necessary. Assistance from a dermatologist (or, if none available, a senior health staff member with sufficient dermatology experience) is vital.<sup>40</sup> A key advantage of this community intervention is that the identity of the person affected by leprosy can be protected since no individual disease disclosure is needed. This non-disclosure approach is of utmost importance, as people affected by leprosy are often stigmatized and discriminated against and are therefore reluctant to share their disease status.<sup>41–43</sup> Moreover, including a wider group of contacts and using an integrated skin diseases approach may overcome the frequently negative associations with leprosy that can prevent people from participating in a leprosy-related intervention.<sup>16</sup> Including approximately 100 contacts per identified leprosy patient in the PEP4LEP skin camps is in line with the risk profiles of the contact groups and is operationally manageable within one skin camp day, also when using time slots to prevent crowding considering COVID-19.6,32,34,37,38,44-47 

#### Health center-based intervention for household contacts

In the second intervention, newly detected leprosy patients will be asked to invite their household contacts to visit a health center to have their skin screened and, if eligible, to be offered SDR-PEP. Clustering of the disease within households is commonly seen.<sup>6,47,48</sup> Household contacts are defined as living under the same roof as the leprosy index patient for a minimum of three months.<sup>11,30,49</sup> To prevent re-infection within a household and for operational management reasons, contacts need to visit the health center within three months after the index patient was included, which is also in-line with contact tracing interventions in literature.<sup>50</sup> Around six household contacts per patient are expected to visit the health center for screening.<sup>11</sup> Previous studies showed that leprosy patients are usually willing to disclose their leprosy diagnosis to their household members to facilitate screening and prophylaxis, but they are often reluctant to share this information with neighbors or other social contacts.41-43 



leprosy). "Integration" in this context refers to combined screening for a minimum of two diseases at the same time in the same communities.<sup>51</sup> In the PEP4LEP project, free topical treatment for the most frequently diagnosed skin diseases will be provided as well as referral advice, in-line with national medical guidelines. The screening for signs and symptoms of skin diseases, as well as the chemoprophylaxis distribution, will follow standard operating procedures (SOPs) in which the eligibility criteria for SDR-PEP are clearly stated. In both interventions, the integrated skin diseases approach will be used and supported by the SkinApp, a mHealth tool developed by NLR and Erasmus University Medical Center (Erasmus MC). The SkinApp will support peripheral health workers in recognizing and treating signs and symptoms of skin diseases, including skin-NTDs like leprosy.<sup>27,28</sup> A senior health staff member with sufficient dermatology experience 

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2 3	228	(preferably a dermatologist) will attend in person or via secure medical messaging via the
4	229	application (app) Siilo. <sup>52</sup>
5 6		
7	230	
8	231	Post-exposure prophylaxis
9 10	232	Chemoprophylaxis with SDR-PEP has been adopted in the 2018 WHO Guidelines for the
11	233	diagnosis, treatment and prevention of leprosy. <sup>4</sup> The SDR-PEP dosages used in this project
12 13	234	(Table 2) are consistent with the WHO guidelines and the LPEP program. <sup>4,11,53</sup>
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1 2 3 4	236	Table 2. DED41 ED single dage rifempicin desegoe <sup>4 10</sup>				
5 6		Table 2. PEP4LEP single-dose rifampicin dosages <sup>4,10</sup> Age and had unsight of context				
7 8		Age and body weight of contact Rifampicin dosage				
9		≥ <b>15 years</b> 600 mg				
10 11		<b>10-14 years</b> 450 mg				
12 13		6-9 years and body weight of ≥20 kg 300 mg				
14		≥2 years old and body weight between 10-20 kg 150 mg				
15 16	237					
17	238	Contacts who are temporarily ineligible to receive SDR-PEP (e.g., because of pregnancy, Table				
18 19	239	1) will receive skin screening and a SDR-PEP voucher, useable in an affiliated PEP4LEP health				
20 21	240	center when becoming eligible (e.g., after giving birth). Contacts receiving SDR-PEP will also				
21	241	receive a SDR-PEP Red Card to keep in their homes. This card indicates that the person has				
23 24	242	received SDR-PEP for leprosy prevention and is ineligible to receive this again within the next				
25	243	two years. These methods were previously used as part of the LPEP program in Tanzania. <sup>11</sup> In				
26 27	244	PEP4LEP, serious adverse events (SAEs) will be reported and followed up according to national				
28	245	and PEP4LEP guidelines (see ethical section). <sup>54</sup>				
29 30	246					
31 32	247	Outcomes				
33	248	The primary objectives of this study are to identify the most effective and feasible approach for				
34 35	249	screening contacts of leprosy patients in combination with administering chemoprophylaxis to				
36	250	prevent leprosy. Because of the long incubation period of leprosy, it will not be possible to				
37 38	251	observe reduced transmission at the population level, in terms of a reduced new case detection				
39 40	252	rate, during this project period. The active case finding component and raised awareness,				
41	253	however, are expected to lead to more cases improved early case detection (i.e., a shorter case				
42 43	254	detection delay) and reduced child cases and disability at the time of diagnosis.				
44	255					
45 46	256	Primary outcome measures				
47 48	257	The primary outcome measures of effectiveness in the comparison of the two interventions are:				
40 49	258	1) Case detection delay, measured in months since the first signs or symptoms of leprosy until				
50 51	259	diagnosis and in the number of patients with G2D.				
52	260	2) Number of new patients with leprosy, subdivided into child proportion, female proportion, and				
53 54	261	multibacillary (MB) / paucibacillary (PB) classification.				
55	262	3) Number of contacts screened and receiving SDR-PEP.				
56 57	263					
58 59	264	Secondary outcome measures				
60						

Feasibility will be assessed by looking at outcome measures related to cost-effectiveness and acceptability. A cost-effectiveness analysis will be undertaken in the third year of the project. The perspective will be social, which encompasses the costs incurred by the health system and the beneficiaries (out-of-pocket expenditure). The acceptability of both interventions will be determined by comparing the number of index patients and contacts included, as well as by using qualitative research methods such as interviews and focus group discussions (FGDs) with relevant stakeholders. 

#### Additional objectives

The additional objectives are to assess the acceptability of integrated skin screening and the use of the SkinApp as well as health workers' capacity regarding the integrated skin screening approach. This will be measured by the number of contacts diagnosed with skin diseases and NTDs and by observing use of the SkinApp during contact screening. The capacity of health workers to diagnose leprosy and other skin diseases will be determined by a series of four assessments: before (baseline) and after PEP4LEP training, during the study, at the end of the study. Additionally, qualitative methods including interviews, FGDs, and potentially observations will be used for both objectives.

C.

#### Case detection delay

Case detection delay is defined by Muthuvel et al. as the number of months between the onset of signs and symptoms of leprosy and the time of diagnosis, including both "patient delay" and "health-system delay".<sup>55</sup> Several studies have investigated delay in leprosy diagnosis in countries like Bangladesh, Brazil, India, Colombia, and Paraguay.<sup>55–62</sup> However, recent literature on delay in diagnosis is limited and mainly focuses on other geographical regions. Therefore, delay in this study will be determined with a, for this project, structured questionnaire designed in the project countries, with input from several stakeholders, which will be shared open access (publication expected). The questionnaire includes two annexes: a set of clinical photos of signs of leprosy and a context-specific calendar indicating important local dates, such as festivities, agricultural seasons and religious celebrations.<sup>63,64</sup> The questionnaires were culturally validated in all three countries, based on the conceptual framework of Herdman et al. (publication expected).65 

#### Table 3. PEP4LEP project outcomes and statistical methods

58 59	Objective	Outcome	Hypothesis	Outcome	Method of
60				measure	analysis

1 2					
3	1.1 To compare the	Primary:	Reduction in case	Number of	Descriptive
4 5 6	effectiveness of a	Case detection	detection delay is	months since first	statistics; linear
	skin camp	delay	expected to be	signs or	mixed models;
7 8	prophylaxis		greater in the	symptoms of	non-parametric
9	intervention with a		community-based	leprosy until	tests
10 11	health center-based		intervention	diagnosis; G2D	
12 13	prophylaxis		compared with the	percentage	
13 14	intervention in terms		health center-	among newly	
15 16	of the rate of leprosy		based household	diagnosed	
17	patients detected		contact approach	leprosy patients	
18 19	and delay in case	Primary:	The community-	Number of	Descriptive
20	detection	Number of	based intervention	contacts	statistics;
21 22		contacts	will identify more	diagnosed with	Pearson's chi
23 24		diagnosed with	cases of leprosy	leprosy; child	square test;
25		leprosy	from contact	proportion;	Fisher's exact
26 27		lopicey	screening	female	test; multivariate
28			compared with the	proportion;	logistic regression
29 30			health center	MB/PB	analysis
31			household contact-	classification of	anarysis
32 33			based approach	newly diagnosed	
34 35				leprosy patients	
36		Primary:	The community-	Number of	Descriptive
37 38		Number of	based intervention	contacts	statistics
39		contacts who	will allow more	screened;	3141131103
40 41		received	contacts to be	number of	
42			screened and	contacts who	
43 44		chemoprophylax	receive SDR-PEP	received SDR-	
45 46		is		PEP	
47			compared with the	PEP	
48 49			health center-		
50			based household		
51 52		Coordon	contact approach	Number of index	
53 54	1.2 To compare the	Secondary:	The community-	Number of index	Health economic
55	feasibility of the two	Cost-	based intervention	patients included;	evaluations
56 57	chemoprophylaxis	effectiveness of	will be more	number of	
58	interventions	each	expensive but will	contacts	
59 60	(screening	intervention	have a greater	screened;	
	household contacts		impact compared	number of cases	

or screening		with the health	prevented;	
contacts via skin		center-based	number of	
camps) in terms of		household contact	disabilities	
cost- effectiveness		approach	avoided;	
and acceptability			operational costs;	
			out-of-pocket	
			expenses	
	Secondary:	Both interventions	Number of index	Descriptive
	Acceptability of	will be accepted in	patients included;	statistics;
	each	participating	number of	qualitative
	intervention	countries	contacts	content analysis
			screened; and	of interviews;
			qualitative	FGDs and
			methods	potentially
				observations
2.1 To assess the	Additional:	The community-	Number of	Descriptive
acceptability of an	Number of	based intervention	contacts	statistics;
integrated skin	contacts	will identify more	diagnosed with	Pearson's chi
diseases approach	diagnosed with	cases of other skin	skin diseases	square test;
and the use of the	other skin	diseases from	including and with	Fisher's exact
SkinApp	diseases	contact screening	NTDs that	test; multivariate
		compared with the	manifest with skin	logistic regression
		health center-	lesions	analysis
		based household		
		contact approach		
	Additional:	The integrated skin	Number of	Descriptive
	Acceptability of	screening	contacts	statistics;
	an integrated	approach will	diagnosed with	sensitivity and
	skin screening	encourage	skin diseases and	specificity;
	approach and	screening	with NTDs that	positive and
	the use of the	participation, and	manifest with skin	negative
	SkinApp	the SkinApp will	lesions; utilization	predictive values
		help health workers	of the SkinApp	qualitative
		to diagnose skin	during contact	content analysis
		diseases	screening; and	of interviews,
			qualitative	FGDs, and
			methods	

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49 50	312
51	313
52 53	314
54	315
55 56	316

				potentially
				observations
2.2 To compare the	Additional:	Participation in	Results of health	Descriptive
capacity of health	Capacity of	training and the	worker capacity	statistics;
workers in	health workers	use of the SkinApp	assessments and	qualitative
diagnosing leprosy,	in diagnosing	will improve health	qualitative	content analysis
other skin diseases	leprosy and	worker capacity	methods	of interviews,
and other NTDs that	other skin			FGDs, and
manifest with skin	diseases			potentially
lesions before the				observations
start of the study				
with their capacity in				
the third year				

Abbreviations: FGD: focus group discussion; G2D: grade-2 disability; MB: multibacillary; NTD: neglected tropical disease; PB: paucibacillary; SDR-PEP: single-dose rifampicin

## 300 <u>Sample size</u>

The sample size calculation was based on case detection delay as main outcome measure. The 1 mean or median delay will be compared between both interventions and with the baseline. For 2 3 the sample size calculation, a literature-based estimated average case detection delay of 24 months for leprosy patients was used, with the conservative assumption that a minimal delay 4 difference of three months would be detected between the two interventions.<sup>66,67</sup> In order to 5 6 achieve this, we aim to include at least 675 index patients in the study: 270 in the community-7 based intervention areas (30 per country per year) and 405 new patients in the health center-8 based intervention areas (45 per country per year). Approximately 100 contacts will be screened 9 per index patient in the community-based intervention areas, and approximately 6 contacts will be 0 screened per index patient in the health center-based intervention areas; thus, a total of approximately 30,000 contacts will be screened (Figure 3). All fully trained health staff involved in 1 the PEP4LEP project will be asked to consent to enroll in the capacity assessment. 2

## 314 <u>Randomization</u>

PEP4LEP used randomization without blinding at the (clustered) health center level (health
 centers/posts), ensuring that clusters were similar in size. Blinding is impossible because of the
 varying interventions' characteristics. Cluster randomization is commonly used when trying to
 capture the impact of an intervention at community level on both infectiousness and
 susceptibility.<sup>68</sup> This method is stated to be feasible logistically, and contamination (e.g.,

information-sharing between participants from both interventions) is unlikely.<sup>68</sup> Randomization was performed using the statistical software package R.<sup>69</sup> Per country, health centers were randomly divided into the community-based intervention or health center-based intervention. Data collection and management The PEP4LEP data management plan was developed by Erasmus MC in collaboration with the consortium. Regarding quantitative data, collectors will record their findings onto paper-based forms. Information from the forms will be entered into the Research Electronic Data Capture (REDCap) system from Vanderbilt University.<sup>70</sup> The REDCap software will be linked to a centralized database server hosted by Erasmus MC. Qualitative data collection will be audio-recorded and/or paper-based. Data will be transcribed (verbatim) and entered into computer-assisted qualitative data analysis software.<sup>71</sup> The transcriptions will be securely stored at Erasmus MC after analysis. A system of identification (ID) codes has been developed to record and maintain data systematically, as well as to maintain "pseudo-anonymity." Data analysis Data from the PEP4LEP study will be analyzed primarily through quantitative methods using descriptive analysis for all variables (Table 3). Mean and median case detection delays will be compared between both interventions and the established baseline. This includes newly diagnosed cases identified through each contact screening intervention as well as those detected through ongoing passive case finding, the current main method of detection in routine leprosy programs in the three countries. The p-values for each statistical test will be two-tailed with  $p \le p$ 0.05 considered significant and 95% confidence intervals (CI) presented for regression analyses. Quantitative analysis will be conducted using statistical software such as SPSS.72 The acceptability and capacity assessments will include gualitative research data (Table 3), which will be coded and analyzed using computer-assisted qualitative data analysis software, including Atlas.ti.<sup>71,73</sup> Data coding is necessary to categorize and define what the data signify by identifying concepts, patterns, relations, and themes.<sup>74</sup> Data reanalysis will occur until no new topics are emerging and data saturation is reached.<sup>75</sup> Availability of data and materials Data will be stored for 25 years according to EU regulation 536/2014 considering clinical medication-related research projects.<sup>59</sup> Data will be made available in a repository for potential authorized re-use for future data analysis or study replication. Sharing data and study materials as well as open access publishing are important values of the EU research and innovation 

