LEPROSY RESEARCH INITIATIVE

Annual report 2015

Contents

Postal address
P.O. Box 95005
1090 HA Amsterdam
The Netherlands

Visiting address
Wibautstraat 137k
1097 DN Amsterdam
The Netherlands

E-mail info@leprosyresearch.org
Internet www.leprosyresearch.org

1. Introduction

This is the first Annual Report of the Leprosy Research Initiative (LRI), which has been registered since June 1st 2015 as a Foundation under Dutch law. The LRI is a unique model of cooperation and coordination in the funding of research. In 2015, five NGOs, committed to the fight against leprosy, combined their funding for leprosy-related research in a joint fund under one policy, and allocated about € 1.4 million to 20 research projects. Included in this amount is the very substantial contribution of € 0.5 million provided by the Turing Foundation as co-funder.

The 5 LRI partners working together in the LRI in 2015 were:
American Leprosy Missions (ALM)
German Leprosy Relief Association (GLRA)
effect:hope (The Leprosy Mission Canada)
The Leprosy Mission International (TLMI)
Netherlands Leprosy Relief (NLR)

As a Foundation the LRI is managed by the director of Netherlands Leprosy Relief (NLR), implementing the decisions of the LRI Executives Group and supervised by the Supervisory Board of NLR. This annual report aims to give account to the LRI partners and other stakeholders of the LRI proceedings and actions taken in 2015. The financial proceedings have been audited by an independent auditor.

The LRI partners have confirmed their participation in the LRI for a minimum of 3 years and have agreed to decide annually about extension of this three year commitment by another year. In 2015 the LRI was therefore able to fund research projects with a duration of up to three years.

The small and hardworking LRI office team was again assisted by many outstanding professionals and experts who are members of the LRI Steering Committee, members of the Scientific Review Committee or independent reviewers.

The LRI is open to welcome new partners and co-funders in its exciting model of funding research that offers perspectives for innovation and increasing effectiveness in the various aspects of the fight against leprosy and its consequences.

We wish to thank everyone who contributed to the LRI work in 2015 via personal involvement, financial support or co-operation.

Jan van Berkel	Bram van Ojik
Director NLR	Chair NLR Supervisory Board

2. Vision and Policy

Vision

A world free from leprosy

Mission

To contribute to our vision by:

1. promoting, facilitating and funding high-quality leprosy research;
2. strengthening research capacity in endemic countries, and;
3. facilitating translation of research results into policy and practice.

Purpose

1. To establish and maintain a joint research fund to support leprosy research that fits with the LRI priorities.
2. To secure funding from external sources for research projects related to the LRI joint research agenda that cannot be funded (solely) by the LRI fund.

Objectives

1. To facilitate the development of research funding proposals in collaboration with concerned research groups.
2. To establish and maintain a joint research fund for leprosy research.
3. To facilitate adequate resourcing of leprosy research projects.
4. To provide an efficient, transparent and scientifically rigorous selection process of research proposals that fit the priorities set in the joint research policy.
5. To provide a scientifically high-quality monitoring mechanism of research projects supported by the LRI.
6. To expand the number of partners in the LRI.

Current research priorities

Based on current global research needs, the partners of the LRI have agreed on a joint policy with clearly defined research priorities. Research results should be directly applicable to leprosy services or to the wellbeing of persons affected by leprosy. In addition research projects need to generate results that can be used in the short- or medium term.

5 research areas are selected as main priorities. The projects should aim to:

1. Early detection

Promote and enable early detection of leprosy

Early detection is important to reduce further transmission, but particularly because it reduces the risk of permanent impairments. The LRI will support studies that examine approaches, methods or tools to improve early case detection. This will include health systems approaches to promote community awareness, appropriate health-seeking behaviour of patients and access to services, as well as the testing of lab-based tools for subclinical infection or disease. It may also include interventions to reduce community stigma, if this is a barrier to early detection in a given setting.

2. Nerve function impairment and reactions

Promote prevention, early detection and effective treatment of nerve function impairment (NFI) and reactions

Neural and ocular impairments and disabilities are the main causes behind the many problems persons affected by leprosy may experience. The LRI will therefore support studies of approaches and interventions for primary prevention of nerve or ocular damage, methods to improve detection and interventions and treatment regimen to improve the prognosis of NFI and leprosy reactions.

3. Inclusion

Promote inclusion of persons affected by leprosy in society

Exclusion from society is the most feared and severe consequence of leprosy. This may happen overtly, as when people are sent away from their home or faced divorce, or in much more subtle ways, such as loss of status, gossip, avoidance, etc. The LRI will support research that promotes inclusion and participation of persons affected by leprosy in any aspect of society. Important aspects are relationships, including marriage and promotion of the sexual and reproductive health and rights of affected persons, livelihoods and labour participation, education, and participation in civil organisations, such as disabled people's organisations. Participation of affected persons in leprosy services in the broadest sense is another aspect that deserves specific attention.

4. Prevention of disability

Improve the coverage of prevention of disability activities and their integration in national programmes and integrated wound and limb care programmes

Prevention of disabilities (POD) is a core component of leprosy services. Appropriate methods and tools are already available, but often they are not used and not used adequately. Examples are nerve function assessment and self-care training. Usually, POD interventions or activities are carried out in a leprosy-only mode, while there are many people with similar problems who would also benefit from such interventions and activities (e.g. people with diabetic neuropathy). The LRI will support implementation research that explores or provides ways to improve the use of existing methods and tools for POD, the integration of POD interventions in national leprosy policies and programmes, and the integration of leprosy-related POD in general wound and limb care programmes (or vice versa).

5. Interrupt transmission

Test methods and tools to interrupt the transmission and incidence of leprosy, including increasing the coverage of effective contact management and chemoprophylaxis

The ultimate goal of leprosy control services is to interrupt the transmission of leprosy. Current approaches to case detection and treatment with MDT have not led to a sufficient decrease in incidence of leprosy in many countries or areas within countries. Recent research has shown that strategies aim at contacts of leprosy patients are the most promising and cost-effective options to further reduce the incidence of leprosy. Therefore, the LRI will support implementation research aimed at introducing or scaling up effective contact management or chemoprophylaxis

interventions. Testing of additional contact examination interventions, chemoprophylaxis regimen or other prophylaxis approaches, such as immune-prophylaxis, would be eligible for support. Studies aimed at reducing or removing barriers to the effective use of contact-based interventions are also eligible for support.

4. Received and approved proposals

The application procedure for LRI research funds is structured as follows:

- Step 1: Submission of Letter of Intent (LoI) outlining the intended research
- Step 2: The first selection is made by the Steering Committee (SC), using a review format
- Step 3: Feedback is given to the applicant. This can be:
    - An invitation for full proposal submission
    - Recommendations on a major revision of the proposal (not an invitation)
    - Rejection
- Step 4: Submission of the full research proposal
- Step 5: Proposal is reviewed by two independent reviewers
- Step 6: Feedback of the reviewers is sent to the applicants
- Step 7: Applicants submit their rebuttal
- Step 8: The Scientific Review Committee makes recommendations on which projects to fund.
- Step 9: The SC reviews the recommendations and add their feedback and ranking.
- Step 10: The Executive group decides which proposals to fund

In December 2013 a call for proposals was published, inviting to present letters of intent by April 1st 2014. The deadline for full proposals was June 1st 2014. Projects that were approved started in 2015.

Letters of Intent received

In 2014 a total number of 50 Letters of Intent (LoI) were received, of which 23 (46%) were rated positive, 8 needed major revisions and 19 were rejected. Applications were received from both leprosy endemic and non-endemic countries. 60% of the lead applicants were from leprosy endemic countries.

	Number	Invitation for full proposal	Approved	Success rate
Lead applicant from leprosy endemic country	30	14	5	17%
Lead applicant from leprosy non-endemic country	18	8	6	33%
Lead applicants from endemic + non-endemic countries	2	1	1	50%
Total	50	23	12	24%

Table 1: Letters of intent received for budget round 2016. Number of Letters of Intent (LoIs) and their origin received for budget round 2016, the number of applicants that were invited to write a full proposal, approved projects and the success rate.