1 2		
3 4	356	program Horizon 2020, the European and Developing Countries Clinical Trials Partnership
5	357	(EDCTP) and the PEP4LEP consortium. <sup>59,76</sup>
6 7	358	
8	359	Patient and public involvement
9 10	360	Community leaders, people affected by leprosy, and representatives of disabled people
11 12	361	organizations (DPO) are and will be involved in monitoring the study as well as in mobilizing
13	362	community participation.
14 15	363	
16	364	
17 18	365	
19	366	Ethics
20 21	367	Ethical approval was obtained in Ethiopia, Tanzania, and Mozambique according to national
22 23	368	guidelines. Erasmus MC, as European consortium member, received a waiver of full medical
24	369	ethics review and approval from its ethical board according to the Dutch Medical Research
25 26	370	Involving Human Subjects Act (Wet Medisch-Wetenschappelijk Onderzoek met mensen,
27	371	WMO). <sup>77</sup>
28 29	372	
30 21	372	Written (or thumbprint) informed consent will be obtained from all study participants. If a
31 32 33 34 35 36 37 38 39 40 41 42	374	participant is below 18 years old, a parent or legal guardian will be asked for consent. Study
	374	information given to the study participants contains the study purpose, the right to withdraw,
		possible side effects of SDR-PEP (i.e., urine discoloration), the incidental findings procedure and
	376 377	national contact information. AEs are expected to be rare after SDR-PEP. In LPEP program's
		interim analysis, one adverse event was reported (a severe allergic reaction to rifampicin in
	378	
	379	Brazil) after administering SDR-PEP to 109,727 contacts of leprosy patients in seven countries. <sup>44</sup> Nevertheless, in (chemo)prophylaxis programs AEs are of utmost importance because large
43	380	
44 45	381	numbers of healthy individuals are involved. In PEP4LEP, SAEs will be reported following
46	382	national pharmacovigilance guidelines and by using the PEP4LEP AE Form for registration and
47 48	383	to inform the principal investigator. <sup>10,54</sup> An emergency allergy kit was recommended to be
49 50	384	available at community study sites where no health center is located. All participants with
50 51	385	suspected AEs will be referred for proper medical management and treated free of charge
52 53	386	according to national standard treatment guidelines.54
54	387	
55 56	388	During both screening interventions and research projects involving human subjects, incidental
57	389	findings with potential health importance may be observed. <sup>78</sup> Incidental findings are discoveries
58 59	390	made during a research or screening project which are outside the scope of the project. <sup>79</sup>
60	391	Examples of possible incidental findings when performing full body skin screening include: signs
		18
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

 Page 20 of 54

of cancer, venous insufficiency, bleeding diathesis, herniation, dental problems, or indications of possible abuse. Incidental findings in a research setting are often not explicit enough to be used for diagnosis, treatment, or clinical care.80 The procedures for reporting both SAEs and incidental findings are included in the evidence-based PEP4LEP SOPs, on the participant information sheet and in the health workers' training <sup>54,78,79,81,82</sup> The importance will also be emphasized during ongoing monitoring activities, including field visits.44 During the developmental phase of this project, the COVID-19 pandemic emerged. Regarding COVID-19, national governmental and WHO guidelines will be followed.<sup>31–34</sup> Information about COVID-19 and project implications (e.g., physical distancing, working in time slots) are included in the project's SOPs, IEC-materials and health workers' training. Hand washing facilities and personal protective equipment (PPE) such as gloves, face masks and aprons, will be made available at the study sides. A code of conduct will be designed for the PEP4LEP consortium, based on the code of conducts from WHO and All European Academies (ALLEA).83,84 All researchers in the project are encouraged to participate in good clinical practice (GCP) courses, facilitated by the research consortium.<sup>85</sup> National data-safety monitoring boards, an international publication committee, and an international scientific steering committee were formed to monitor the project (Figure 1). Trial registration The PEP4LEP project is registered at The Netherlands Trial Register (NTR), receiving trial registration number NL7294 (NTR7503), registration date September 10, 2018.86 Discussion The PEP4LEP study will use an integrated skin screening approach, which is also recommended by the WHO.<sup>1,16,17</sup> Skin diseases are among the most common human illnesses, affecting almost 900 million people worldwide.<sup>20</sup> They are thought to be the fourth leading cause of global non-fatal disease burden and can result in disabilities, stigmatization, and discrimination.<sup>20,87</sup> Additionally, dermatological problems can be the first expression of systemic or chronic diseases, including HIV/AIDS, diabetes, and NTDs.<sup>14,88</sup> Integrated skin screening is therefore expected to generate a greater health benefit compared with vertical health programs which focus on one disease only. Pooling diseases in projects like PEP4LEP can also be helpful in educating and in raising awareness, as health workers' knowledge of NTDs like leprosy has been declining.<sup>51,89,90</sup> For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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This was reflected in a study performed by Abeje et al. among general health workers diagnosing leprosy in Ethiopia, which revealed that only 18% diagnosed leprosy correctly.<sup>91</sup> Detecting skin NTDs like leprosy therefore requires capacity-strengthening programs.<sup>14,16,22-26</sup> This study will also use mHealth solutions to support peripheral health workers in recognizing and treating signs and symptoms of skin diseases. Evidence indicates that mobile technology tools can substantially benefit healthcare workers, their patients, and adequate health care delivery.92 In dermatology, electronic health (eHealth) was adopted early, with teledermatology as a widespread example, fostering the possibility of remote patient care and education.<sup>93,94</sup> This is especially valuable if health services are scarce and during periods of service disruption (e.g., flooding, civil unrest, COVID-19 pandemic).<sup>34,52,94–96</sup> We emphasize the importance of studying the effect of mHealth technologies, aimed at capacity strengthening, like NLR's SkinApp, before fully focusing on upscaling.<sup>27,28,92,96</sup> Despite the conclusion of the expert meeting that SDR-PEP poses negligible risk of generating rifampicin resistance in *M. tuberculosis*, ongoing resistance surveillance is important to consider.<sup>13,97–99</sup> However, because of the limited study period, resistance surveillance in the PEP4LEP implementation areas alone would add no value to the project as the number of patients will be too small and the project duration would be too short for any resistance to emerge during that period. It is therefore recommended to integrate the surveillance of rifampicin resistance in the PEP4LEP project areas with the resistance surveillance systems for TB and leprosy during the project period and beyond, consistent with WHO recommendations on resistance surveillance.97-99 Although SDR-PEP has been adopted in the WHO guidelines on leprosy, little is known about the feasibility of several implementation methods of SDR as chemoprophylaxis for leprosy in combination with varying and integrated contact screening methods, especially in sub-Saharan Africa.<sup>4</sup> Tanzania was the only sub-Sahara African country included in the LPEP Program.<sup>11</sup> Ortuno-Gutierrez et al. recently outlined the Post-Exposure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE) study protocol.<sup>100</sup> PEOPLE assesses the effectiveness of different modalities of SDR-PEP, using door-to-door surveys and a double dose of SDR-PEP. Both the PEOPLE and the PEP4LEP research questions comply with the Aligned Research Agenda for Zero Leprosy from the Global Partnership for Zero Leprosy (GPZL) regarding the call for more operational studies and research focusing on SDR-PEP and on digital health.<sup>101,102</sup> Too often, innovative medical interventions fail because the factors contributing to success are poorly understood and hence not considered.<sup>103</sup> Therefore, our goal is to share key insights gained from the PEP4LEP study to foster the implementation of integrated skin screening and chemoprophylaxis for leprosy in the sub-Sahara African context. 

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2 3	464					
4 5	465	Declarations				
6 7	466	<u>Acknowledgments</u>				
8 9 10	467	Our thanks go to all those involved in the PEP4LEP project, including the study participants; th	е			
10	468	full research consortium; and our funders European and Developing Countries Clinical Trials				
11 12	469	Partnership (EDCTP) and Leprosy Research Initiative (LRI).				
13 14 15	470					
	471	Author contributions				
16 17	472	LM, CK, JHR, AS, TH and RvW designed the study. KB, FM, SEM, EM, AM, NM, TL, AMM, D	∕K,			
18	473	AME, LR, BN supported the development of country-specific protocols, materials and coordina	te			
19 20	474	the study implementation. AS, TH and RvW have drafted the manuscript. All authors have				
21	475	reviewed the draft manuscript and have read and approved the final version.				
22 23	476					
24 25	477	Funding				
26	478	This project was supported by the EDCTP2 program under Horizon 2020 (grant number				
27 28 29	479	RIA2017NIM-1839-PEP4LEP). The project also received funding from the Leprosy Research				
	480	Initiative (LRI; www.leprosyresearch.org) under LRI grant number 707.19.58. Both funding bodies				
30 31	481	reviewed and approved the study proposal.				
32 33	482					
34	483	Competing interests				
35 36	484	No competing interest have been declared by the authors.				
37 38 39	485					
	486					
40 41	487	References				
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Page 23 of 54

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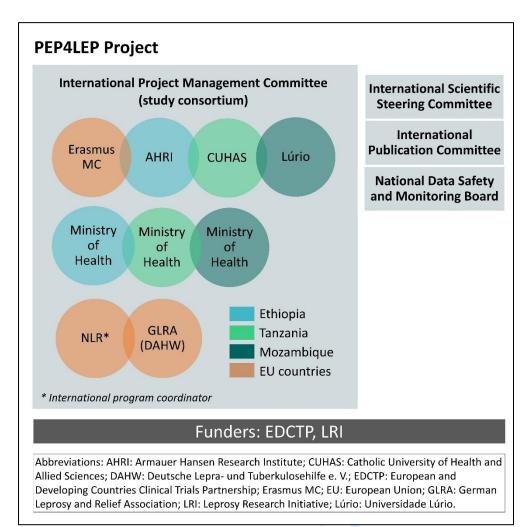
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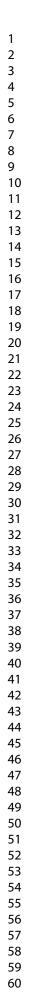
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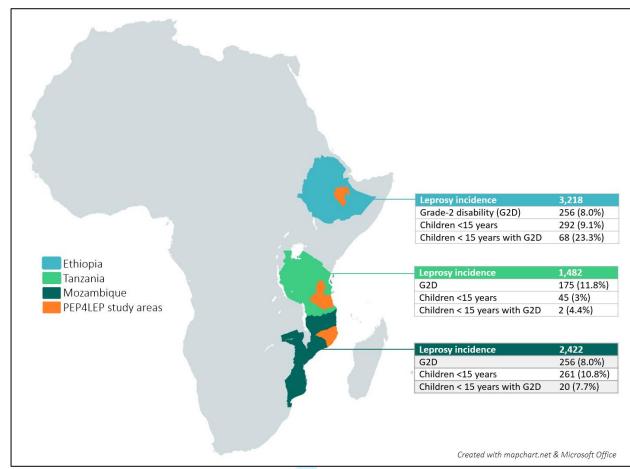


Figure 2. PEP4LEP countries' leprosy incidence (2018) according to the World Health Organization<sup>29</sup>

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	Index patients	Contacts
Inclusion criteria	<ul> <li>Consent to participate in the PEP4LEP project</li> <li>Diagnosed with leprosy (preferred maximum of 6 months prior to inclusion)</li> <li>Residence in the PEP4LEP districts for ≥3 months prior to the date of diagnosis</li> <li>Index patient has started MDT</li> <li>Community-based skin camp intervention: Leprosy patient gives permission for the setup of a skin camp in his/her community (sharing their leprosy diagnosis with their contacts is not needed)</li> <li>Health center-based household screening intervention: Leprosy patient with household contacts, and who is willing to inform these contacts about PEP4LEP</li> </ul>	<ul> <li>Consent to participate in the PEP4LEP project</li> <li><u>Community-based skin camp</u> <u>intervention</u>: Community contact of the index patient for ≥3 months</li> <li><u>Health center-based household screening</u> <u>intervention</u>: Contact which is a household member of the index patient for ≥3 months, visiting the screening health center ≤3 months after the index patient was included</li> </ul>
Exclusion criteria	<ul> <li>Index patient or parents/legal guardians unable to understand the purpose and risks of participating in the PEP4LEP study</li> </ul>	<ul> <li>Contact or parents/legal guardians unable to understand the purpose and risks of participating in the PEP4LEP study</li> <li>Age &lt;2 years and/or &lt;10 kg of weight*</li> <li>Pregnancy*</li> <li>Receiving or having received rifampicin for any reason in the last 2 years</li> <li>Known allergy to rifampicin</li> <li>History of liver or renal disorders</li> <li>Individuals with leprosy and those who have possible signs and/or symptoms of leprosy (e.g., leprosy-like skin lesions or nerve manifestations) until their disease status has been clarified<sup>35</sup>**</li> <li>Individuals with possible signs and/or symptoms of TB (cough for more than two weeks or cough in known HIV/AIDS patients, night sweats, unexplained fever, weight loss) until their disease status has been clarified<sup>35</sup>**</li> <li>Individuals with possible signs and/or symptoms of COVID-19 (self-assessed temperature ≥38°C, respiratory or cold-like symptoms, sudden loss of smell/taste) or possible contact with a COVID-19 patient in the past 14 days.<sup>31-</sup></li> </ul>

center when this person becomes eligible (e.g., after giving birth). \*\* If referral was needed and no leprosy is detected, repeated skin screening and SDR-PEP can be provided in a PEP4LEP affiliated health center.

\*\*\* Skin screening and SDR-PEP can only be provided in a PEP4LEP affiliated health center after the contact is tested negative for COVID-19/TB (according to national guidelines).<sup>31–34</sup>

Abbreviations: COVID-19: Coronavirus Disease 2019; MDT: multidrug therapy; SDR-PEP: single-dose rifampicin postexposure prophylaxis; TB: tuberculosis Page 35 of 54

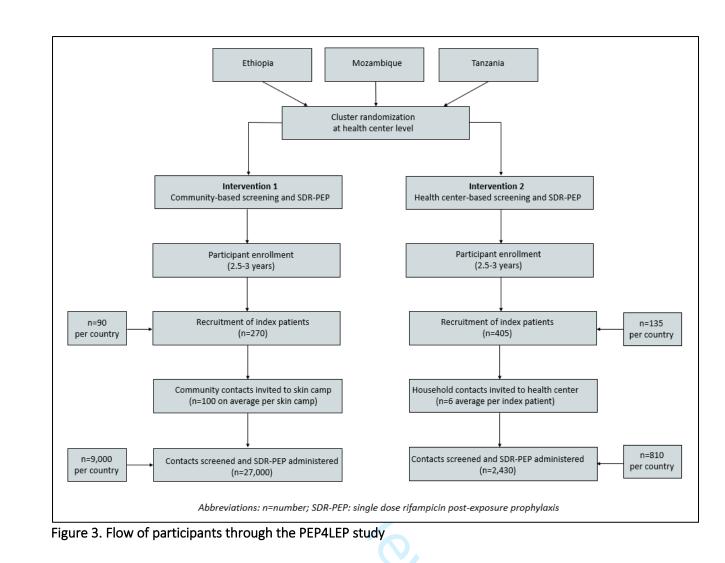


Table 2. PEP4LEP single-dose rifampicin dosages<sup>4,10</sup>

Age and body weight of contact ≥15 years 10-14 years	Rifampicin dosage
10-14 years	Kindinipieni desuge
10-14 years	600 mg
	450 mg
6-9 years and body weight of ≥20 kg	300 mg
≥2 years old and body weight between 10-20 kg	150 mg

#### Table 3. PEP4LEP project outcomes and statistical methods

Objective	Outcome	Hypothesis	Outcome measure	Method of analysis
1.1 To compare the effectiveness of a skin camp prophylaxis	Primary: Case detection delay	Reduction in case detection delay is expected to be	Number of months since first signs or symptoms of	Descriptive statistics; linear mixed models; nor
intervention with a health center-based prophylaxis intervention in terms of the rate of leprosy patients detected and delay in case detection		greater in the community-based intervention compared with the health center-based household contact approach	leprosy until diagnosis; G2D percentage among newly diagnosed leprosy patients	parametric tests
	Primary: Number of contacts diagnosed with leprosy	The community- based intervention will identify more cases of leprosy from contact screening compared with the health center household contact- based approach	Number of contacts diagnosed with leprosy; child proportion; female proportion; MB/PB classification of newly diagnosed leprosy patients	Descriptive statistics; Pearson chi square test; Fisher's exact test multivariate logist regression analysi
	Primary: Number of contacts who received chemoprophylaxis	The community- based intervention will allow more contacts to be screened and receive SDR-PEP compared with the health center-based household contact approach	Number of contacts screened; number of contacts who received SDR-PEP	Descriptive statistics
1.2 To compare the feasibility of the two chemoprophylaxis interventions (screening household contacts or screening contacts via skin camps) in terms of cost- effectiveness and acceptability	Secondary: Cost-effectiveness of each intervention	The community- based intervention will be more expensive but will have a greater impact compared with the health center-based household contact approach	Number of index patients included; number of contacts screened; number of cases prevented; number of disabilities avoided; operational costs; out-of-pocket expenses	Health economic evaluations
	Secondary: Acceptability of each intervention	Both interventions will be accepted in participating countries	Number of index patients included; number of contacts screened; and qualitative methods	Descriptive statistics; qualitative conter analysis of interviews; FGDs and potentially observations
2.1 To assess the acceptability of an integrated skin diseases approach and the use of the SkinApp	Additional: Number of contacts diagnosed with other skin diseases	The community- based intervention will identify more cases of other skin diseases from contact screening	Number of contacts diagnosed with skin diseases including and with NTDs that manifest with skin lesions	Descriptive statistics; Pearson chi square test; Fisher's exact test multivariate logist regression analysi

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Acceptability of an integrated skin screening approach and the use of the SkinAppscreening approach will encourage screening participation, and the SkinApp will help health workers to diagnose skin diseasesdiagnosed with skin diseases and with NTDs that manifest with skin lesions; utilization of the SkinApp during contact screening; and qualitative methodsstatistics; sensitivit and specificity; positive and negative predictive values; qualitative content analysis of interviews, FGDs, and potentially observations2.2 To compare the capacity of health workers in diagnosing leprosy, other skin diseases and other NTDs that manifest with skin lesions before the start of the study with their capacity in the third yearAdditional: Capacity of health worker capacity skin diseasesParticipation in training and the use of the SkinApp will improve health worker capacity assesments and qualitative methodsDescriptive statistics; qualitative content analysis of interviews, FGDs, and potentially observations2.2 To compare the capacity of health workers in diagnosing leprosy and other skin diseasesParticipation in training and the use of the SkinApp will worker capacity assessments and qualitative methodsDescriptive statistics; qualitative analysis of interviews, FGDs, and potentially observations2.2 To compare the capacity of health workers in diagnosing leprosy and other study with their capacity in the third yearAdditional: Capacity of bealth worker capacity study with their capacity in the third yearSkinApp during training and the use of the SkinApp will<	Acceptability of an integrated skin screening approach and the use of the SkinAppscreening approach and the use of the SkinAppscreening participation, and the SkinApp will help health workers to diagnose skin diseasesdiagnosed with skin diseases and with NTDs that manifest with skin lesions; utilization of the SkinApp during contact screening; and qualitative methodsstatistics; sensitivit and specificity; positive and negative predictive values; qualitative content analysis of interviews, FGDs, and qualitative methods2.2 To compare the capacity of health workers in diagnosing leprosy, other skin diseases and other NTDs that manifest with skin lesions before the start of the study with their capacity in the third yearAdditional: Capacity of health workers in diagnosing leprosy and other skin diseasesParticipation in training and the use of the SkinApp will improve health worker capacityResults of health worker capacity assessments and qualitative methodsDescriptive statistics; and yotentially observations2.2 To compare the capacity of health workers in diagnosing leprosy and other skin diseasesAdditional: Capacity of health worker capacityParticipation in training and the use of the SkinApp will improve health worker capacityResults of health worker capacity assessments and qualitative methodsDescriptive statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; statistics; s		Additional:	compared with the health center-based household contact approach	Number of contacts	Descriptive
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Ref.No. MoSHE//RD/ レントレント 10116120 Date: 17 FEB 2020

#### Armuer Hansen Research Institute (AHRI) <u>Addis Ababa</u>

#### Subject: Letter of Approval

The Ministry of Science and Higher Education (MoSHE) via its National Research Ethics Review Committee has reviewed "Comparing the Effectiveness and Feasibility of a Skincamp Intervention to a Healthcentre Based Intervention as Countries Scale-up Use of Chemoprophylaxis for Leprosy" project protocol in an expedited manner. We are writing to advise you that MoSHE has granted full approval to the above named project, for a period of one year (February 17, 2020- February 16, 2021)..

All your most recently submitted documents have been approved for use in this study. The study should comply with the international and national scientific and ethical standard guidelines. Any change to the approved protocol or consent material must be reviewed and approved through the amendment process prior to its implementation. In addition, any adverse or unanticipated events should be reported within 24-48 hours to MoSHE. Please ensure that you submit biannual progress report to MoSHE once in six months and annual renewal application 30 days prior to the expiry date.

We, therefore, request you as PI and your esteemed organization to ensure the commencement and conduct of the study accordingly and wish for the successful completion of the project.

<u>Cc.</u>

> Office of the State Minister (Sector for Science, Research and Community

Science and Research Affairs Directiorate General

Research Ethics Directorate

#### MoSHE

Dr.Kidest Bobosha ( PI) <u>Addis Ababaw</u>

www.moshe.gov.et

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www.facebook.com/SHE.Ethio

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## Scanned by CamScanner

Solomon Benor Belay (PhD)

and Research Affairs

Service) General for Science



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Ref.No. MoSHE//RD//4/11/01/6/20 Date: 17 FEB 2020

#### Armuer Hansen Research Institute (AHRI) Addis Ababa

#### Subject: Letter of Approval

The Ministry of Science and Higher Education (MoSHE) via its National Research Ethics Review Committee has reviewed "Comparing the Effectiveness and Feasibility of a Skincamp Intervention to a Healthcentre Based Intervention as Countries Scale-up Use of Chemoprophylaxis for Leprosy" project protocol in an expedited manner. We are writing to advise you that MoSHE has granted full approval to the above named project, for a period of one year (February 17, 2020- February 16, 2021)..

All your most recently submitted documents have been approved for use in this study. The study should comply with the international and national scientific and ethical standard guidelines. Any change to the approved protocol or consent material must be reviewed and approved through the amendment process prior to its implementation. In addition, any adverse or unanticipated events should be reported within 24-48 hours to MoSHE. Please ensure that you submit biannual progress report to MoSHE once in six months and annual renewal application 30 days prior to the expiry date.

We, therefore, request you as PI and your esteemed organization to ensure the commencement and conduct of the study accordingly and wish for the successful completion of the project.

incerely

Solomon Benor Belay (PhD)

<u>Cc.</u>

- Office of the State Minister (Sector for Science, Research and Community Service)or General for Science and Research Affairs
- Science and Research Affairs Directionate General
- Research Ethics Directorate
  - MoSHE

Dr.Kidest Bobosha ( PI) Addis Ababaw

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#### REPÚBLICA DE MOÇAMBIQUE MINISTÉRIO DA SAÚDE COMITÉ NACIONAL DE BIOÉTICA PARA A SAÚDE IRB00002657

Exmo. Senhor Dr. Fernando Mitano Unilúrio

Data 15 de Julho de 2020

#### Ref:342/CNBS/20

Assunto: Renovação da aprovação do protocolo de estudo intitulado: "*Ensaio de implementação* médica sobre triagem cutânea e administração de rifampicina como profilaxia pósexposição para contactos de pessoas afetadas pela lepra em Murrupula, Meconta e Mogovolas"

O Comité Nacional de Bioética para a Saúde (CNBS) analisou o pedido de renovação anual da aprovação do protocolo de estudo intitulado: "*Ensaio de implementação médica sobre triagem cutânea e administração de rifampicina como profilaxia pós-exposição para contactos de pessoas afetadas pela lepra em Murrupula, Meconta e Mogovolas", e sobre* o mesmo o CNBS chegou a seguinte conclusão:

Não havendo nenhum inconveniente de ordem ética que impeça a continuação do estudo, o CNBS dá a autorização.

Todavia, recomenda aos investigadores que mantenham o CNBS informado do decurso do estudo.

A aprovação da renovação tem a validade de um ano, terminando esta a 15 de Julho de 2021. Os investigadores deverão submeter o pedido de renovação da aprovação um mês antes de terminar o prazo.

Sem mais de momento, queiram aceitar as nossas cordiais saudações.



Endereço: Ministério da Saúde - 2º andar dto Av. Eduardo Mondlane / Salvador Allende Maputo - Moçambique C.Postal: 264 Telefone: +258 82 406 6350 E-mail: cnbsmocambique@gmail.com





REPÚBLICA DE MOÇAMBIQUE MINISTÉRIO DA SAÚDE COMITÉ NACIONAL DE BIOÉTICA PARA A SAÚDE IRB00002657

Exmo. Senhor Professor Doutor Francisco Mitano CIBS-Unilúrio

Ref:385/CNBS/19

#### Data 16 de Agosto de 2019

Assunto: Aprovação do Comité Nacional de Bioética para Saúde (CNBS) referente ao protocolo de estudo intitulado: "Ensaio de implementação médica sobre triagem cutânea e administração de rifampicina como profilaxia pós-exposição para contactos de pessoas afectadas pela Lepra em Morrupula, Meconta e Mogovolas"

O Comité Nacional de Bioética para Saúde (CNBS) analisou as correcções efectuadas no protocolo de estudo intitulado: "Ensaio de implementação médica sobre triagem cutânea e administração de rifampicina como profilaxia pós-exposição para contactos de pessoas afectadas pela Lepra em Morrupula, Meconta e Mogovolas"

Registado no CNBS com o número 31/CNBS/2019, conforme os requisitos da Declaração de Helsínguia.

Não havendo nenhum inconveniente de ordem ética que impeça a realização do estudo, o CNBS dá a sua devida aprovação aos seguintes documentos:

- Protocolo de estudo, versão S/N de Fevereiro de 2019
- Consentimento informado, versão S/N de Fevereiro de 2019
- Instrumento de recolha de dados, versão S/N de Fevereiro de 2019

Todavia, o CNBS informa que:

- Qualquer alteração a ser introduzida no protocolo, incluindo os seus anexos deve ser submetida ao CNBS para aprovação.
- 2- A presente aprovação não substitui a autorização administrativa.
- 3- Não houve declaração de conflitos de interesse por nenhum dos membros do CNBS.
- 4- A aprovação terá a validade de um ano, terminando esta a 16 de Agosto de 2020. Os investigadores deverão submeter o pedido de renovação da aprovação um mês antes de terminar o prazo.
- 5- Recomenda-se aos investigadores que mantenham o CNBS informado do decurso do estudo.
- 6- A lista actualizada dos membros do CNBS esta disponível na secretaria do Comité.

Sem mais do momento, queiram aceltar as nossas mais cordiais saudações.

ERIO D. residente emando Lima Schwalbach Dr. João EBIOET

Endereço:

Ministério da Saúde - 2º andar dto Av. Eduardo Mondlane / Salvador Allende Maputo - Moçambique C.Postal: 264 Telefone: +258 82 406 6350 E-mail: cnbsmocambique@gmail.com

16 August 2019

Subject: Approval of the National Committee on Bioethics in Health (Comisión Nacional de Bioética en Saúde, CNBS)

Referring to the protocol of the study "Chemoprophylaxis for leprosy: comparing the effectiveness and feasibility of a skin camp intervention to a health centre-based intervention" ("PEP4LEP").

CNBS analyzed the corrections made to the protocol of the studio "PEP4LEP" registered at CNBS with number 31/CNBS/2019. According to the requirements of the Declaration of Helsinki, there are no ethical inconvenience found that impede the realization of the study. Therefore, the CNBS gives its approval to the following documents:

- PEP4LEP Study Protocol, version February 2019
- PEP4LEP Informed Consent Forms, version February 2019
- PEP4LEP Data Collection Forms, version February 2019

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## THE UNITED REPUBLIC OF TANZANIA



National Institute for Medical Research 3 Barack Obama Drive P.O. Box 9653 11101 Dar es Salaam Tel: 255 22 2121400 Fax: 255 22 2121360 Email: <u>nimrethics@gmail.com</u> Ministry of Health, Community Development, Gender, Elderly &Children University of Dodoma, College of Business Studies and Law Building No. 11 P.O. Box 743 40478 Dodoma

20<sup>th</sup> July 2020

NIMR/HQ/R.8c/Vol. I /1530

Dr. Beatrice Mutayoba Ministry of Health, Community Development, Gender, Elderly & Children National TB and Leprosy Programme P O Box 9083 Dar es Salaam

## **RE: APPROVAL FOR EXTENSION OF ETHICAL CLEARANCE**

This letter is to confirm that your application for extension on the already approved proposal: PEP4LEP: comparing the effectiveness and feasibility of a skin camp intervention to a health center based intervention as countries scale up use of chemoprophylaxis for leprosy. An implementation trial in Mozambique, Ethiopia and Tanzania (Mutayoba B. et al), has been approved.