Full proposals received

21 full proposals were received, with a total requested budget of almost € 8.5 million. More than half (57%) of the proposals came from leprosy endemic countries, requesting 25% of the total requested budget. Their budgets ranged from € 10,013 to € 905,408. Proposals received from non-endemic countries added up to 8, requesting 71% of the total requested budget, ranging from €104,889 to € 1.5 million.

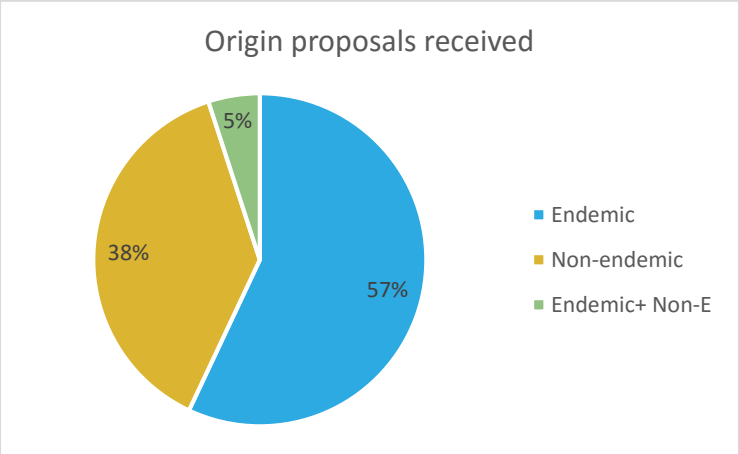


Figure 1. Origin of the full proposals received for budget round 2015
Budget round 2015, n=21.

	Number	Budget requested
Full proposals received	21	€ 8,469,822
From endemic countries	12	€ 2,137,018 (25%)
From non-endemic countries	8	€ 5,967,468 (71%)
From endemic + non-endemic	1	€ 365,335 (4%)

Table 2. Overview of the origin, number of proposals and requested budget

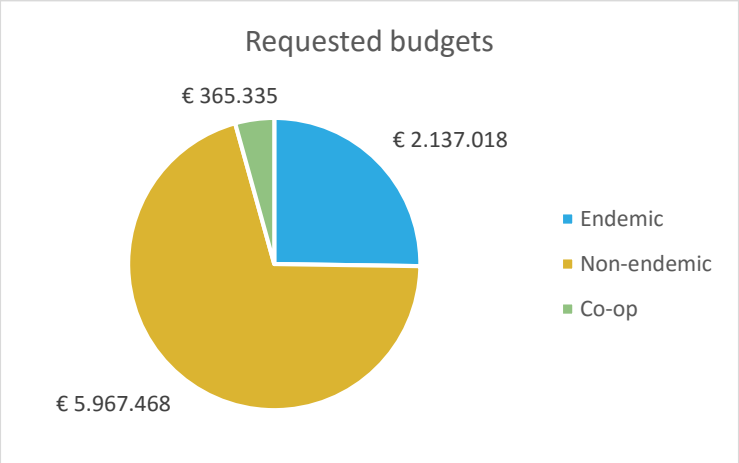


Figure 2. Budget requested for the 2015 budget The distribution of the requested LRI budget 2015 is given, divided by the origin of the applicant. Total requested budget 2015: € 8,469,822.

The majority of the proposals addressed research priority 1 (Early detection). Figure 3 shows the number of proposals received per LRI research priority.

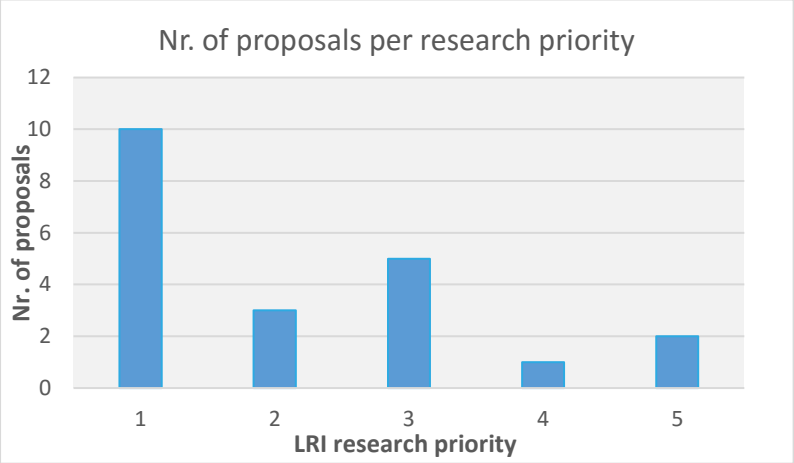


Figure 3. Number of proposals received per research priority (budget 2015)
The total number of the proposals equals the number of proposals received (n=21)

External review

73 external reviewers were approached, of which 45 responded positively to the request to review a research proposal. In the end, 42 reviewers sent their feedback. The majority (15) of the proposals were reviewed by 2 reviewers, 3 proposals by 1 reviewer and 3 proposals by 3 reviewers.
The feedback of the reviewers was shared with the applicants.

Funding decisions

After careful consideration of the advice of the SRC and LRI SC, the EG made the following decisions:

- 6 projects to be fully funded (29%)
- 5 projects to be funded with a reduced budget (24%)
- 1 project to be funded as a pilot project (5%)
- 9 projects were rejected (43%)

Figure 4 shows the number of approved and rejected proposals per LRI research priority. The majority (7) of the funded projects addresses priority 1, followed by priority 2 (3). Priority 3 and 5 are addressed by 1 projects each. There are no projects approved addressing research priority 4 (prevention of disability).

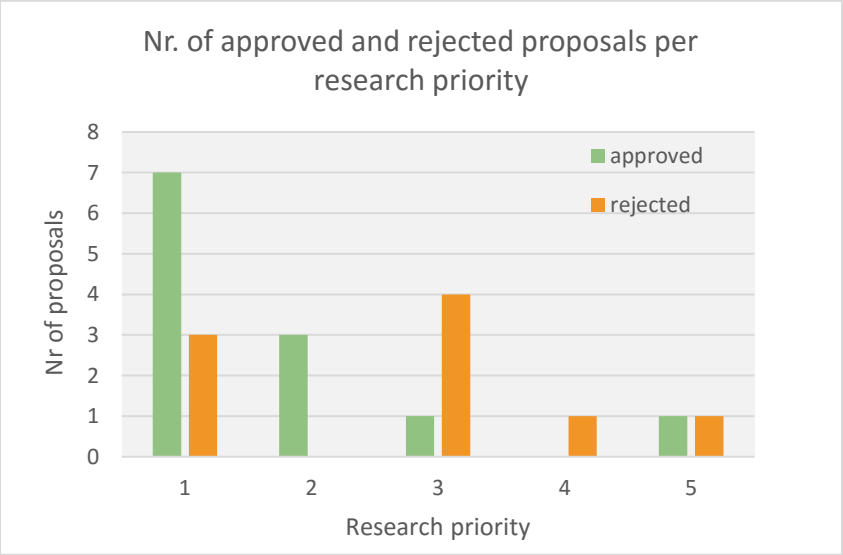


Figure 4 Number of proposals approved and rejected per research priority (budget 2015) The total number of proposals approved (n=12) and total number reject (n= 9) divided by research priority areas.

5. Funded research projects 2015

A total of 12 new projects started in 2015. 5 projects were ongoing with start dates before 2015.

Projects covering research priority 1: Early detection

1.1 Delays in diagnosis & treatment, Leprosy in Nepal

Coordination:	Mr Dhaka Ram Budha Magar
Institute:	International Nepal Fellowship
Grant:	€ 99,893
Started:	April 2015
Focus:	Nepal
Duration:	33 months

'Delays' are of critical importance in leprosy control work. A delay is the time span between awareness of the first symptom through to the start of proper anti-leprosy treatment. In Nepal, delays are often long. The longer the delays, the greater the chance for a transmission of the disease to others and for lasting negative consequences upon the life of the individual: physically; socially; emotionally; and economically. The proposed project: "Delays in Diagnosis and Treatment, Leprosy in Nepal" will research and address causes of long delays. Present patterns of delays will be documented and investigated, risk categories identified, and key barriers looked into. This will be done by a combination of qualitative and quantitative research in two of Nepal's five Development Regions: the West and the Mid-West.