The extension approval is based on the progress report dated 22<sup>nd</sup> June, 2020 on the project, Ref. NIMR/HQ/R.8a/Vol. IX/3131, dated 17<sup>th</sup> June, 2019. Extension approval is valid until 16<sup>th</sup> June, 2021.

The Principal Investigator must ensure that other conditions of approval remain as per ethical clearance letter. The PI should ensure that progress and final reports are submitted in a timely manner.

Name: Prof. Yunus Daud Mgaya

Signature CHAIRPERSON MEDICAL RESEARCH COORDINATING COMMITTEE

Name: Prof. Abel Nkono Makubi

Signature (

CHIEF MEDICAL OFFICER MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY & CHILDREN

Page 45 of 54

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National Institute for Medical Research 3 Barack Obama Drive P.O. Box 9653 11101 Dar es Salaam Tel: 255 22 2121400 Fax: 255 22 2121360 E-mail: nimrethics@gmail.com

NIMR/HQ/R.8a/Vol. IX/3131

Dr. Beatrice Mutayoba Ministry of Health, Community Development, Gender, Elderly & Children National TB and Leprosy Programme P. O. Box 9083 Dar es Salaam Ministry of Health, Community Development, Gender, Elderly & Children University of Dodoma, College of Business Studies and Law Building No. 11 P.O. Box 743 40478 Dodoma

17<sup>th</sup> June, 2019

#### RE: ETHICAL CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: PEP4LEP: comparing the effectiveness and feasibility of a skin camp intervention to a health centre based intervention as countries scale up use of chemoprophylaxis for leprosy. An implementation trial in Mozambique, Ethiopia and Tanzania (Mutayoba B. et al), has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

- 1. Progress report is submitted to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
- 2. Permission to publish the results is obtained from National Institute for Medical Research.
- 3. Copies of final publications are made available to the Ministry of Health, Community Development, Gender, Elderly & Children and the National Institute for Medical Research.
- 4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III Section 10(2).
- 5. Sites: Lindi District Council in Lindi region, Morogoro District Council and Mvomero District Council in Morogoro region.

Approval is valid for one year: 17<sup>th</sup> June 2019 to 16<sup>th</sup> June 2020.

Name: Prof. Yunus Daud Mgaya

Signature CHAIRPERSON MEDICAL RESEARCH COORDINATING COMMITTEE

CC: Director, Health Services -TAMISEMI, Dodoma RMO of Lindi and Morogoro regions DMO/DED of respective districts Name: Prof. Muhammad Bakari Kambi

Signature CHIEF MEDICAL OFFICER MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY & CHILDREN



Medische Ethische Toetsings Commissie Erasmus MC www.erasmusmc.nl/commissies/metc/

Prof.dr. J.H. Richardus Afdeling iMGZ Maatsch.Gezondheidszorg Algemeen Kamer NA-2322 Erasmus MC

Betreft: MEC-2019-0130, Besluit onderzoek is niet WMO-plichtig Multicenter, Erasmus MC initieert

#### Protocol titel:

'Chemoprophylaxis for leprosy: comparing the effectiveness and feasibility of a skin camp intervention to a health centre based intervention. An implementation trial in Mozambique, Ethiopia and Tanzania'

Protocol versie 3.2 d.d. 28 december 2018

Geachte heer Richardus,

De Medisch Ethische Toetsings Commissie Erasmus MC heeft het door u ingediende bovenvermeld onderzoeksvoorstel, volledig conform de eisen van de METC ontvangen op 24 februari 2019 ter beoordeling van de WMO-plichtigheid.

Het dagelijks bestuur van de commissie heeft beoordeeld of dit onderzoek al dan niet binnen de reikwijdte van de WMO valt. In verband hiermee is het dagelijks bestuur tot de conclusie gekomen dat:

- de proefpersonen <u>wel</u> aan een handeling worden onderworpen of er wordt hen een gedragswijze opgelegd.
- de proefpersonen <u>niet</u> aan een handeling worden onderworpen en er wordt hen geen gedragswijze opgelegd, beide zoals bedoeld in de WMO.

Omdat aan één van beide voorwaarden voor WMO-plichtigheid niet is voldaan, heeft het dagelijks bestuur van de commissie d.d. 2 april 2019 besloten <u>dat bovenvermeld onderzoek</u> <u>niet WMO-plichtig is</u>. U mag dit onderzoek uitvoeren in het Erasmus MC en u kunt de resultaten te zijner tijd voor publicatie aanbieden aan een wetenschappelijk tijdschrift.

De commissie attendeert u op de volgende punten

- De commissie heeft alleen de WMO-plichtigheid beoordeeld. Er heeft verder geen inhoudelijke toets van het onderzoek plaatsgevonden.
- U en uw afdeling zijn verantwoordelijk voor de correcte uitvoering van het onderzoek volgens de geldende wet- en regelgeving. Hierbij vestigen wij uw aandacht op het volgende:

Doorkiesnummer +31 10 7033625/34428 Kamernummer Ae-337 E-mail metc@erasmusmc.nl Ons kenmerk WT/aj/MEC-2019-0130 Datum 11 april 2019

> Postadres Postbus 2040 3000 CA Rotterdam

Bezoekadres Dr. Molenwaterplein 40 3015 CD Rotterdam

Parkeergarage Westzeedijk 361 3015 AA Rotterdam

Voorzitters Prof.dr. H.W. Tilanus Prof.dr. H.J. Metselaar

Secretarissen Mw. mr. C.P. Bronvan Vliet Mw.drs. N. Loekabino Mw.dr. F.M. Spoelstra Mw.ing. W.C.M. Tielemans

Secretaresses Mw. A. de Jong Mw. S. Sneevliet

Het secretariaat is geopend van maandag tot en met vrijdag van 08.30 tot 17.00 uur

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 Voor prospectief onderzoek, waarbij gegevens van proefpersonen worden verzameld en verwerkt, is toestemming van de proefpersonen nodig. U vindt een voorbeeld patiënteninformatie- en toestemmingsformulier voor niet WMO-plichtig onderzoek op de site van de METC. (www.erasmusmc.nl /commissies/metc/)

 Voor retrospectief onderzoek, waarbij gegevens van proefpersonen gecodeerd worden verzameld en verwerkt is toestemming van de proefpersonen nodig. U vindt een voorbeeld patiënteninformatie- en toestemmingsformulier voor niet WMO-plichtig onderzoek op de site van de METC (<u>www.erasmusmc.nl</u> /commissies/metc/).
 (Bij retrospectief *anoniem* onderzoek is toestemming niet verplicht, hierbij zijn de gegevens nooit meer herleidbaar tot de proefpersonen.)

- Wanneer in een onderzoek gegevens worden verzameld van proefpersonen, dient hiermee correct te worden omgegaan zoals bepaald in de Gedragscode Gezondheidsonderzoek (Code Goed Gedrag), het Privacy Reglement Erasmus MC en de Algemene Verordening Gegevensbescherming (AVG). U vindt hierover meer informatie op de website van de METC (www.erasmusmc.nl /commissies/metc/) en op de website van FEDERA (www.federa.org).
- Wanneer in een onderzoek (lichaams)materiaal van proefpersonen wordt verzameld en verwerkt dient hiermee correct te worden omgegaan zoals bepaald in de Code Goed Gebruik. U vindt hierover meer informatie op de website van FEDERA (www.federa.org).
- Vergunningplichtig bevolkingsonderzoek moet worden ingediend bij de Commissie Bevolkingsonderzoek ter toetsing conform de Wet bevolkingsonderzoek. U vindt hierover meer informatie op de website van de CCMO (www.ccmo.nl).
- Niet WMO-plichtig Fase IV Geneesmiddelen onderzoek dat wordt geïnitieerd door de farmaceutische industrie dient te worden getoetst en uitgevoerd conform de Gedragscode Geneesmiddelenreclame. U vindt hierover meer informatie op de site van de stichting code geneesmiddelen reclame (www.cgr.nl).
- Amendementen en/of addenda bij dit onderzoek dienen aan de commissie ter beoordeling te worden voorgelegd zodat kan worden beoordeeld of het onderzoek nog steeds buiten de reikwijdte van de WMO blijft, of dat er door het amendement/addendum sprake is van WMO-plichtig onderzoek.
- Onderzoekers in het Erasmus MC dienen zich te houden aan de research codes, zoals vastgelegd in de uitgave 'Research Codes' van de afdeling Onderzoeksbeleid, te vinden op Intranet.
- Voor ethische toetsing van <u>Onderwijsonderzoek</u> verwijst de commissie u naar de website van de NVMO-ERB (www.nvmo.nl).

Page 48 of 54

Pagina 3/3 Ons kenmerk WT/aj/MEC-2019-0130 Datum 11 april 2019



- De commissie verzoekt u haar op de hoogte te brengen van de volgende gegevens betreffende dit onderzoek:
  - Startdatum (datum inclusie eerste proefpersoon) en/of start gegevens onderzoek

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- einddatum (datum stop studie laatste proefpersoon) en/of stop gegevens onderzoek
- publicaties en/of eindrapport

Wanneer u vragen heeft over het opzetten, financieren, of uitvoeren van wetenschappelijk onderzoek, kunt u terecht bij het Consultatiecentrum Patiëntgebonden Onderzoek (CPO) voor advies en hulp. Het CPO organiseert ook meerdere keren per jaar de BROK cursus (Basiscursus Regelgeving en Organisatie van Klinisch Onderzoek), die door de commissie van harte wordt aanbevolen. Het volgen van de BROK cursus is, conform landelijke afspraken, <u>alleen verplicht bij WMO-plichtig onderzoek</u>. Voor informatie over de BROK-cursusdata kunt u contact opnemen met het Congresbureau, intern tel.nr. 43584.

Op de site van de METC kunt u links terugvinden naar de hierboven vermelde wet- en regelgeving. Wanneer u vragen heeft over dit METC besluit, kunt u contact opnemen met het secretariaat van de METC.

Met vriendelijke groet,

namens de Medisch Ethische Toetsings Commissie Erasmus MC,

Tailod 1.0.

Mw.ing. W.C.M. Tielemans Secretaris

To whom it may concern,

The Daily Board of the Medical Ethics Committee Erasmus MC (hereafter the Committee) of Rotterdam, The Netherlands, has reviewed the above mentioned research proposal. As a result of this review, the Committee informs you that the rules laid down in the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO), do not apply to this research proposal.

#### Please indicate the above MEC-number in every correspondence on this study

Yours sincerely, On behalf of the Medical Ethics Committee Erasmus MC,

Mrs. W.C.M. Tielemans, BASc Secretary of the Committee

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# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ltemNo	Description	BMJ Open
Administrativ	e inform	ation	
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Page 1, Trial registration
Funding	4	Sources and types of financial, material, and other support	Page 14, Funding
Roles and responsibilitie s	5a	Names, affiliations, and roles of protocol contributors	Page 1 Page 14, Authors' contributions
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 11, Availability of data and materials Page 3, Objectives (details study consortium) Page 14, Funding
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 11, Data collection ar management Page 12, Ethics, paragraph

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3, Objectives
	6b	Explanation for choice of comparators	Page 8, Outcomes
Objectives	7	Specific objectives or hypotheses	Page 3, Objectives Page 9, Table 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6, Study Design Page 7, Figure 3
Methods: Pa	rticipants	s, interventions, and outcomes	
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4, Study setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 4, Participants and eligibility criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 6, Community based skin camp intervention Page 6, Health center-based intervention for household contacts
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 4, Participants and eligibility criteria Page 5, Table 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 4, Participants and eligibility criteria Page 5, Table 1

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 8, Outcomes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 4, Study setting Page 6, Study Design Page 7, Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 10, Sample size
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10, Sample size
Methods: Ass	signmen	t of interventions (for controlled trials)	
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign	Page 11, Data collection and management, paragraph 3
		interventions	

Implement ation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 11, Data collection and management, paragraph 3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Dat	a collect	tion, management, and analysis	
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 11, Data collection and management
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 11, Data collection and management
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 11, Data collection and management
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 11, Data analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 11, Data analysis

1				
2		20c	Definition of analysis population relating to	Page 11, Data analysis
3			protocol non-adherence (eg, as randomised	
4				
5			analysis), and any statistical methods to	
6			handle missing data (eg, multiple	
7			imputation)	
8			. ,	
9	Methods: Mo	nitoring		
10			<b>.</b>	
11	Data	21a	Composition of data monitoring committee	Page 12, Ethics, paragraph 5
12	monitoring		(DMC); summary of its role and reporting	
13			structure; statement of whether it is	
14			independent from the sponsor and	
15				
16			competing interests; and reference to	
17			where further details about its charter can	
18			be found, if not in the protocol. Alternatively,	
19			an explanation of why a DMC is not needed	
20			an explanation of why a blue is not needed	
21		21b	Description of any interim analyses and	N/A
22		210	. , , ,	
23			stopping guidelines, including who will have	
24			access to these interim results and make	
25			the final decision to terminate the trial	
26				
27	Harms	22	Plans for collecting, assessing, reporting,	Page 12, Ethics, paragraph 2
28			and managing solicited and spontaneously	
29			reported adverse events and other	
30			-	
31			unintended effects of trial interventions or	
32 33			trial conduct	
33 34	A	00		Deve 40 Ethics means when 5
35	Auditing	23	Frequency and procedures for auditing trial	Page 12, Ethics, paragraph 5
36			conduct, if any, and whether the process	
37			will be independent from investigators and	
38			the sponsor	
39				
40	Ethics and di	ssemina	tion	
41				
42	Research	24	Plans for seeking research ethics	Page 12, Ethics, paragraph 1
43	ethics		committee/institutional review board	
44				
45	approval		(REC/IRB) approval	
46	Protocol	25	Plans for communicating important protocol	Page 12 Ethics paragraph 1
47		20	• • •	
48	amendments		modifications (eg, changes to eligibility	
49			criteria, outcomes, analyses) to relevant	
50			parties (eg, investigators, REC/IRBs, trial	
51			participants, trial registries, journals,	
52			regulators)	
53 54				
54 55	Consent or	26a	Who will obtain informed consent or assent	Page 12 Ethics paragraph 2
55 56				
50 57	assent		from potential trial participants or authorised	
57			surrogates, and how (see Item 32)	
58 59				
59 60				
00				