The International Nepal Fellowship (INF), a Christian Mission involved in leprosy work in Nepal since the 1950s, is a counterpart to the government in leprosy control in the two regions and the project will be taken forward by INF. There will be a structured questionnaire to gather quantitative data from a large number of patients visiting INF clinics combined with in-depth information from inpatients in two of INF's hospitals and from patients on anti-leprosy treatment within the government health services. And, there will be some community studies. In focus will be the patient's perceptions and help-seeking process combined with his/her assessment of the primary cause/s of the delay. When possible and appropriate, what has been learnt through talks and interviews at peripheral treatment centers will be followed by home and community visits during which the beliefs, opinions, attitudes, and actions of others involved in the help-seeking process are scrutinized - all to learn about triggers and obstacles along the route to presentation and the start of treatment. Forthcoming ideas about reasons for short versus long delays will be investigated and tools and techniques for shortening of delays will be piloted and pre-tested before the closure of the project which is believed to make a tangible impact upon leprosy control strategies and Nepal's pace towards a leprosy-free society.

1.2 Contact cohorts: how long to continue annual examinations?

Coordination:	Dr David Khan
Institute:	Leprosy Field Research in Bangladesh, TLM Bangladesh
Grant:	€ 55,256
Started:	May 2015
Focus:	Bangladesh
Duration:	8 months

It is known from various studies that examination of people in close contact with known leprosy cases is a very important way for identifying more new cases. The members of the same household & close neighbours are especially important because they are at greater risk of developing leprosy than the general population. Currently field staff routinely perform annual contact examinations up to 2 years in case of PB cases or up to 5 years in case of MB cases. In Bangladesh still many new leprosy cases are found every year from contact case examination. However it is not really known what the ideal period or intervals is for follow up of affected households. Evidence-based Guidelines are needed for how long staff should do this contact examination. IN this project households will be studied which are now at different time points (1-20 years) after diagnosis & treatment of the first cases, in a cross-sectional approach, as far as possible examining all household members originally resident with the first case (even if they have since left that household) and new comers to household.

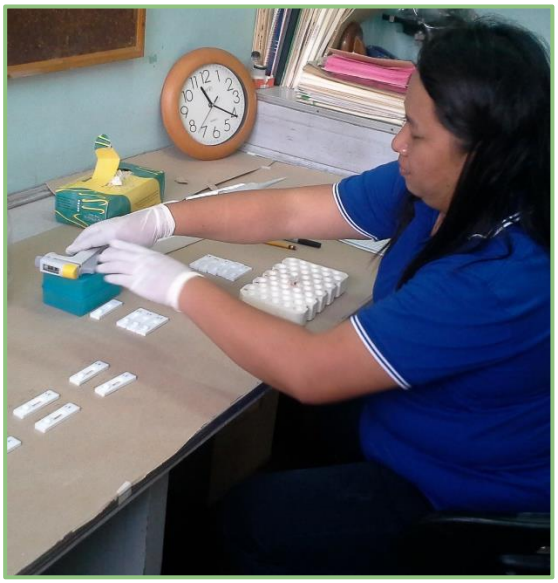
The number of new cases found each year will be recorded, and type of case found (classification, sex, adult/child), for members of households examined at the different time points after diagnosis of the first case. Results will be analysed according to both characteristics of the first cases and those of the new cases detected, to try and identify factors with mean some people are at higher risk than others, as well as to discover the changes in case detection rate amongst contacts, over time since first case diagnosed in that household.

1.3 Integration of rapid diagnostic tests to facilitate case management of leprosy

Coordination:	Dr Malcolm Duthie
Institute:	Infectious Disease Research Institute
Grant:	€ 390,000
Started:	May 2015
Focus:	Philippines
Duration:	48 months
Co-funder:	Turing Foundation

Detection and management of leprosy cases currently relies heavily on examination by expert clinicians. This requirement significantly limits the scope, reach, efficiency and even feasibility of surveillance programs intended to actively detect leprosy cases. As a result, patients are not detected as early in their disease development as they potentially could be and may be more prone to treatment complications. The research group will evaluate the potential of two recently developed tests that detect anti-leprosy antibodies in blood and/or serum samples to address this deficit. They will evaluate, in parallel, the ability of serological tests and scheduled clinical evaluations to identify the development of leprosy among at-risk individuals and also to identify treatment complications within recognized patients.

Within the study, samples will be collected and examined in conjunction with clinical exams, with the clinical exams being used as the benchmark for diagnosis and case management. Samples could, however, be collected and tests conducted by technical staff following only a minor amount of training. The researchers hypothesize that positive tests results could to serve as a simple, quantifiable and robust measurement to facilitate referral for expert clinical exam. The investigative strategy will determine the acceptance, utility and practicality of these tests within surveillance programs while testing this hypothesis.



1.4 Field evaluation of novel immunodiagnostic tools for early detection of leprosy in a BCG vaccination field trial amongst contacts of leprosy patients

Coordination:	Prof Jan Hendrik Richardus
Institute:	Erasmus MC - Rotterdam LUMC - Leiden
Grant:	€ 1,495,00
Started:	January 2015
Focus:	Bangladesh
Duration:	48 months
Co-funder:	Turing Foundation

Although a combination of antibiotics (multidrug therapy) is very effective at curing clinical leprosy, it is insufficient to reduce transmission of *M. leprae* in endemic populations as witnessed by stable new case detection rates in many leprosy endemic countries. It is therefore important to identify risk factors, transmission patterns and preventive measures that may be used as tools for early detection and prevention of leprosy.

This study aims to identify compounds of the immune system that are characteristic for the occurrence of leprosy. Such compounds are called leprosy-specific biomarkers. The set of biomarkers identified in a previous, small cohort study (IDEAL 2008-2010) will be evaluated in a large cohort and optimized/ extended in order to identify those individuals who should best be targeted for prophylactic treatment of leprosy. Promising biomarkers will then be applied in a diagnostic test (developed by us in a distinct project) for use in field circumstances all over the world.

The aim of the study is to understand in more detail how people respond immunologically to the presence of *M. leprae*, the causative bacteria of leprosy, in order to obtain insight into which immunological responses in people indicate that they are susceptible to developing leprosy disease. In addition, since the BCG vaccine can induce protection against leprosy, BCG vaccination of contacts of leprosy patients will allow identification of immune responses that reflect protection against leprosy.

For the aim of this study the research group will:

a) Determine the effect of chemo- and immunoprophylactic interventions on biomarkers of *M. leprae* infection and clinical leprosy.
b) Identify immune- and transcriptomic host profiles that indicate infection and/or predict disease development or that are indicative of protection using a two year follow-up approach to estimate which individuals develop disease.
c) Design a biomarker profile applicable in a user-friendly test platform based on the most specific and sensitive diagnostic biomarkers identified in this study.

This is a long term project to test many leprosy patients, their contacts, and people from the general population in Bangladesh on the presence of infection with *M. leprae* and the effect of BCG vaccination and treatment with an antibiotic (rifampicin) of contacts on host biomarker profiles. The infrastructure for the project was developed and intake of participants started in January 2013 as part of the MALTALEP and IDEAL projects of 2012, 2013 and 2014.

In a distinct project field-friendly tests will be developed based on differences in the immune- and genetic markers between those that develop disease and those that are exposed to the bacterium but remain healthy.

Early diagnosis followed by (prophylactic) treatment of people who will otherwise develop leprosy will prevent transmission of the bacteria and possibly life-long disabilities in many of these people. Through this project those individuals who are at risk of developing leprosy disease will be identified. Through treatment it will be avoided that leprosy will ever become manifest in their lives.

1.5 A pilot study using participatory, translational, social science research methods to promote earlier detection of leprosy

Coordination:	Assoc. Prof. Pim Kuipers
Institute:	Griffith University The Leprosy Mission, India
Grant:	€ 23,409
Started:	June 2015
Focus:	India
Duration:	10 months

Making sure that leprosy is detected early (that diagnosis is not delayed) is vital to preventing individuals from being permanently disabled by nerve damage, blindness or other conditions; as well as preventing them from experiencing the multiple flow on psychological, health, livelihood and social effects that are linked with the disease. Early detection and treatment is also crucial to stopping the spread of the disease within families and the community. While there have been advances

in medical aspects of improving diagnosis, other factors that prevent people from being diagnosed early are still not well understood or implemented. These factors, which include psychological, attitudinal, social, community, service related factors (and even structural and environmental issues like transport and organisational or government policies), need to be understood in a more comprehensive and theoretically integrated way. They need to be explored using questions which are relevant to answering complex problems. They need to be explored from the perspective of the key people involved, and the research needs to go beyond 'exploring' to create real change in local settings.

Many of these research methods are quite new in the leprosy research area. There is a need to test how well they will work and refine accordingly. This pilot study will explore how these innovative social science research methods will work in research to promote early detection of leprosy.

The project will use a number of strategies (such as training a person affected by leprosy to conduct important parts of the research) to ensure that the findings are as accurate and meaningful as possible. To ensure that the findings of the research have the most impact:

- The project will then document what people with leprosy, community members and others say about the findings in 'reflection and discussion' groups, to establish ways of preventing delay.
- It will translate the findings for a key service provider (TLM), facilitating a workshops to decide on practical strategies the organisation can use to promote early detection.
- The project will also translate the findings for regional leaders of relevant NGOs, INGOs and government departments in formal workshops to consider strategies they might use in each setting, to facilitate early detection.

1.6 A comparison of three types of targeted, community-based health education aimed at promoting early detection

Coordination:	Dr Annamma John
Institute:	The Leprosy Mission Trust India
Grant:	€ 171,859
Started:	September 2015
Focus:	India
Duration:	36 months

This study is planned following on from a pilot done at one location where two of the methods – education and motivation of the Index case to bring all contacts for examination, and training of local practitioners, yielded good results in terms of increased new case detection. The pilot was a hospital based study and the research group wants to test these strategies in the community to see if they can be applied successfully in the field.

The research group aims to find out which of the methods that are tested will be more effective in promoting early case detection:

1. Training local non formal practitioners;
2. Health education to newly diagnosed leprosy patients or
3. Increasing awareness in the community regarding early signs of leprosy.

A previous study has shown in various Indian states that knowledge regarding early signs of leprosy is poor among the community as well as local practitioners of indigenous medicine, who are the first resort, for any health issues among a large portion of these rural populations. Due to the knowledge gap regarding leprosy there is delay in reporting to a centre which will diagnose and provide treatment for leprosy.

The second method is to involve the index case reporting to a health centre, in a participatory modified way to detect contacts. The third is to conduct an awareness campaign to improve the community's knowledge regarding early signs of leprosy and treatment facilities, in the expectation that it will lead to early voluntary reporting.

Field friendly methods need to be devised and tested to detect leprosy patients in rural communities early and treat them. Two of the methods mentioned above have been tried in a base hospital setting and have shown encouraging results. The study hopes to prove that these methods will increase early case detection which will be evidenced by a rise in the number of new leprosy cases registered for treatment/detected.

1.7 Evaluation of the qPCR in household contact monitoring

Coordination:	Dr Milton Ozório Moraes
Institute:	Laboratório de Hanseníase Fundação Oswaldo Cruz/ FIOCRUZ
Grant:	€ 60,269
Started:	August 2015
Focus:	Brazil
Duration:	36 months

Leprosy is a disease caused by a bacterium and proper diagnosis can completely cure patients, but clinical signs of the disease are sometimes difficult to detect. The bacteria infect skin and nerves and late diagnosis are generally associated with permanent nerve injuries. It is well known that the group of individuals at greatest risk are the family members that live with close contact to patients. Nevertheless, there are no diagnostic tests that could predict whether or not a "contact" will develop the disease. In the past few years, novel technologies to amplify the causative agent, Mycobacterium leprae, of leprosy DNA are available and these tests are accurate, and faster and becoming cheaper. Here, the research group suggests that detection of M.leprae DNA, by a specific in vitro amplification, could predict the development of leprosy. This data can help define health policies to preventive treatment to avoid new and severe cases of leprosy.

Projects covering research priority 2: Nerve function impairment and reactions

2.1 Treatment of Early Neuritis in Leprosy (TENLEP)

Coordination:	Dr Erik Post
Institute:	Royal Tropical Institute
Grant:	€ 1,329,584
Started:	January 2010
Focus:	Bangladesh, India, Indonesia, Nepal
Duration:	6 years
Co-Funder	Turing Foundation

The TENLEP Trials use a randomised, double-blind placebo-controlled study design to prove or disprove the following hypotheses:

Trial 1:
Steroid treatment of subclinical nerve damage at the point of diagnosis of leprosy will reduce the number of patients that will end up with permanent nerve damage.

Trial 2:
Steroid treatment of 32 weeks is more effective than one of 20 weeks in restoring nerve function of patients with recently damaged nerves. as caused by leprosy.

Trial 1 was finalised in October 2015, with an intake of 363 patients. A preliminary analysis showed that there is no difference between the effect of treatment and that of placebo in preventing nerve damage in new leprosy patients. About 8.7% of patients progressed to develop clinical nerve damage, and had to be treated on an individual basis.

Trial 2 was finalised in April 2015, with an intake of 867 patients. No difference was found between 20 weeks and 32 weeks steroid treatment of recent nerve damage. Recovery rates were close to 80% in both groups in the trial. It is therefore recommended that 20 weeks steroids is the preferred treatment for recent nerve damage, with individualised treatment if needed.

2.2 Trial for effective plantar pressure reduction

Coordination:	Robert Bowers
Institute:	The Leprosy Mission International, Bangladesh
Grant:	€ 23,760
Started:	April 2015
Focus:	Bangladesh
Duration:	12 months

Health care interventions are continually evolving and developing, but the use of micro-cellular rubber (MCR) footwear as the first-line intervention for protecting the feet of people with sensory loss has remained unchanged since the early 1960's. Though MCR is not available in commercially produced footwear, other comfort-enhancing products have been developed and are readily available in many markets. As MCR has a long and successful history of reducing foot ulcers, it would be ill-advised to recommend replacement materials without evidence of their efficacy. The research group proposes to use technology which measures the precise force applied on various parts of the sole of the foot while wearing different types of footwear. These will be compared to the force measurements of traditional MCR footwear. Materials which meet or exceed the standard set by MCR will be then used by 4 simultaneous pairs of groups of individuals with poor sensation in their feet in a two-step trial. Half of the participants will begin with one of four selected styles of market footwear for four months, and then will wear MCR footwear for four months. The other half of the participants will follow the opposite schedule, beginning with MCR and ending with one of four styles of market footwear. The "cross-over" design allows for control of several variables including weather and seasonal work patterns which may influence walking and footwear use patterns. Both groups will have regular monitoring for foot condition. The study is expected to generate evidence showing the impact of the market footwear versus MCR on rate of ulcer development and whether one group developed more ulcers than the other group.

2.3 Development and validation of severity scale for erythema nodosum leprosum

Coordination:	Dr Steve Walker
Institute:	London School of Hygiene Tropical Medicine
Grant:	€ 65,698
Started:	May 2015
Focus:	Bangladesh, Brazil, Ethiopia, India, Indonesia, Nepal, Philippines
Duration:	23 months
Funder:	Austrian Leprosy Relief Association

ENL is severe complication of leprosy which is associated with death and increased economic hardship. ENL is a difficult condition to treat and many affected individuals do not have access to safe, effective long term therapies. In order to determine which therapies are most effective, a way of measuring the severity of ENL before, during and at the end of treatment needs to be developed. This will make it possible to compare different treatments.

This project aims to develop and test the first reliable method of measuring the severity of ENL and brings together leprosy workers from around the globe to meet this challenge. Once this barrier to improving the lives of people affected by ENL has been overcome the research group is committed to finding better ways to treat the condition and engaging with policy makers to make them available.