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentialit y	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 11, Data collection and management, paragraph 3
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14, Competing interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11, Availability of data and materials
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Disseminatio n policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 11, Availability of data and materials
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 11, Availability of data and materials
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Added to supplementary materials of submission
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the

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2	protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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#### The PEP4LEP study protocol: Integrated skin screening and SDR-PEP administration for leprosy prevention. Comparing the effectiveness and feasibility of a community-based intervention to a health center-based intervention in Ethiopia, Mozambique and Tanzania

Journal:	BMJ Open
Manuscript ID	bmjopen-2020-046125.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Jun-2021
Complete List of Authors:	Schoenmakers, Anne; NLR Hambridge, Thomas; Erasmus Medical Center van Wijk, Robin; NLR Kasang, Christa; DAHW Richardus, Jan Hendrik; Erasmus Medical Center, Department of Public Health Bobosha, Kidist; Armauer Hansen Research Institute Mitano, Fernando; Lurio University Mshana, Stephen E.; Catholic University of Health and Allied Sciences, Department of Microbiology and Immunology Mamo, Ephrem; Armauer Hansen Research Institute Marega, Abdoulaye; Lurio University Mwageni, Nelly; Catholic University of Health and Allied Sciences, Department of Microbiology and Immunology Letta, Taye; Ethiopia Ministry of Health Muloliwa, Artur; Ministry of Health, Mozambique Kamara, Vedastus; Ministry of Health, Tanzania Eman, Ahmed; DAHW, Ethiopia Raimundo, Litos; NLR, Mozambique Njako, Blasdus; DAHW, Tanzania Mieras, Liesbeth; NLR
<b>Primary Subject Heading</b> :	Infectious diseases
Secondary Subject Heading:	Public health, Dermatology
Keywords:	Public health < INFECTIOUS DISEASES, Infectious diseases & infestations < DERMATOLOGY, Tropical medicine < INFECTIOUS DISEASES

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1 2		
3	1	The PEP4LEP study protocol: Integrated skin screening and SDR-PEP
4 5	2	administration for leprosy prevention. Comparing the effectiveness and
6 7	3	feasibility of a community-based intervention to a health center-based
8 9	4	intervention in Ethiopia, Mozambique and Tanzania
10 11	5	
12 13	6	A. Schoenmakers <sup>1*</sup> , T. Hambridge <sup>2*</sup> , R. van Wijk <sup>1</sup> , C. Kasang <sup>3</sup> , J.H. Richardus <sup>2</sup> , K. Bobosha <sup>4</sup> , F.
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21 22	12	Tanzania, <sup>7</sup> Ministry of Health, Ethiopia; <sup>8</sup> Ministry of Health, Mozambique; <sup>9</sup> Ministry of Health,
23	13	Tanzania; <sup>10</sup> GLRA, Ethiopia; <sup>11</sup> NLR, Mozambique, <sup>12</sup> GLRA, Tanzania
24 25	14	
26 27	15	*Both authors contributed equally to this article.
27 28	16	Correspondence: t.hambridge@erasmusmc.nl
29 30	17	
31	18	Abstract
32 33		
34	19	Introduction
35 36	20	Leprosy, or Hansen's disease, remains a cause of preventable disability. Early detection,
37	21	treatment and prevention are key to reducing transmission. Post-exposure prophylaxis with
38 39	22	single-dose rifampicin (SDR-PEP) reduces the risk of developing leprosy when administered to
40	23	screened contacts of patients. This has been adopted in the World Health Organization (WHO)
41 42	24	leprosy guidelines. The PEP4LEP study aims to determine the most effective and feasible
43 44	25	method of screening people at risk of developing leprosy and administering chemoprophylaxis to
44 45	26	contribute to interrupting transmission.
46 47	27	
48	28	Methods and analysis
49 50	29	PEP4LEP is a cluster-randomized implementation trial comparing two interventions of integrated
51	30	skin screening combined with SDR-PEP distribution to contacts of leprosy patients in Ethiopia,
52 53	31	Mozambique, and Tanzania. One intervention is community-based, using skin camps to screen
54	32	approximately 100 community contacts per leprosy patient and to administer SDR-PEP when
55 56	33	eligible. The other intervention is health center-based, inviting household contacts of leprosy
57 58	34	patients to be screened in a local health center and subsequently receive SDR-PEP when
58 59	35	eligible. The mobile health (mHealth) tool SkinApp will support health workers' capacity in
60	36	integrated skin screening. The effectiveness of both interventions will be compared by assessing

the rate of leprosy patients detected and case detection delay in months, as well as feasibility in terms of cost-effectiveness and acceptability. Ethics and dissemination Ethical approval was obtained from the national ethical committees of Ethiopia (MoSHE), Mozambigue (CNBS) and Tanzania (NIMR/ MoHCDEC). Study results will be published open access in peer-reviewed journals, providing evidence for the implementation of innovative leprosy screening methods and chemoprophylaxis to policymakers. **Trial registration:** The PEP4LEP project is registered at the Netherlands Trial Register (NTR), receiving trial registration number NL7294 (NTR7503), registration date September 10, 2018. Keywords: leprosy, Hansen's disease, NTD, chemoprophylaxis, prevention, skin screening, case detection, single dose rifampicin, SDR-PEP, post-exposure prophylaxis, detection delay, skin camps, Ethiopia, Mozambique, Tanzania, Africa, feasibility, acceptability, cost-effectiveness, mHealth, eHealth ez.e Article Summary Strengths and Limitations • In both interventions, a combination of screening contacts and providing SDR-PEP will be used according to the World Health Organization's guidelines to reduce the contacts' risk of developing leprosy • An integrated skin screening approach will be used in which multiple diseases can be detected and treated at once, overcoming the often negative associations with leprosy The SkinApp will be used as a mHealth tool to support peripheral health workers in recognizing and treating signs and symptoms of skin diseases; while innovative and potentially increasing capacity, the accuracy and reproducibility of this tool awaits further investigation Since the epidemiological impact on new case detection rate will not become apparent within the study duration, the primary outcome measures are case detection delay, number of contacts diagnosed with leprosy and number of contacts who received chemoprophylaxis 

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 Because difficulties in recalling the first signs and symptoms are expected to increase over a longer duration of the disease, only recently diagnosed index patients will be included in this study to establish case detection delay

#### 76 Introduction

Leprosy, or Hansen's disease, is a communicable disease caused by Mycobacterium leprae that is still a public health problem in many countries. It is formally recognized by the World Health Organization (WHO) as a neglected tropical disease (NTD).<sup>1</sup> The annual reported number of newly detected leprosy patients was 202,185 in 2019.<sup>2</sup> If left untreated, leprosy potentially results in disability, which can have severe consequences such as stigma and poverty.<sup>3</sup> Leprosy has a long and variable incubation time, ranging from 2 to 20 years, during which it is assumed that transmission can take place.<sup>4</sup> The risk of developing leprosy is higher in household contacts and neighbors of patients than it is in the general community.<sup>5</sup> Moet et al. demonstrated that physical and genetic distance were independently associated with the risk of a contact developing leprosy.<sup>6</sup> According to the WHO, contract tracing should be offered to a person who has been in contact with an untreated leprosy index case for at least 20 hours per week during at least 3 months in the previous year.<sup>4,7,8</sup> An index case is defined as a person diagnosed with leprosy for the first time.7 

The WHO has provided multidrug therapy (MDT) free of charge to all leprosy patients since 1995.<sup>9</sup> However, to overcome ongoing transmission in high-endemic areas, innovative measures are needed.<sup>8,10</sup> In 2008, a large randomized controlled trial in Bangladesh (Chemoprophylaxis of Leprosy study, COLEP) demonstrated that a single dose of rifampicin (SDR) given to contacts of newly diagnosed leprosy patients is effective in reducing the risk of leprosy by 57% (95% CI: 24–75%).<sup>11</sup> SDR-PEP was found to be cost-effective in Bangladesh.<sup>12</sup> In the Leprosy Post-Exposure Prophylaxis (LPEP) program, SDR-PEP was implemented in areas representing various health systems across three continents and eight countries, to evaluate the feasibility, effectiveness and impact.<sup>13</sup> The implementation of SDR-PEP within the routine leprosy control programs was proven to be safe and generally well accepted. Based on the LPEP program and a microsimulation leprosy model (SIMCOLEP), SDR-PEP was also found to be cost-effective in India.<sup>14</sup> The concern that SDR-PEP could lead to increased rifampicin resistance in other diseases, such as tuberculosis (TB), was considered in an expert consultation that concluded that SDR-PEP given to contacts of leprosy patients, in the absence of symptoms of active TB, poses a negligible risk of generating resistance in *Mycobacterium tuberculosis* in individuals and in populations.<sup>15</sup> In 2018, SDR-PEP was included in the WHO "Guidelines for the Diagnosis, 

107 Treatment and Prevention of Leprosy". Once contact tracing has been established, SDR-PEP
108 can be included into the routines of leprosy control programmes with minimal additional efforts
109 and costs.<sup>7,16</sup>

Skin screening is an important detection strategy for skin-NTDs such as leprosy, and is recommended to be embedded in leprosy programmes.<sup>1,7,17,18</sup> Screening for multiple skin diseases at once (integrated or common skin screening) is promoted by WHO.<sup>1,8,19,20</sup> Integration is considered to increase effectiveness and efficiency by minimizing costs and expanding intervention coverage.<sup>19,21</sup> An important obstacle for integrated skin screening is the scarcity of dermatologists in many areas with a high skin NTD endemicity.<sup>22</sup> In sub-Saharan Africa, the situation is critical, with approximately 1 dermatologist per 500,000-1 million inhabitants and even larger shortages in Mozambigue and Tanzania according to field reports from PEP4LEP consortium members.<sup>23,24</sup> According to the WHO, community health workers (CHWs) and village volunteers can play a role in screening for skin diseases, but improved knowledge, capacity, and motivation of health workers and community volunteers is essential.<sup>17,19,25–29</sup> As both integrated skin screening for NTDs and SDR-PEP against leprosy are promoted by the WHO, additional implementation studies are necessary to establish whether a combined intervention is acceptable, feasible, and cost-effective in leprosy endemic areas.<sup>1,4,8,19</sup> 

#### 127 Objectives

The PEP4LEP project is a collaboration among study consortium members in five countries in sub-Saharan Africa and the European Union (EU) (Figure 1). The overall aim of this cluster-randomized implementation trial is to contribute to the interruption of *M. leprae* transmission by identifying the most effective and feasible method of screening people at risk of developing leprosy and by administering post-exposure chemoprophylaxis in Ethiopia, Mozambigue, and Tanzania. The primary study objectives are to compare the effectiveness and feasibility of a community-based screening and prophylaxis (skin camp) intervention with a health center-based screening and prophylaxis intervention solely for household contacts of a leprosy patient. The case detection delay will be the primary outcome measure to assess effectiveness. Additional objectives are to assess the cost-effectiveness, acceptability and health workers' capacity regarding the integrated skin diseases approach and the use of the supportive mobile health (mHealth) tool SkinApp.<sup>30,31</sup> 

# Figure 1. PEP4LEP Project organization chart Figure 1. PEP4LEP Project organization chart

1 ว		
2 3 4	143	
- 5 6	144	
7 8 9	145	Methods and analysis
10	146	Study setting
11 12	147	This study will take place in three countries in sub-Saharan Africa: Ethiopia, Mozambique, and
13 14	148	Tanzania. The three countries differ socioculturally and in the endemicity for NTDs like leprosy
15	149	(Figure 2). <sup>2</sup> Districts within these countries were purposefully chosen because of endemicity and
16 17	150	the focal distribution of reported leprosy cases. In Ethiopia, three endemic districts are located in
18	151	East Hararghe Zone (Oromiya region): Girawa, Jarso, and Midega. In Mozambique, the included
19 20	152	districts are located in Nampula province: Meconta, Mogovolas, and Murrupula. The Tanzanian
21 22	153	districts are Lindi in Lindi Region and Morogoro and Mvomero in Morogoro Region. The original
23	154	overall study period was October 2018 until January 2023, with an estimated duration of 2.5–3
24 25	155	years for the inclusion of leprosy patients and their contacts. A study extension is expected due to
26 27	156	the impact of COVID-19.
27 28	157	
29 30	158	
31	159	Figure 2. PEP4LEP countries' leprosy incidence in 2019 according to the World Health
32 33 34	160	Organization (2020) <sup>2</sup>
35	161	
36 37	162	
38 39	163	Participants and eligibility criteria
40	164	Leprosy patients enrolled in the PEP4LEP study are referred to as "index patients". These
41 42	165	patients derived from the leprosy programme registries, and preferably diagnosed up to 6 months
43 44	166	prior to inclusion to prevent recall problems when assessing the delay in case detection. <sup>32</sup> The
44 45	167	inclusion and exclusion criteria for index patients and contacts are summarized in Table 1 and
46 47	168	are based on the WHO guidelines and the LPEP program. <sup>4,13</sup> Following the emergence of the
48 49 50 51 52	169	Coronavirus Disease 2019 (COVID-19) pandemic, a suspicion of a COVID-19 infection was
	170	added as contact exclusion criteria for this study, as physical distancing cannot be guarded when
	171	performing skin screening. <sup>33–36</sup> Index patients with suspected COVID-19 can still be included after
53	172	they have been tested negative and are symptom-free for at least 2 weeks. <sup>33–35</sup>
54 55	173	
56	174	The target population for the feasibility component of this study as well as the other research
57 58	175	objectives, consists of various stakeholders, including: (index) patients, household contacts,
59 60	176	community contacts, community leaders, health workers, community health volunteers and health
00	177	policy decision makers. If applicable, contacts refusing to take SDR-PEP but who are willing to