2.4 Helminth influences in leprosy: indicators, treatment, reactions and clinical outcome

Coordination:	Dr Deanna Hagge
Institute:	The Leprosy Mission Nepal
Grant:	€ 200,000
Started:	September 2015
Focus:	Nepal
Duration:	48 months

More than 94% of global new leprosy cases are living in areas endemic for soil-transmitted helminths (STH, intestinal worms). Recent evidence indicates that intestinal worms depress immunity in general, suppressing host capacity to evict or manage other co-infection(s). For instance, current studies now indicate that allergies are more common in developed nations than nations with high rates of intestinal worms. Basically, the worms long-term suppress the inflammatory responses evidenced in allergies.

In Brazilian leprosy patients, intestinal worm infections were more common in those with higher leprosy bacterial loads. Essentially, the worms suppressed the patient's normal immune defences, likely allowing M. leprae to grow to higher numbers and thereby placing patients at higher risk for complications.

Growing evidence from other diseases such as HIV, tuberculosis and malaria indicate that deworming patients can benefit immune health and restore normal immune responses, although recovery times seem to vary on malnutrition, the specific worm(s), duration and degree of infection and if the patient has any other health conditions. Deworming seems of obvious benefit; however, there is a risk that restored immunity may suddenly overreact with strong inflammation towards co-infections that developed during the time of worm-induced immune suppression.

Roughly 30-50% of leprosy patients develop immune complications called leprosy reactions, which often involve inflammation of the skin and nerve. Because the nerves can be permanently damaged, reactions are the major factor for disability development in leprosy. Reactions typically are sudden shifts in the immune response, unpredictable and often requiring months to years of immunosuppressive medications before they resolve.

It is unknown what triggers leprosy reactions. Surprisingly, though, in recent years it was discovered that some arthritis treatments that suppressed immunity long term and then were halted could unmask previously subclinical leprosy by manifesting intense inflammation against leprosy bacteria once immunity was restored. In some African HIV patients, normal immunity had been decimated by the HIV virus over a long period.

After receiving immune boosting medications, some unexpectedly manifested a leprosy reaction, intense inflammation by a restored immune system attacking leprosy bacteria that had sought to thrive while HIV kept defences low. Combining these patterns with what is being learned about worm co-infections, the research group proposes that worms and deworming may also be related to signs of leprosy and leprosy reaction development.

Worm co-infection may also be blocking leprosy blood test signals. In Bangladesh, malnourished children with confirmed tuberculosis and worm co-infection more often received unreadable blood test results. This was because their worm infection had suppressed the signals the test was designed to evaluate. Some developing leprosy diagnostics are targeting similar signals. Therefore, the research group also proposes that worm co-infection in leprosy may be silencing or diminishing immune responses that could be detectable by blood test. Deworming suspect leprosy cases before these blood tests and then allowing for immune recovery may allow better readout with improved sensitivity and accuracy.

The main research question is: Are common worm co-infections and deworming relevant to leprosy indicators, clinical care and outcomes?

Projects covering research priority 3: Inclusion

3.1 Stigma Assessment and Reduction of Impact (SARI) Project

Coordination:	Dr Wim van Brakel
Institute:	VU University Amsterdam, Disabilities Studies
Grant:	€ 992,382
Started:	January 2010
Focus:	Indonesia
Duration:	7 years

The SARI Project responds to the need of finding and testing strategies and interventions that can be used by individuals, communities, organisations and the State when dealing with leprosy or impairment-related stigma. Different studies show evidence that people affected by leprosy are excluded, segregated and denied access to basic services. Stigma is one of the factors that have a strong impact on how governments, the society and individuals in general deal with the disease. Indonesia is one among many countries where leprosy-related stigma is a persistent social problem that needs attention.

Governmental and non-governmental organisations are still looking for strategies that can reduce stigma and its impact on the lives of people. Previous studies have shown certain strategies, such as counselling, socio economic rehabilitation and contact to be effective in reducing stigma against people with mental illness or HIV. The current study aimed to adapt and use interventions based on these strategies and evaluate their impact on stigma against participants affected by leprosy.

The SARI Project worked with communities in Cirebon, West Java, Indonesia. Using a participatory approach, the project first collected information regarding the general living situation of the persons affected by leprosy. Such information helped to improve the measurement instruments and to develop locally appropriate interventions in line with the above strategies.

The project was monitored continuously and evaluated after two years. The results show that all three interventions had a positive impact in the lives of many participants, reducing the all types of stigma and increasing self-confidence, personal motivation, quality of life and social participation. Participants also appreciated the information about leprosy they received. The counselling sessions gave people opportunities to share experiences and to gain self-confidence and learn about the disease, human rights and life skills in general.

The final results have been shared with the academic community and the social actors involved, in workshops organized in Cirebon and Jakarta. A unique aspect of this project is that it combined research (three PhD students carried out academic research) and action that intended to benefit all participants and especially the people affected by leprosy, their families and communities. FKDC, a DPO in Cirebon, that four of the research assistants are members of, has agreed to continue developing work in the field of leprosy once the project has ended.

3.2 Building Responses in Diverse Global Enabling Settings (BRIDGES): Brazilian and Indonesian community programmes sharing experiences to generate knowledge towards Inclusive CBR

Coordination:	Dr Beatriz Miranda
Institute:	Disability Studies in The Netherlands
Grant:	€ 100,677
Started:	July 2015
Focus:	Brazil, Indonesia
Duration:	12 months

In view of leprosy as a medical-social public health problem, community based rehabilitation (CBR) could offer some hope for improving the lives of people affected by the disease. However, in community based initiatives sustainability is a common problem.

This research aims to generate knowledge about feasible and effective ways to achieve sustainability in CBR initiatives of persons affected by leprosy in Indonesia and Brazil. Given the difference in experiences and contexts in both countries, knowledge could be gained first, by looking at what is happening within each country and second, by learning between countries. Learning interaction which is required to succeed in such a venture must be exercised by the people affected by leprosy themselves. In view of this, three main problems appear: leprosy CBR initiatives that are still fragile; Inclusive (disability and leprosy) CBR experiences are also weak and infrequent; insufficient spaces exist for sharing knowledge

and developing an interactive learning process within countries and between countries that can strengthen such initiatives. Consequently, the current project was designed for Indonesia and Brazil to fill these gaps. The participatory research study aims to:

1. Explore general CBR initiatives existent in the countries selected looking at the specific topic of sustainability;
2. Analyse the lessons learned from those initiatives regarding sustainability;
3. Propose a kit of tools that can help CBR initiatives (especially small disabled people's organisations (DPOs) or those that are in process of strengthening) to explore, analyse and build on the component of sustainability.

While in Indonesia, the interest is in learning about sustainability from different CBR initiatives; Brazil will look only at the experience of leprosy self-help groups (SGH) and self-care groups (SCG) or other small-scale community-based organisations that provide a replicable model.

The main research question this participatory research study seeks to answer is: What lessons regarding sustainability can small DPOs, SGH and SCG leprosy and leprosy-inclusive CBR initiatives in Indonesia and Brazil learn from small DPOs, SCG/SHG or other groups in these countries in order to become sustainable in the future. It attempts to strengthen the capacity of leprosy and inclusive (disability and leprosy) CBR initiatives that are taking place in urban and rural areas in ex-colonies or communities where people affected by leprosy live in Indonesia and Brazil.

Projects covering research priority 5: Interrupt transmission

5.1 Macroepidemiology & Microepidemiology of Leprosy in Cebu, Philippines

Coordination:	Dr Marivic Balagon
Institute:	Leonard Wood Memorial Center for Leprosy Research
Grant:	€ 474,697
Started:	January 2011
Focus:	Philippines
Duration:	5 years
Co-Funder	Turing Foundation

The purpose of this project is to increase our knowledge about the spread of leprosy in Cebu. This information will help us understand the types of bacteria causing the disease and the types of leprosy prevailing in the island. It will also help us understand various factors affecting the spread of leprosy such as the source of infection, mobility of untreated patients, economic status of the population which affect their defence or vulnerability to the germs causing the disease and the role of funding support to sustain active (house-to-house visit) case finding activities within the community.

A better understanding on various factors affecting the spread of leprosy in the community will help to improve leprosy control strategies both locally and globally by redirecting attention to high risk populations (eg: children, family members, urban slum, etc.) who may need closer monitoring or intake of drugs that will protect them from developing leprosy.

The findings of the project suggest that despite the declining trend, the number of new leprosy cases detected each year and the average age of children developing the disease stays the same, suggesting that spread of leprosy in Cebu is still active and recent.

In addition, there seems to be a slight shift of leprosy towards the more severe type suggesting that a huge reservoir of infection is still present in the area. The substantial number of cases detected in recent years also confirms the importance of continued funding support to sustain active case finding activities.

5.2 International collaboration for translation of *Mycobacterium leprae* molecular viability assay (MVA) to the clinical setting and application of MVA to a chemoprophylaxis-of-contacts model

Coordination:	Dr Linda Adams
Institute:	National Hansen's Disease Programs
Grant:	€ 318,145
Started:	July 2015
Focus:	Ethiopia, Nepal, Philippines
Duration:	36 months
Co-funder:	Turing Foundation

Discerning the difference between live and dead bacteria is the most fundamental procedure in microbiology and has been one of the primary obstacles impeding research in leprosy. The inability to easily culture *M. leprae* and determine its viability makes monitoring the progress of treatment in patients challenging and limits the ability to design improved drug therapy regimens and chemoprophylaxis programs. It is difficult to follow the transmission of leprosy bacilli between individuals, and the contribution to leprosy pathology of the accumulation of large numbers of presumably dead bacilli in the nerves and skin of patients under therapy is not really understood. Modern molecular methods can bridge this gap with new technology that can better serve both persons affected by leprosy and leprosy workers in a variety of settings.

Recently, a reverse transcription-PCR based molecular viability assay (MVA) for *M. leprae* was developed by the research group and found to be rapid and accurate as a biological indicator of bacterial viability in experimental animal tissues. Therefore, with the ultimate goal of translating the MVA to the clinical setting, initial studies in animal models will be used to thoroughly define the technical limits of the MVA, to establish a standardized protocol and data reporting format, and to test potential chemo-prophylactic regimens.

Concomitantly, MVA analyses will be performed on a full range of patient specimens collected by laboratories in leprosy

endemic countries and training to their personnel will be provided to facilitate a rapid deployment of this new technology to clinical settings. Thus, the collaborators in this project will actively participate in testing their own samples and gain the expertise and resources necessary to provide this service in their area as well as to educate others.

The MVA has great potential for determining *M. leprae* viability in clinical specimens. It could be invaluable for monitoring treatment efficacy and possible relapse, ultimately limiting transmission.
In addition, implementation of effective chemoprophylaxis in leprosy contacts could also significantly limit transmission. The sensitivity of the MVA lends well to experiments on new drug development, and MVA studies should allow establishment of a short-term model for chemoprophylaxis-of contacts and an objective definition of the most practical and effective drug regimens.

Ongoing projects

Immunopathology of leprosy: dissecting mechanisms of immune-mediated tissue damage in leprosy, and identification of new targets for intervention

Coordination:	Prof. Tom Ottenhoff
Institute:	Leiden University Medical Center
Grant:	€ 275,199
Started:	July 2011
Focus:	The Netherlands
Duration:	48 months
Co-funder:	Turing Foundation

Leprosy is a contagious disease caused by infection with the bacterium Mycobacterium leprae. M. leprae infects professional phagocytes such as macrophages, and also has a high affinity for Schwann cells. These cells form the myelin sheath surrounding peripheral nerves, which are thereby protected from harmful influences. The majority of individuals who come into contact with M. leprae is able to develop a protective immune response and to neutralize the bacteria, without further complications. A small percentage of infected people, however, develops clinical leprosy. There are different forms of the disease, with at one end of the spectrum multibacillary (MB) or lepromatous (LL), and on the other hand paucibacillary (PB) or tuberculoid leprosy (BT-TT). MB/LL patients develop diffuse forms of the disease, do not have adequate cellular immune responses to the bacillus and are therefore not able to eliminate it. PB/BT-TT patients, by contrast, develop a strong cellular response, and generally have small numbers of lesions containing little or no detectable bacteria. Between these two extremes the so-called borderline forms of leprosy are found. In almost all forms of leprosy nerve impairment and nerve damage is an important issue.

One of the biggest problems in leprosy are leprosy reactions. These are episodes of sudden greatly increased cellular immunity. Patients with reactions have a substantially increased risk of nerve damage, the main complication of leprosy. To prevent irreversible nerve damage and associated lifelong disabilities, it is important to gain a better understanding of the processes that underlie this phenomenon. Of critical importance in its prevention is also early diagnosis of the disease. The goal of this research project is to understand which immune cells and immune cell products (signalling molecules like cytokines) play a key

role in causing Schwann cell and nerve damage in leprosy. The research group's hypothesis is that dysregulation of the immune response against M.leprae is responsible for the uncontrolled inflammatory / immune response in leprosy reactions; and that unravelling the mechanisms involved will lead to the identification and development of new agents to treat leprosy reactions or even prevent it. It is postulated that the delicate balance between pro- and anti-inflammatory cells (macrophages and T cells) determines the outcome of the immune response against M.leprae, namely protection and adequate immunity or (severe) tissue damage due to an inadequate response (immunopathology). A better understanding of the mechanisms of nerve damage and leprosy reactions is also of importance in the identification of biomarkers for early diagnosis or prediction of leprosy (reactions), and to develop new treatments and better prevention of leprosy reactions.

In this project the subtle balance and cross-talk between different subsets of cell types in leprosy was studied, especially macrophage (MF1 / MF2) and T cell subsets (Treg, Th1 and Th17 / Th22) as well as human Schwann cells. These important cell types were studied by using state of the art immunological and cell biological techniques in combination with whole genome transcriptomics (mRNA expression using microarrays or RNAseq). The precise interactions and communication between these cells led to the discovery of a macrophage subset that is superior in controlling mycobacteria. Other subsets were found to induce regulatory T cell responses, which impair mycobacterial control. Ways to shift macrophage subsets towards the subset that is superior in controlling mycobacteria were also discovered, pointing towards the possibility of using this in therapeutic regimens. The cell biological processes which play a role in the infection of human Schwann cells and macrophages by live M. leprae bacilli were also examined. By assessing gene expression patterns and genetic screens, novel drug targets could be identified. Also novel compounds with efficacy against intracellular mycobacteria were discovered. This could pave the way for novel host directed therapies that can help controlling infection and preventing tissue damage, which is so characteristic of leprosy.

The project thus resulted in a better understanding of the immuno-pathogenesis of leprosy and leprosy reactions leading to nerve injury. Novel therapeutic strategies were discovered, which impact on inflammation and mycobacterial control. The research group has the ultimate future goal to develop better tools to predict, early-diagnose and prevent nerve damage in leprosy.

How mycobacteria lyse the phagosomal membrane

Coordination:	Prof. Peter Peters
Institute:	Maastricht University
Grant:	€ 446,828
Started:	January 2011
Focus:	The Netherlands
Duration:	48 months
Co-funder:	Turing Foundation

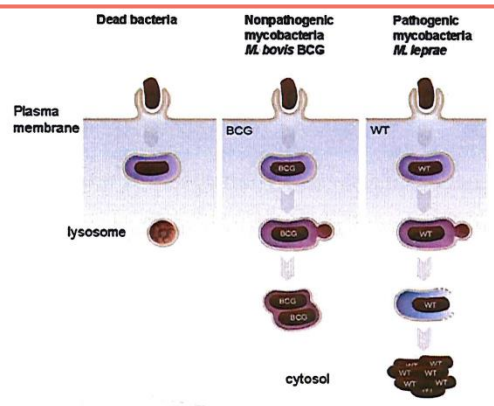
The research group has previously determined that the localisation of mycobacteria in host cells is dependent on a pump or 'needle of a syringe' called type 7 secretion system (T7SS). All mycobacteria that cause disease (pathogenic) have such a T7SS and use it to lyse a membrane that surrounds the bacteria after ingestion by its host cell. This membrane originates from the lysosome, an organelle in the cell that represents the stomach of the cell. By disrupting that membrane, pathogenic

mycobacteria can float freely in the cytosol (blue in the figure) and cause cell damage. The research group has shown that after uptake in the cell non-pathogenic mycobacteria like the vaccine strain BCG remain surrounded by the membrane. When the T7SS of pathogenic mycobacteria was introduced back in vaccine strain BCG, it changed its localisation and also lysed the membrane as the pathogenic bacteria.