4 5 6 18 7 8 18 9 18 10 11 18 12 13 14 18 15	<ul> <li>the acceptat</li> <li>The exclusion</li> <li>participate.</li> </ul>	h the qualitative study component will also be in bility component of the study. On criterium for these stakeholders is refusal to P eligibility criteria patients and contacts <sup>4,7,13</sup>	
18 19		Index patients	Contacts
	Inclusion criteria	<ul> <li>Consent to participate in the PEP4LEP project</li> <li>Diagnosed with leprosy (preferred maximum of 6 months prior to inclusion)<sup>32</sup></li> <li>Residence in the PEP4LEP districts for ≥3 months prior to the date of diagnosis</li> <li>Index patient has started MDT</li> <li>Community-based skin camp intervention: Leprosy patient gives permission for the set-up of a skin camp in his/her community (sharing their leprosy diagnosis with their contacts is not needed)</li> <li>Health center-based household screening intervention: Leprosy patient with household contacts, and who is willing to inform these contacts about PEP4LEP</li> </ul>	<ul> <li>Consent to participate in the PEP4LEP project</li> <li><u>Community-based skin camp</u> intervention: Community contact (living in the 20 closest houses to the index-patient) for ≥3 months</li> <li><u>Health center-based household</u> <u>screening intervention</u>: Contact which is a household member of the index patient for ≥3 months, visiting the screening health center ≤3 months after the index patient was included</li> </ul>

criteria       unable to understand the purpose and         risks of participating in the PEP4LEP       unable to understand the purpose and         study       Age <2 years and/or <10 kg of         weight*       Pregnancy*         Receiving or having received       rifampicin for any reason in the         years       Known allergy to rifampicin         History of liver or renal disorde       Individuals with leprosy and the         who have possible signs and/o       symptoms of leprosy (e.g., lepr         like skin lesions or nerve       manifestations) until their diseas         status has been clarified <sup>37***</sup> Individuals with possible signs         symptoms of TB (cough for mo       two weeks or cough in known         HIV/AIDS patients, night sweat       unexplained fever, weight loss)         their disease status has been       clarified <sup>37***</sup>			
<ul> <li>who have possible signs and/o symptoms of leprosy (e.g., lepr like skin lesions or nerve manifestations) until their disea status has been clarified<sup>37**</sup></li> <li>Individuals with possible signs symptoms of TB (cough for mo two weeks or cough in known HIV/AIDS patients, night sweat unexplained fever, weight loss) their disease status has been clarified<sup>37***</sup></li> <li>Individuals with possible signs</li> </ul>	Exclusion criteria	risks of participating in the PEP4LEP	<ul> <li>PEP4LEP study</li> <li>Age &lt;2 years and/or &lt;10 kg of weight*</li> <li>Pregnancy*</li> <li>Receiving or having received rifampicin for any reason in the last 2 years</li> <li>Known allergy to rifampicin</li> <li>History of liver or renal disorders</li> </ul>
Individuals with possible signs			<ul> <li>who have possible signs and/or symptoms of leprosy (e.g., leprosy- like skin lesions or nerve manifestations) until their disease status has been clarified<sup>37**</sup></li> <li>Individuals with possible signs and/o symptoms of TB (cough for more that two weeks or cough in known HIV/AIDS patients, night sweats, unexplained fever, weight loss) until their disease status has been</li> </ul>
sudden loss of smell/taste) or possible contact with a COVID-			<ul> <li>Individuals with possible signs and/o symptoms of COVID-19 (self- assessed temperature ≥38°C, respiratory or cold-like symptoms,</li> </ul>

***	Skin screening and SDR-PEP can only be provided in a PEP4LEP affiliated health center after the
cor	tact is tested negative for COVID-19/TB (according to national guidelines).33-36
Ab	breviations: COVID-19: Coronavirus Disease 2019; MDT: multidrug therapy; SDR-PEP: single-dos
rifa	mpicin post-exposure prophylaxis; TB: tuberculosis
186	
187	Study design
188	The study is a two-arm, cluster-randomized implementation trial (Figure 3). One intervention is
189	community-based, using skin camps to screen approximately 100 community contacts
190	(household members and neighbors) of a leprosy index patient and to provide them with SDR-
191	PEP when eligible. The second intervention is health center-based, inviting the household
192	contacts of an index patient to be screened and given SDR-PEP when eligible.
193	
194	Community-based skin camp intervention
195	A skin camp will be organized when a leprosy patient is diagnosed by inviting approximately 100
196	people from the same community (Table 1) living in the surrounding area (field definition:
197	inhabitants from the 20 closest houses). Community contacts from outside of the 20 closest
198	households who attend a skin camp can still receive skin screening or referral, but will not be
199	given SDR-PEP. Health camps are designed to bring specialized care closer to the community,
200	thus expanding access. <sup>38</sup> Besides preventive and curative treatment, these camps often also pla
201	a significant role to create awareness. <sup>39</sup> Community "skin health camps" have been proposed as
202	an effective way to screen for leprosy and other NTDs. <sup>7,40</sup> Skin camps are organized at the
203	community level and in close collaboration with community leaders and local organizations. <sup>38,41</sup> Ir
204	a skin camp, health staff screen individuals for skin diseases and then treat or refer patients if
205	necessary. Assistance from a dermatologist (or, if none available, a senior health staff member
206	with sufficient dermatology experience) is vital. <sup>42</sup> A key advantage of this community intervention
207	is that the identity of the person affected by leprosy can be protected since no individual disease
208	disclosure is needed. This non-disclosure approach is of utmost importance, as people affected
209	by leprosy are often stigmatized and discriminated against and are therefore reluctant to share
210	their disease status.43-45 Moreover, including a wider group of contacts and using an integrated
211	skin diseases approach may overcome the frequently negative associations with leprosy that car
212	prevent people from participating in a leprosy-related intervention. <sup>19</sup> Including approximately 100
213	contacts per identified leprosy patient in the PEP4LEP skin camps is in-line with the risk profiles
214	of the contact groups and is operationally manageable conduct within 1-2 days, also when using
215	time slots to prevent crowding taking COVID-19 into consideration. <sup>6,13,34,36,39,40,46–48</sup>
216	
217	Health center-based intervention for household contacts
218	In the second intervention, newly detected leprosy patients will be asked to invite their household
	8

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contacts to visit a health center to have their skin screened and, if eligible, to be offered SDR-PEP. Clustering of the disease within households is commonly seen.<sup>6,48,49</sup> Household contacts are defined as living under the same roof as the leprosy index patient for a minimum of 3 months (Table 1).<sup>13,50,51</sup> To prevent re-infection within a household and for operational management reasons, contacts need to visit the health center within 3 months after the index patient was included, which is also in-line with contact tracing interventions in literature.<sup>52</sup> Around 6 household contacts per patient are expected to visit the health center for screening.<sup>13</sup> Previous studies showed that leprosy patients are usually willing to disclose their leprosy diagnosis to their household members to facilitate screening and prophylaxis, but they are often reluctant to share this information with neighbors or other social contacts.43-45 

Figure 3. Flow of participants through the PEP4LEP study 

#### Integrated skin screening

For contact screening in both interventions, an integrated skin diseases approach - also called common skin screening approach - will be used to diagnose common skin diseases (e.g., eczema), skin conditions related to HIV/AIDS (e.g., Kaposi's sarcoma), and skin-NTDs (e.g., leprosy). "Integration" in this context refers to combined screening for a minimum of two diseases at the same time in the same communities.<sup>53</sup> In the PEP4LEP project, free topical treatment for the most frequently diagnosed skin diseases will be provided as well as referral advice, in-line with WHO and national medical guidelines.<sup>54–58</sup> The screening for signs and symptoms of skin diseases, as well as the chemoprophylaxis distribution, will follow standard operating procedures (SOPs) in which the eligibility criteria for SDR-PEP are clearly stated. In both interventions, the integrated skin diseases approach will be used and supported by the SkinApp, a mHealth tool developed by NLR and Erasmus University Medical Center (Erasmus MC).<sup>30,31</sup> The SkinApp will support peripheral health workers in recognizing and treating signs and symptoms of skin diseases, including skin-NTDs like leprosy.<sup>30,31</sup> A senior health staff member with sufficient dermatology experience (preferably a dermatologist) will attend in person or via secure medical messaging via the application (app) Siilo.59 

#### Post-exposure prophylaxis

Chemoprophylaxis with SDR-PEP has been adopted in the 2018 WHO "Guidelines for the diagnosis, treatment and prevention of leprosy".<sup>4</sup> The SDR-PEP dosages used in this project (Table 2) are consistent with these WHO guidelines, the in 2020 published WHO document 

1 2 3 4 5 6 7 8 9 10	254 255 256 257	5 and the LPEP program. <sup>4,7,13</sup>				
11 12						
13 14		Age and body weight of contact	Rifampicin dosage			
15 16		≥15 years	600 mg			
17		10-14 years	450 mg			
18 19		6-9 years and body weight of ≥20 kg	300 mg			
20		≥2 years old and body weight between 10-20 kg	150 mg			
21 22	258					
23 24	259	Contacts who are temporarily ineligible to receive SDI	R-PEP (e.g., because of p	oregnancy, Table		
25	260	1) will receive skin screening and a SDR-PEP voucher, useable in an affiliated PEP4LEP health				
26 27	261	center when becoming eligible (e.g., after giving birth). Contacts receiving SDR-PEP will also				
28	262	receive a SDR-PEP Red Card to keep in their homes. This card indicates that the person has				
29 30	263	received SDR-PEP for leprosy prevention and is ineligible to receive this again within the next				
31 32	264	two years. These methods were previously used as p	art of the LPEP program i	n Tanzania. <sup>13</sup> In		
33	265	PEP4LEP, serious adverse events (SAEs) will be rep	orted and followed up acc	ording to national		
34 35	266	and PEP4LEP guidelines (see ethical section). <sup>60</sup>				
36	267					
37 38 39 40	268	Outcomes				
	269	The primary objectives of this study are to identify the	most effective and feasib	le approach for		
41	270	screening contacts of leprosy patients in combination with administering chemoprophylaxis to				
42 43	271	prevent leprosy (Table 3). Because of the long incubation period of leprosy, it will not be possible				
44	272	to observe reduced transmission at the population level, in terms of a reduced new case				
45 46	273	detection rate, during this project period. The active case finding component and raised				
47 48	274	awareness, however, are expected to lead to more detected cases, improved early case				
49	275	detection and reduced child cases and disability rates at the time of diagnosis. We hypothesize				
50 51	276	that enhanced case finding and integrated skin screening will lead to an overall reduction of				
52	277	detection delay in the community-based intervention over the study duration, driven by diagnosis				
53 54	278	of patients with early signs of leprosy (and shorter delays) that would otherwise go undetected.				
55	279					
56 57	280	Primary outcome measures				
58 59	281	The primary outcome measures of effectiveness in the	e comparison of the two ir	nterventions are:		
60						
	10					

Page 13 of 41

BMJ Open

1		
2 3	282	1) Case detection delay, measured in months since the first signs or symptoms of leprosy until
4 5	283	diagnosis and in the number of patients with G2D.
6	284	2) Number of new patients with leprosy, subdivided into child proportion, female proportion, and
7 8	285	multibacillary (MB) / paucibacillary (PB) classification.
9	286	3) Number of contacts screened and receiving SDR-PEP.
10 11	287	
12 13	288	Secondary outcome measures
14	289	Feasibility will be assessed by looking at outcome measures related to cost-effectiveness and
15 16	290	acceptability (Table 3):
17	291	<ul> <li>A cost-effectiveness analysis will be undertaken in the third year of the project,</li> </ul>
18 19	292	encompassing the costs incurred by the health system and the beneficiaries (out-of-
20 21	293	pocket expenditure). It will include collecting indicators such as unit costs, costs per case
22	294	detected, costs per disability-adjusted life years (DALY) averted and costs per extra case
23 24	295	found. The current practice "routine service provision" will be compared with the two study
25	296	interventions.
26 27	297	The acceptability of both interventions will be determined by comparing the number of
28 29	298	index patients and contacts included, as well as by using qualitative research methods,
30	299	such as semi-structured interviews guided by topic lists, focus group discussions (FGDs)
31 32	300	with relevant stakeholders and potentially ethnographic observations during the
33	301	interventions for further data validation. More in-depth (country-specific) protocol
34 35	302	descriptions on the acceptability and cost-effectiveness side-studies will be developed
36 37	303	together with a health economist and social scientist.
38	304	
39 40	305	Additional objectives
41	306	The additional objectives are to assess the acceptability of integrated skin screening and the use
42 43	307	of the SkinApp as a supporting mHealth tool in the field, as well as health workers' capacity
44 45	308	regarding the integrated skin screening approach (Table 3). This will be measured by the number
46	309	of contacts diagnosed with skin diseases and NTDs and by recording the use of the SkinApp
47 48	310	during contact screening. The capacity of health workers to diagnose leprosy and other skin
49	311	diseases will be determined by a series of 4 assessments in which the SkinApp can be used:
50 51	312	before (baseline) and after PEP4LEP training, during the study, at the end of the study.
52 53	313	
54	314	The 4 assessments were designed in collaboration with an educational specialist and each
55 56	315	include 30 questions (20 multiple choice questions on leprosy and 10 skin disease cases of which
57	316	5 formulated as open questions). The primary PEP4LEP health worker training is conducted over
58 59	317	several days and consists of interactive training modules focusing on: the PEP4LEP research
60	318	project, integrated skin screening including the use of mHealth tools (NLR's SkinApp and Siilo),

Page 14 of 41

clinical leprosy and the administration of SDR-PEP.<sup>4,27,28,30,59,61,62</sup> Refresher trainings will also be organized. The capacity of health workers to diagnose leprosy and other skin diseases will be determined by the series of assessments in which the SkinApp can be used. Additionally, qualitative methods including semi-structured interviews, FGDs, and potentially ethnographic field observations will be used to gain a more in-depth understanding of these objectives. Case detection delay Case detection delay is defined by Muthuvel et al. as the number of months between the onset of signs and symptoms of leprosy and the time of diagnosis, including both "patient delay" (period in months between noticing the first sign/symptom to the first health care provider consultation) and "health-system delay" (period in months between the first health care provider consultation and the patient receiving the leprosy diagnosis).<sup>63</sup> Several studies have investigated delay in leprosy diagnosis in countries like Bangladesh, Brazil, India, Colombia, and Paraguay.<sup>63–70</sup> However, recent literature on delay in diagnosis is limited and mainly focuses on other geographical regions. Therefore, for this project, delay will be determined with a structured questionnaire designed in the project countries, with input from several stakeholders, which will be shared open access (publication expected). The questionnaire includes two annexes: a set of clinical photos of signs of leprosy and a context-specific calendar indicating important local dates, such as festivities, agricultural seasons and religious celebrations.<sup>71,72</sup> A "Question-by-Question Guide" 

was designed to provide support in the administration of the guestionnaire. The guestionnaires were culturally validated in all three countries, based on the conceptual framework of Herdman et al. (publication expected).<sup>73</sup>

#### Table 3. PEP4LEP project outcomes and statistical methods

42 43	Objective	Outcome	Hypothesis	Outcome	Method of
44				measure	analysis
45 46	1.1 To compare the	Primary:	Reduction in case	Number of	Descriptive
47 48	effectiveness of a	Case detection	detection delay is	months since first	statistics;
48 49	skin camp	delay	expected to be	signs or	multivariate
50 51	prophylaxis		greater in the	symptoms of	models; non-
52	intervention with a		community-based	leprosy until	parametric tests
53 54	health center-based		intervention	diagnosis	
55	prophylaxis		compared with the	(including	
56 57	intervention in terms		health center-	assessing both	
58 59	of the rate of leprosy		based household	"patient delay"	
60	patients detected		contact approach	and "health-	

1 2					
3	and delay in case			system delay");	
4 5	detection			G2D percentage	
6				among newly	
7 8				diagnosed	
9				leprosy patients	
10 11		Primary:	The community-	Number of	Descriptive
12		Number of	based intervention	contacts	statistics;
13 14		contacts	will identify more	diagnosed with	Pearson's chi
15 16		diagnosed with	cases of leprosy	leprosy; child	square test;
17		leprosy	from contact	proportion;	Fisher's exact
18 19		lopicoy	screening	female	test; multivariate
20		0	compared with the	proportion;	logistic regression
21 22			health center	MB/PB	analysis
23			household contact-	classification of	anarysis
24 25			based approach	newly diagnosed	
26 27					
27		Drimon <i>u</i>		leprosy patients Number of	Descriptive
29 30		Primary:	The community-		Descriptive
31		Number of	based intervention	contacts	statistics
32 33		contacts who	will allow more	screened;	
34		received	contacts to be	number of	
35 36		chemoprophylax	screened and	contacts who	
37		is	receive SDR-PEP	received SDR-	
38 39			compared with the	PEP	
40			health center-		
41 42			based household		
43 44			contact approach		
45	1.2 To compare the	Secondary:	The community-	Number of index	Health economic
46 47	feasibility of the two	Cost-	based intervention	patients included;	evaluations
48	chemoprophylaxis	effectiveness of	will be more	number of	
49 50	interventions	each	expensive but will	contacts	
51	(screening	intervention	have a greater	screened;	
52 53	household contacts		impact compared	number of cases	
54 55	or screening		with the health	prevented;	
56	contacts via skin		center-based	number of	
57 58	camps) in terms of		household contact	disabilities	
59	cost- effectiveness		approach	avoided;	
60	and acceptability			operational costs;	
			12		

			out-of-pocket expenses	
	Secondary: Acceptability of each intervention	Both interventions will be accepted in participating countries	Number of index patients included; number of contacts screened; and qualitative methods	Descriptive statistics; qualitative content analysis of interviews; FGDs and potentially observations
2.1 To assess the acceptability of an integrated skin diseases approach and the use of the SkinApp	Additional: Number of contacts diagnosed with other skin diseases	The community- based intervention will identify more cases of other skin diseases from contact screening compared with the health center- based household contact approach	Number of contacts diagnosed with skin diseases including and with NTDs that manifest with skin lesions	Descriptive statistics; Pearson's chi square test; Fisher's exact test; multivariate logistic regressio analysis
	Additional: Acceptability of an integrated skin screening approach and the use of the SkinApp	The integrated skin screening approach will encourage screening participation, and the SkinApp will help health workers to diagnose skin diseases	Number of contacts diagnosed with skin diseases and with NTDs that manifest with skin lesions; utilization of the SkinApp during contact screening; and qualitative methods	Descriptive statistics; sensitivity and specificity; positive and negative predictive values qualitative content analysis of interviews, FGDs, and potentially observations
2.2 To compare the capacity of health workers in diagnosing leprosy,	Additional: Capacity of health workers in diagnosing	Participation in training and the use of the SkinApp	Results of health worker capacity assessments and	Descriptive statistics; qualitative content analysis

1										
2 3		other skin diseases	leprosy and	will improve health	qualitative	of interviews,				
4 5		and other NTDs that	other skin	worker capacity	methods	FGDs, and				
6		manifest with skin	diseases			potentially				
7 8		lesions before the				observations				
9 10		start of the study								
10 11		with their capacity in								
12 13		the third year								
14		Abbreviations: FGD: f	ocus group discuss	sion; G2D: grade-2 dis	ability; MB: multibac	illary; NTD:				
15 16		neglected tropical dise	ease; PB: paucibac	illary; SDR-PEP: sing	le-dose rifampicin					
17 18	343	•								
19	344	Sample size								
20 21	345	The sample size ca	alculation was base	ed on case detection d	lelay as the main out	come measure				
22 23	346	for comparing the e	effectiveness of eac	ch intervention. This m	neasure was used fo	r the calculation				
24	347	because the epider	miological impact (i	i.e. reduction in overal	I new case detection	rate in PEP4LEP				
25 26	348	districts) will not become apparent within the study duration due to the long incubation time								
27	349	leprosy. The mean	or median delay w	ill be compared betwe	en both intervention	s and with the				
28 29	350	baseline. A baselin	baseline. A baseline case detection delay will be estimated in each country by interviewing							
30 31	351	recently diagnosed	recently diagnosed leprosy patients with the same structured questionnaire prior to the start of							
32	352	the study. For the s	the study. For the sample size calculation, a literature-based estimated average case detection							
33 34	353	delay of 24 months	delay of 24 months for leprosy patients with a standard deviation of 8 months was used, with the							
35 36	354	conservative assur	conservative assumption that a minimal delay difference of 3 months would be detected between							
37	355	both interventions.	both interventions. <sup>74,75</sup> In order to achieve this, we aim to include at least 675 index patients in the							
38 39	356	study: 270 in the co	ommunity-based in	tervention areas (30 p	er country per year)	and 405 new				
40	357	patients in the heal	th center-based int	ervention areas (45 p	er country per year).	Approximately				
41 42	358	100 contacts will be	e screened per ind	ex patient in the comn	nunity-based interver	ntion areas, and				
43 44	359	approximately 6 co	ntacts will be scree	ened per index patient	in the health center-	based				
45	360	intervention areas;	thus, a total of app	proximately 30,000 cor	ntacts will be screene	ed (Figure 3). We				
46 47	361	expect no major dif	ferences in case d	etection delay betwee	n clusters and within	clusters, thus no				
48	362	significant design e	effect is foreseen. F	or the feasibility study	component and add	ditional research				
49 50	363	objectives, interview	ws and FGDs are p	planned. For the interv	riews, a minimum of	10 index patients,				
51 52	364	10 household conta	acts, 10-20 commu	nity contacts, 10 heal	th workers / commur	ity volunteers, 4				
53	365	health decision ma	kers and 10 comm	unity leaders will be in	cluded. For the FGE	0s, 6-10				
54 55	366	participants will be	included: 2 groups	of index patients, 2 g	roups of household o	contacts, 2				
56	367	groups of commun	ity contacts, 2 grou	ps with health workers	s and 1-2 groups wit	h decision				
57 58	368		U U	R-PEP but who are w	0 1 1	•				
59 60	369	· ·	2	mbers outside of the 2		·				
00	370	in intervention 1 wi	Il also be included.	The qualitative resear	rch sampling will be	purposive,				
				15						

371 according to the defined target groups, and balanced according to e.g. gender, age, education
 372 level, religion and/or socio-cultural background. All fully trained health staff involved in the
 373 PEP4LEP project will be asked to consent to enroll in the capacity assessment.

# 9 375 <u>Randomization</u>

PEP4LEP used randomization without blinding at the (clustered) health center level (health centers/posts), ensuring that clusters were similar in size. There are 17 health facilities included in Ethiopia, 22 in Mozambique and 23 in Tanzania. Blinding is not possible because of the varying operational components of the interventions. Cluster randomization is commonly used when trying to capture the impact of an intervention at community level on both infectiousness and susceptibility.<sup>76</sup> This method is stated to be feasible logistically, and contamination (e.g., information-sharing between participants from both interventions) is unlikely.<sup>76</sup> Randomization was performed using the statistical software package R.<sup>77</sup> Per country, health centers were randomly divided into the community-based intervention or health center-based intervention. 

### 27 386 Data collection and management

The PEP4LEP data management plan was developed by Erasmus MC in collaboration with the consortium. Regarding quantitative data, collectors will record their findings onto paper-based forms. Information from the forms will be entered into the Research Electronic Data Capture (REDCap) system from Vanderbilt University.<sup>78</sup> The REDCap software will be linked to a centralized database server hosted by Erasmus MC. 

To determine the cost-effectiveness, data for establishing costs (such as infrastructure, human resources, transportation) and output (such as number of contacts seen, rifampicin capsules provided, patients diagnosed with other NTD related skin diseases and treatments provided) will be derived from the ongoing surveillance data. Other costs (such as general programme costs, treatment costs and other direct or indirect costs) will be collected from ancillary studies. 

Besides quantitative data, qualitative data will also be collected for the acceptability and health workers' capacity assessment. Data from (semi-)structured interviews, FGDs, and possible ethnographic observations will be audio-recorded and/or paper-based. Data will be transcribed (verbatim), translated to English and entered into computer-assisted qualitative data analysis software.<sup>79</sup> The transcriptions will be securely stored at Erasmus MC after analysis. A system of identification (ID) codes has been developed to record and maintain data systematically, as well as to maintain "pseudo-anonymity." 

59 406

407 Data analysis

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Data from the PEP4LEP study will be analyzed primarily through quantitative methods using descriptive analysis for all variables (Table 3). Mean and median case detection delays will be compared between both interventions and the established baseline. This includes newly diagnosed cases identified through each contact screening intervention as well as those detected through ongoing passive case finding, currently the primary method of detection in routine leprosy programs in the three countries. The p-values for each statistical test will be two-tailed with  $p \le p$ 0.05 considered significant and 95% confidence intervals (CI) presented for regression analyses. Quantitative analysis will be conducted using statistical software such as SPSS.<sup>80</sup> The acceptability and capacity assessments will include qualitative research data (Table 3),

which will be coded and analyzed using computer-assisted qualitative research data (rable 3), including Atlas.ti.<sup>79,81</sup> Data coding is necessary to categorize and define what the data signify by identifying concepts, patterns, relations, and themes.<sup>82</sup> Data reanalysis will occur until no new topics are emerging and data saturation is reached, which means that no significant new themes are emerging.<sup>83</sup>

### 424 <u>Availability of data and materials</u>

Data will be stored for 25 years according to EU regulation 536/2014 considering clinical
 medication-related research projects.<sup>67</sup> Data will be made available in a repository for potential
 authorized re-use for future data analysis or study replication. Sharing data and study materials
 as well as open access publishing are important values of the EU research and innovation
 program Horizon 2020, the European and Developing Countries Clinical Trials Partnership
 (EDCTP) and the PEP4LEP consortium.<sup>67,84</sup>

### 432 Patient and public involvement

Community leaders, people affected by leprosy, and representatives of disabled people organizations (DPO) are and will be involved in monitoring the study as well as in mobilizing community participation. Results will be reported back to the communities via community workshops. Capacity building is an important part of this project. Besides training health staff and community volunteers, four PhD-candidates will obtain a PhD from this project, of which three candidates originate from the endemic countries included in this project to increase local research capacity.61 

60 443 **Ethics** 

444 445 446 447 448 449	Erasmus MC, as European consortium member, received a waiver of full medical ethics rev and approval from its ethical board according to the Dutch Medical Research Involving Hum Subjects Act (Wet Medisch-Wetenschappelijk Onderzoek met mensen, WMO). <sup>85</sup>				
450	Country	Ethical board	Outcome	Primary approval/waiver date	
	Ethiopia	National Research Ethics Review Committee from the Ministry of Science and Higher Education (MoSHE)	Approved	17 February 2020	
	Mozambique	Comité Nacional de Bioética para a Saúde (CNBS) from the Ministério da Saúde	Approved	16 August 2019	
	Tanzania	Ethical Clearance Committee linked to the National Institute for Medical Research (NIMR) and Ministry of Health, Community Development, Gender, Elderly & Children (MoHCDEC)	Approved	17 June 2019	
	The Netherlands	Medical Ethics Committee Erasmus	Waiver	11 April 2019	

> Written (or thumbprint) informed consent will be obtained from all study participants. If a participant is below 18 years old, a parent or legal guardian will be asked for consent. Study information given to the study participants prior to asking for consent contains details about: leprosy; the study purpose; the right to withdraw; the fact that SDR-PEP leads to a leprosy risk reduction and not absolute prevention (i.e. awareness of leprosy signs/symptoms remains important after taking SDR-PEP); possible side effects of SDR-PEP (i.e., urine discoloration) and AEs; the incidental findings procedure; and national contact information. AEs are expected to be rare after SDR-PEP. In the LPEP study, in which SDR-PEP was administered to 151,928 screened contacts, a single adverse event was reported (an allergic reaction to rifampicin in Brazil) and no serious adverse events were seen.<sup>13</sup> Urine discoloration, a common rifampicin side-effect, was not considered as an AE requiring follow-up in LPEP. Nevertheless, in

Page 21 of 41

1

2		
3	464	(chemo)prophylaxis programs AEs are of utmost importance because large numbers of healthy
4 5	465	individuals are involved. In PEP4LEP, SAEs will be reported following national pharmacovigilance
6 7	466	guidelines and by using the PEP4LEP AE Form for registration and to inform the principal
8	467	investigator. <sup>13,60</sup> The PEP4LEP project's SOP on rifampicin administration therefore included the
9 10	468	availability of an emergency allergy kit at community study sites where no health center is
11	469	located, which should be used according to national medical/pharmacological guidelines. <sup>56–58</sup> All
12 13	470	participants with suspected AEs will be referred for proper medical management and treated free
14	471	of charge according to national standard treatment guidelines.60
15 16	472	
17 18	473	Throughout both screening interventions and research projects involving human subjects,
18 19	474	incidental findings with potential health importance may be observed. <sup>86</sup> Incidental findings are
20 21	475	discoveries made during a research or screening project which are outside the scope of the
22	476	project. <sup>87</sup> Examples of possible incidental findings when performing full body skin screening
23 24	477	include: signs of cancer, venous insufficiency, bleeding diathesis, herniation, dental problems, or
25	478	indications of possible abuse. Incidental findings in a research setting are often not explicit
26 27	479	enough to be used for diagnosis, treatment, or clinical care.88
28 29	480	The procedures for reporting both SAEs and incidental findings are included in the evidence-
30	481	based PEP4LEP SOPs, on the participant information sheet and in the health workers' training
31 32	482	<sup>60,86,87,89,90</sup> The importance will also be emphasized during ongoing monitoring activities, including
33	483	field visits. <sup>13</sup>
34 35	484	
36 37	485	During the developmental phase of this project, the COVID-19 pandemic emerged. Regarding
38	486	COVID-19, national governmental and WHO guidelines will be followed. <sup>33–36</sup> Information about
39 40	487	COVID-19 and project implications (e.g., physical distancing, working in time slots) are included
41	488	in the project's SOPs, Information, Education and Communication (IEC) materials and health
42 43	489	workers' training. Hand washing facilities and personal protective equipment (PPE) such as
44 45	490	gloves, face masks and aprons, will be made available at the study sides.
46	491	
47 48	492	A code of conduct will be designed for the PEP4LEP consortium, based on the code of conducts
49	493	from WHO and All European Academies (ALLEA).91,92 All researchers in the project are
50 51	494	encouraged to participate in good clinical practice (GCP) courses, facilitated by the research
52 53	495	consortium.93 National data-safety monitoring boards, an international publication committee, and
55	496	an international scientific steering committee were formed to monitor the project (Figure 1).
55 56	497	
57	498	Trial registration
58 59	499	The PEP4LEP project is registered at The Netherlands Trial Register (NTR), receiving trial
60	500	registration number NL7294 (NTR7503), registration date September 10, 2018.94
		10