With these results the group has established new tools for improving the BCG vaccine which is used to prevent tuberculosis and possibly leprosy. These diseases are caused by related bacteria: *Mycobacterium leprae* and *Mycobacterium tuberculosis.* Currently the vaccine for both diseases is the same and originates from another mycobacterium: *M. bovis.* After culturing *M. bovis* for several years in extreme conditions, scientists realized that the strain was no longer pathogenic but even protecting against (leprosy) infections. *M. bovis* had lost 13 regions of its genome and became known as the vaccine *M. bovis* BCG already in 1920.

An important deletion in the genome of BCG is the RD1 region also known as T7SS ESX1 that the group has shown to be essential for the localisation. Now the researchers demonstrate that BCG::ESX1 (BCG with the genes that form the T7S) has restored its capacity to lyse the stomach of the cell and therefore may boost the immune system much better. Others have shown that this candidate is more effective in preventing *M. tuberculosis* infections in laboratory animals and with the new data it is now understood how this new rBCG is improved.

However, the downside is that these strains may be too pathogenic for application as a human vaccine and thus this process needs to be further manipulated and reduce the pathogenicity without affecting its localisation in a cell. The research group has identified the factors that facilitate the localisation, giving them tools to manipulate these characteristics to apply these in a novel vaccine.



Uptake of bacteria (brown) in cells. Dead bacteria are taken up and degraded by the lysosomes (stomach) of the cell (left panel). B Vaccine strain BCG are taken up and slowly degraded (middle panel). Bacteria that cause disease lyse the membrane and float in the cytosol (right panel) multiply fast and kill the host cell two day's later in order to reinfect other cells.

6. Future perspectives

The call for proposals to be financed under the LRI 2017 budget was published December 2015. This call included a special invitation for proposals on priority area 4, Prevention of Disabilities and proposals from African researchers, since these were so far underrepresented among the previously approved projects. Decisions about approvals

for the budget 2017 are planned in the Executives Group meeting of November 2016.

In 2016 the LRI Spring Meeting will take place to enable project leaders to present interim results to the members of the Scientific Review Committee and Steering Committee. An important second objective of this meeting will be to promote interactions between researchers.

In 2016 the search for additional partners and new co-funders of LRI approved research projects will go on. The need and requests for leprosy-related research still exceeds the available budget of the LRI and its present co-funders.

7. Who is who in LRI

Executives Group

The LRI Executives Group (EG) consists of the executive directors of the LRI partners.

Mr B. Simmons	CEO, ALM
Mr B. Kömm	CEO, GLRA
Mr P. Derrick	CEO, effect:hope
Mr G. Warne	CEO, TLMI
Mr J. van Berkel	CEO, NLR (Chair)

Steering Committee

The LRI is guided by a Steering Committee (SC). The SC membership comprises the research consultants or coordinators of the LRI partner organisations (ex-officio) and an independent Chair. The current members are:

Prof. Dr W.C.S. Smith, OBE MD MPH PhD	Emeritus Professor of Public Health (Chair)
Dr W.H. van Brakel, MD MSc PhD	Research Coordinator, NLR (Secretary)
Dr P.R. Saunderson, MBBS MSc PhD	Medical Director, ALM
Dr C. Kasang, MSc PhD	Research Coordinator, GLRA
Dr T.P. Gillis, BSc MSc PhD	Research Coordinator, effect:hope
Assoc. Prof. Dr P. Kuipers, BA (Hons) MA PhD	Research Coordinator, TLMI

The LRI SC is responsible to LRI Executives Group (EG).

Scientific Review Committee

The quality, relevance and feasibility of submitted research proposals are assessed by the independent Scientific Review Committee (SRC), comprising experts in leprosy, clinical medicine, public health, rehabilitation and social sciences. This committee makes recommendations to the LRI EG concerning funding. The SRC also monitors the progress of the ongoing projects. The current SRC members are:

Prof. Dr W.R. Faber (Chair)	Emeritus Professor of Tropical Dermatology, Academic Medical Center, University of Amsterdam, The Netherlands
Dr F. van Dijk	Rehabilitation Physician at the Rehabilitation Centre Het Roessingh in the Netherlands
Dr G.J. Ebenezer	Associate Professor, Neurology Department, Johns Hopkins School of Medicine, USA
Dr B.E. Ebenso	Research Fellow, Leeds University, Institute of Health Science, United Kingdom
Prof. Dr V.P.M.G. Rutten	Associate Professor at Department of Infectious Diseases and Immunology, University of Utrecht, The Netherlands and Extraordinary Professor at Department of Veterinary Tropical Diseases, University of Pretoria, South Africa
Dr P.A.M. Schreuder	Medical doctor/leprologist (retired) with long leprosy control field work experience
Prof. Dr T.S. van der Werf	Pulmonologist, Head of the Infectious diseases Service & Tuberculosis unit at the University Medical Centre Groningen, The Netherlands

Office team

Nicole Dinnissen MSc	LRI Programme Officer
Tamara Prinsenberg MSc MPH	Research Funding Officer

8. Finance

Annual Accounts 2015 and Auditor's report

Contents

I. Balance sheet as at 31 December 2015

Amounts in Euros

	Notes	31 December 2015		1 January 2015	
ASSETS					
Fixed assets	1.				
Tangible fixed assets		€ 0		€ 0	
			€ 0		**€ 0**
Current assets	2.				
Contributions due		€ 20,000		€ 0	
Funds and accounts to be received from NLR		€ 481,161		€ 258,137	
Paid in advance		€ 191,099		€ 0	
Cash and cash equivalents		€ 11,767		€ 0	
			€ 704,027		**€ 258,137**
Total assets			**€ 704,027**		**€ 258,137**
LIABILITIES					
Reserves	3.				
Continuity reserves		€ 0		€ 0	
Earmarked reserves		€ 417,195		€ 0	
			€ 417,195		**€ 0**
Short-term liabilities	4.				
Accounts payable			€ 286,832		€ 258,137
Total liabilities			**€ 704,027**		**€ 258,137**

Annual Accounts LRI 2015

II. Statement of Income and Expenses for the year 2015

Amounts in Euros

	Notes		Realisation 2015		Budget 2015
Income	5.				
Income from contributors		€	1,317,636	€	1,142,000
Other income		€	23,118	€	25,000
Total income		**€**	**1,340,754**	**€**	**1,167,000**
Expenses	6.				
Research project costs		€	720,832	€	982,000
Staff costs, housing and office costs		€	178,426	€	174,000
Other operating expenses		€	24,301	€	11,000
Total expenses		**€**	**923,559**	**€**	**1,167,000**
Result of income and expenses		**€**	**417,195**	**€**	**0**

III. Notes accompanying the annual account for 2015

a. General and accounting policies

This is the first annual account of 2015 of LRI (Leprosy Research Initiative). LRI has been registered since June 1st 2015 as a Foundation under Dutch law. Due to the fact that the LRI has taken over all activities from the 1st of January of 2015 from NLR, the annual account is presented for the year 2015, started on the 1st of January and ended December 31st.

Activities
LRI (Leprosy Research Initiative) is a combined venture of NLR, American Leprosy Missions (ALM), German Leprosy and Tuberculosis Relief Association (GLRA), effect:hope (The Leprosy Mission Canada) and The Leprosy Mission International (TLMI). Guided by an allied policy with clearly defined research priorities, the partners have established a joint fund to support leprosy research. The joint fund is reserved for research that is exclusively or strongly related to leprosy. A comprehensive explanation of our mission and goals and a detailed account of the content of our workcan be found in our annual report.