2		
3	501	
4 5	502	
6	503	Dissemination
7 8	504	Study outcomes are expected to be relevant for other sub-Saharan countries, but also for leprosy
9 10	505	endemic areas outside the African context. Results will be shared open-access via peer-reviewed
11	506	journals and at conferences. Tools designed for this study will be made available via
12 13	507	https://www.infolep.org, the international knowledge center for information resources on leprosy.95
14	508	Best practices will be shared with the Global Partnership for Zero Leprosy (GPZL).96
15 16	509	Communities affected and local and national policymakers will be informed on the study
17 18	510	outcomes via community meetings/workshops. In addition, project recommendations will be
19	511	offered to all relevant authorities and the WHO in Ethiopia, Mozambique and Tanzania; the
20 21	512	uptake of SDR-PEP into national leprosy guidelines is advised by the WHO.8
22	513	
23 24	514	Discussion
25	515	Discussion
26 27	- 4 6	
28 29	516	The PEP4LEP study will use an integrated skin screening approach, which is also recommended
30	517	by the WHO. <sup>1,19,20</sup> Skin diseases are among the most common human illnesses, affecting almost
31 32	518	900 million people worldwide. <sup>23</sup> They are thought to be the fourth leading cause of global non-
33	519	fatal disease burden and can result in disabilities, stigmatization, and discrimination. <sup>23,97</sup>
34 35	520	Additionally, dermatological problems can be the first expression of systemic or chronic diseases,
36	521	including HIV/AIDS, diabetes, and NTDs. <sup>17,98</sup> Integrated skin screening is therefore expected to
37 38	522	generate a greater health benefit compared with vertical health programs which focus on one
39 40	523	disease only. Pooling diseases in projects like PEP4LEP can also be helpful in educating and in
41	524	raising awareness, as health workers' knowledge of NTDs like leprosy has been declining. <sup>53,99,100</sup>
42 43	525	This was reflected in a study performed by Abeje et al. among general health workers diagnosing
44	526	leprosy in Ethiopia, which revealed that only 18% diagnosed leprosy correctly. <sup>101</sup> Detecting skin
45 46	527	NTDs like leprosy therefore requires capacity-strengthening programs. <sup>17,19,25–29</sup>
47	528	
48 49	529	This study will also use mHealth solutions to support peripheral health workers in recognizing and
50 51	530	treating signs and symptoms of skin diseases. "Digital health applications in leprosy" is described
52	531	as key research topic in the WHO "Global Leprosy Strategy 2021–2030".8 Evidence indicates that
53 54	532	mobile technology tools can substantially benefit healthcare workers, their patients, and adequate
55	533	health care delivery. <sup>102</sup> In dermatology, electronic health (eHealth) was adopted early, with
56 57	534	teledermatology as a widespread example, fostering the possibility of remote patient care and
58	535	education. <sup>103,104</sup> This is especially valuable if health services are scarce and during periods of
59 60	536	service disruption (e.g., flooding, civil unrest, COVID-19 pandemic). <sup>36,59,62,104,105</sup> We emphasize

### **BMJ** Open

the importance of studying the effect of mHealth technologies, aimed at capacity strengthening, like NLR's SkinApp, before fully focusing on upscaling.<sup>30,31,62,102</sup> 

Despite the conclusion of the expert meeting that SDR-PEP poses negligible risk of generating rifampicin resistance in *M. tuberculosis*, ongoing resistance surveillance is important to consider.<sup>15,106–108</sup> However, because of the limited study period, resistance surveillance in the PEP4LEP implementation areas alone would add no value to the project as the number of patients will be too small and the project duration would be too short for any resistance to emerge during that period. It is therefore recommended to integrate the surveillance of rifampicin resistance in the PEP4LEP project areas with the resistance surveillance systems for TB and leprosy during the project period and beyond, consistent with WHO recommendations on resistance surveillance.<sup>106–108</sup> 

Although SDR-PEP has been adopted in the WHO guidelines on leprosy, little is known about the feasibility of several implementation methods of SDR as chemoprophylaxis for leprosy in combination with varying and integrated contact screening methods, especially in sub-Saharan Africa.<sup>4</sup> Tanzania was the only sub-Sahara African country included in the LPEP Program.<sup>13</sup> Ortuno-Gutierrez et al. recently outlined the Post-Exposure Prophylaxis for Leprosy in the Comoros and Madagascar (PEOPLE) study protocol.<sup>109</sup> PEOPLE assesses the effectiveness of different modalities of SDR-PEP, using door-to-door surveys and a double dose of SDR-PEP. Both the PEOPLE and the PEP4LEP research questions comply with the Aligned Research Agenda for Zero Leprosy from the GPZL regarding the call for more operational studies and research focusing on SDR-PEP and on digital health.<sup>110,111</sup> Too often, innovative medical interventions fail because the factors contributing to success are poorly understood and hence not considered.<sup>112</sup> Lessons learned from SDR-PEP implementation are also expected to be relevant when improved preventive approaches, such as new chemotherapeutic regimens and vaccines, become available in the future.<sup>8,108</sup> Therefore, our goal is to share key insights gained from the PEP4LEP study to foster the implementation of integrated skin screening and chemoprophylaxis for leprosy in the sub-Sahara African context, which may also be relevant for the global leprosy community. 

Declarations

#### Acknowledgments

Our thanks go to all those involved in the PEP4LEP project, including the study participants; the full research consortium; and our funders European and Developing Countries Clinical Trials Partnership (EDCTP) and Leprosy Research Initiative (LRI). 

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2 3	573					
4	574	Autho	or contributions			
5 6	575		CK, JHR, AS, TH and RvW designed the study. KB, FM, SEM, EM, AM, NM, TL, AMM, DVK,			
7						
8 9	576		, LR, BN supported the development of country-specific protocols, materials and coordinate			
10	577		tudy implementation. AS, TH and RvW have drafted the manuscript. All authors have			
11 12	578	revie	wed the draft manuscript and have read and approved the final version.			
13	579	<b>F</b>				
14 15	580	Fund				
16 17	581		project was supported by the EDCTP2 program under Horizon 2020 (grant number			
18	582		017NIM-1839-PEP4LEP). The project also received funding from the Leprosy Research			
19 20	583		tive (LRI; www.leprosyresearch.org) under LRI grant number 707.19.58. Both funding bodies			
21	584	reviev	wed and approved the study proposal.			
22 23	585					
24	586		peting interests			
25 26	587 No competing interest have been declared by the authors.					
27	588					
28 29	589					
30 31	590					
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# BMJ Open

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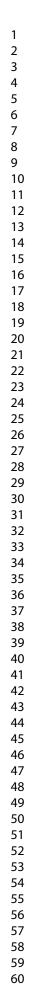
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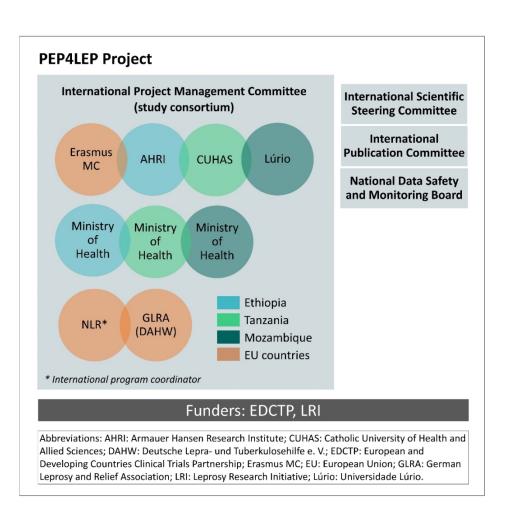
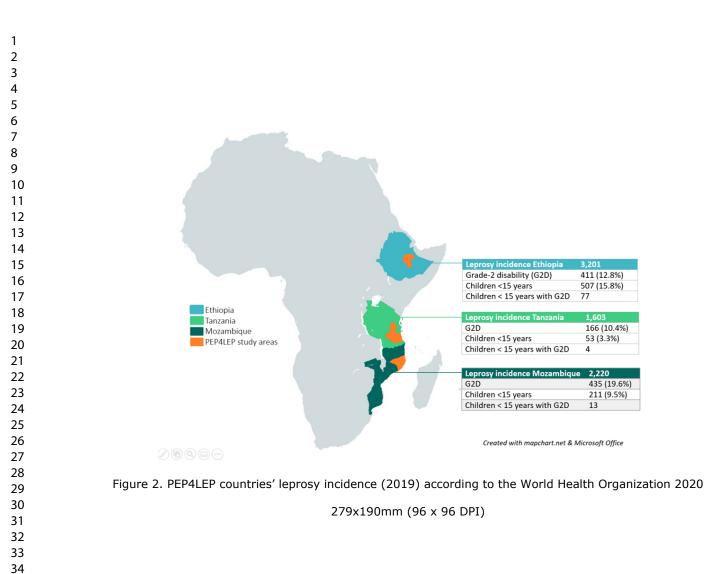
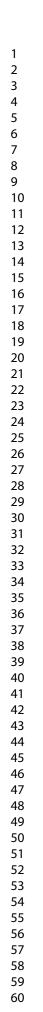


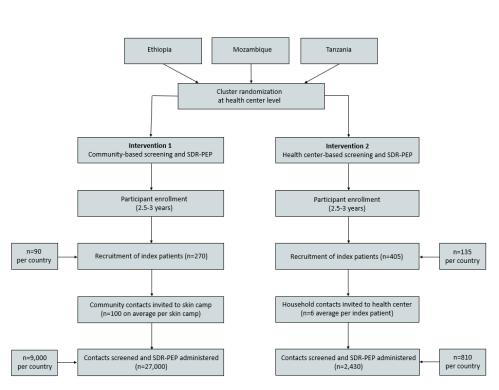
Figure 1. PEP4LEP Project organization chart

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Abbreviations: n: number; SDR-PEP: single-dose rifampicin post-exposure prophylaxis

Figure 3. Flow of participants through the PEP4LEP study

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# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ItemNo	Description	BMJ Open
Administrativ	e inform	ation	
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Page 1, Trial registration
Funding	4	Sources and types of financial, material, and other support	Page 14, Funding
Roles and responsibilitie s	5a	Names, affiliations, and roles of protocol contributors	Page 1 Page 14, Authors' contributions
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 11, Availability of data and materials Page 3, Objectives (details study consortium) Page 14, Funding
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 11, Data collection ar management Page 12, Ethics

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3, Objectives
	6b	Explanation for choice of comparators	Page 7, Outcomes
Objectives	7	Specific objectives or hypotheses	Page 3, Objectives Page 8, Table 3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 5, Study Design Page 6, Figure 3
Methods: Par	ticipants	s, interventions, and outcomes	
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 3, Study setting
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 4, Participants and eligibility criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 5, Community based skin camp intervention Page 6, Health center-based intervention for household contacts
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page 4, Participants and eligibility criteria Page 4, Table 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 4, Participants and eligibility criteria Page 4, Table 1

Outcomes			
	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7, Outcomes
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 3, Study setting Page 5, Study design Page 6, Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 10, Sample size
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 10, Sample size
Methods: Ass	signmen	t of interventions (for controlled trials)	
Allocation:			
Anocation.			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 11, Data collection and management, paragraph 3

Implement ation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 11, Data collection and management, paragraph 3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Dat	ta collect	tion, management, and analysis	
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 11, Data collection and management
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 11, Data collection and management
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 11, Data collection and management
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to	Page 11, Data analysis
		where other details of the statistical analysis plan can be found, if not in the protocol	

1				
2		20c	Definition of analysis population relating to	Page 11, Data analysis
3			protocol non-adherence (eg, as randomised	
4			analysis), and any statistical methods to	
5			• • •	
6			handle missing data (eg, multiple	
7			imputation)	
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9	Methods: Mo	nitoring		
10	Data	21a	Composition of data monitoring committee	Dago 12 Ethics
11		21a	Composition of data monitoring committee	Page 12, Ethics
12	monitoring		(DMC); summary of its role and reporting	
13 14			structure; statement of whether it is	
14			independent from the sponsor and	
16			competing interests; and reference to	
17			where further details about its charter can	
18				
19			be found, if not in the protocol. Alternatively,	
20			an explanation of why a DMC is not needed	
21		046	Description of any interim such as a such	N1/A
22		21b	Description of any interim analyses and	N/A
23			stopping guidelines, including who will have	
24			access to these interim results and make	
25			the final decision to terminate the trial	
26				
27	Harms	22	Plans for collecting, assessing, reporting,	Page 12, Ethics
28			and managing solicited and spontaneously	-
29			reported adverse events and other	
30			-	
31			unintended effects of trial interventions or	
32			trial conduct	
33 34	A 1.1.	00		
35	Auditing	23	Frequency and procedures for auditing trial	Page 12, Ethics
36			conduct, if any, and whether the process	
37			will be independent from investigators and	
38			the sponsor	
39				
40	Ethics and di	ssemina	tion	
41				
42	Research	24	Plans for seeking research ethics	Page 12, Ethics
43	ethics		committee/institutional review board	
44	approval		(REC/IRB) approval	
45	appiovai			
46	Protocol	25	Plans for communicating important protocol	Page 12. Ethics
47	amendments	20	modifications (eg, changes to eligibility	1 ago 12, 24100
48 49				
49 50			criteria, outcomes, analyses) to relevant	
51			parties (eg, investigators, REC/IRBs, trial	
52			participants, trial registries, journals,	
53			regulators)	
54			<b>.</b> ,	
55	Consent or	26a	Who will obtain informed consent or assent	Page 12, Ethics
56	assent		from potential trial participants or authorised	
57	-		surrogates, and how (see Item 32)	
58			canogatos, and now (see item oz)	
59				
60				

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentialit y	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 11, Data collection and management, paragraph 3
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 14, Competing interests
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 11, Availability of data and materials
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Disseminatio n policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 11, Availability of data and materials
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 11, Availability of data and materials
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Added to supplementary materials of submission
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the

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