LRI work proceedings and work activities
The LRI has all its work proceedings and activities fully delegated to NLR. NLR runs the Leprosy Research Initiative's secretariat and all work proceedings and activitities are also performed by NLR. The Supervisory Board of NLR supervises the proceedings and activities as reported by the NLR Director.

Registered address
The registered and actual address of the LRI is Wibautstraat 137k, 1097 DN in Amsterdam, Netherlands.

The annual accounts have been prepared on a historical cost basis of accounting.

Accounting period
The annual accounts have been drawn up by reference for an accounting period of one year. The financial year is equal to the calendar year.

Comparison with prior year(s) and opening balance
On January 1st 2015, LRI has taken over all activities that fall within the objectives of LRI from NLR, including assets and liabilities. NLR is in debt to the amount of €258,137 towards LRI. This amount consists of the accumulated income from the funding of research projects received by NLR from future LRI partners in prior years. This amount was taken under the short term liabilities (debt to LRI partners) and under the receivables (claim on NLR) on 1 January 2015. These funds are allocated for specific research projects and for funding of the current research projects, to grant new projects and for the running costs of the LRI foundation. The comparison with 1 January 2015 is shown on the balance sheet of the annual accounts. Because this is the first annual account of the LRI no comparison with prior year(s) is done.

Budget comparison
Due to the start up year of the LRI no formal budget for the LRI was drawn up. The NLR approved budget for 2015 included the expenses and income for (scientific) research, which in 2015 falls under the Leprosy Research Initiative (LRI), the budget used in these annual accounts for 2015 were formally budgeted under the NLR budget.

Accounting policies for the valuation of assets and liabilities and the determination of the result
The annual account has been prepared in accordance with Dutch GAAP (General Accepted Accounting Principles). All amounts in the annual accounts are in Euros or a multiple of 1,000 Euro, or rounded to the nearest amount in Euros. The amounts are compared to the part for research activities and objectives from the formal NLR budget for 2015 (approved by the Supervisory Board in December 2014).

The financial statements have been prepared in accordance with the principle of continuity.

Income from funding and the allocation of funds
Each LRI partner has committed an annual contribution to the LRI research fund and contributes an equal share to the LRI running costs. The income from partners, associate partners, contributors and co-financiers are recognised in the year to which the item of income relates and are allocated to the year in question on a actual cost basis. The income is shown gross, before any deduction of associated costs, unless otherwise is stated. Necessary costs to realise certain benefits, are presented in the statement of income and expenses as expense.

Accounts receivable
Receivables are initially valued at the fair value of the consideration to be received, including transaction costs if material.

Cash and cash equivalents
Cash and cash equivalents include cash and bank balances and are immediately accessible. LRI does not have any borrowings or loans. LRI does not invest nor does it make use of any financial instruments.

General note on the balance sheet and statement of income and expenses
In general, assets and liabilities are stated at the amounts at which they were acquired or incurred, or current value. If not specifically stated otherwise, they are recognised at the amounts at which they were acquired or incurred. The balance sheet and statement of income and expenses include references to the notes. Notes to the line items of the balance sheet and the statement of income and expenses have been numbered in the financial statements.

Foreign currency
Transactions in foreign currency are converted to Euro at the exchange rate of the transaction date.

Reserves
LRI ensures that contributions are used for the intended cause. If more money was received for a specific research project than needed in that particular year for that project, the LRI will allocate this money to the same project in the following year. If LRI no longer supports the project the following year, LRI will use the funds for a similar project. In the event there are no such projects, we will deposit the money in the general joint fund or refund this to the contributor. The reserves is the result of income and expenses and is held in accordance with budgets for (scientific) research and running costs of the LRI for future years to ensure sustainability of the LRI so that its projects proceedings and activitities are not affected and to grant new research project proposals. The surplus amounts are retained in as safe as possible bank accounts with trustworthy banks. From the result of 2015 an earmarked reserve is formed. The earmarked reserve consists of reserves set aside for specific projects and the reserves set aside for the purpose of funding the LRI activities. The LRI holds no investments.

Management of the LRI and remuneration of Supervisory Board and Executive Group
As a Foundation the LRI is managed by the director of Netherlands Leprosy Relief (NLR), implementing the decisions of the LRI Executive Group and supervised by the Supervisory Board of NLR. No remuneratrion was paid to the Supervisory Board members and Director of NLR, and no loans, advances or guarantees were given. In 2015 no expenses were reimbursed.

Publication
This report is available on www.leprosyresearch.org. The 2015 annual report and the annual accounts are available in a digital format primarily for environmental reasons. A (free of charge) printed copy can be obtained on request.

III b. Notes to the Balance sheet 2015

1. Tangible fixed assets

Tangible fixed assets are used for the main activities and entirely held for operational management. The LRI holds no tangible fixed assets and therefore this is not valued in 2015.

2. Receivables

All receivables are due within one year.

	31 December 2015	1 January 2015
	in €	in €
Contributions due	20,000	0
Funds and accounts to be received from NLR	481,161	258,137
Paid in advance	191,099	0
Cash and cash equivalents	11,767	0
	704,027	**258,137**

The item contributions due relates to the supporting fund from TLM Ireland for the running costs of the LRI for the year 2015. This is expected but not yet received income from partners. The income from contributions are accounted for once the commitment has been confirmed.

The item amounts to be received from NLR relates to the funds and accounts to be received from NLR. On January 1st of 2015, the LRI has taken over all activities that fall within the objectives of LRI from NLR, including assets and liabilities. The amount of €258,137 reflects the amount that is to be received from NLR and consists of the amounts that are received in advance from LRI partners (see under liabilities).

The paid in advance amounts, also prepayments, which are already effectuated in 2015, are payments to research institutes for the first quarter of 2016.

Cash and cash equivalents are cash and bank balances in Euros in the Netherlands held by the LRI office in Amsterdam. The balance of cash and cash equivalents is immediately available. LRI holds its main current account at ING Bank (NL). The cash and cash equivalents balance for the year ended 31 December 2015 is €11,767.

3. Reserves

The reserves are the result of income and expenses and are held in accordance with budgets for (scientific) research and running costs of the LRI for future years to ensure sustainability of the LRI so that its projects proceedings and ongoing activitities are not affected and also to grant new research project proposals.

	31 December 2015	1 January 2015
	in €	in €
Earmarked reserves	417,195	0
	417,195	**0**

General notes on the reserves
In 2015 several projects started later due to the official start-up of the LRI from June 2015, therefore the actual total amount spent was lower than the total amount of allocated projects, which resulted in this scope of amount of reserves and funds. The result of 2015 arrived at €417,195. This amount is added to the earmarked reserves of LRI.
- LRI ensures that contributions are used for the intended cause. If more money was received for a specific research project than needed in that particular year for that project, the LRI will allocate this money to the same project in the following year. From the total amounts received in 2015, a few partners contributed to specific research projects which remained unspent in 2015. The majority of these funds has been allocated to activities in 2016. These consists of financing the current projects, award new research projects and a proportional part for financing the LRI organisation.
- LRI holds no continuity reserve.

The LRI's reserves are as follows:

	Continuity reserves	Earmarked reserves	**Total**
	in €	in €	in €
Balance as per 1 January 2015	0	0	0
- Movements	0	0	0
- Withdrawals and additions	0	417,195	417,195
Balance as per 31 December 2015	**0**	**417,195**	**417,195**

4. Short-term liabilities

All current liabilities fall due in less than one year. The fair value of the current liabilities approximates the book value due to its short-term character.

	31 December 2015	**1 January 2015**
	in €	in €
Accounts payable/creditors	286,832	258,137
	286,832	**258,137**

On January 1st of 2015, the LRI has taken over all activities that fall within the objectives of LRI from NLR, including assets and liabilities. The amount of €258,137 consists of amounts that are received in advance from LRI partners.

Accounts payable are mainly amounts payable for (scientific) research in 2015, not yet formally invoiced by the researchers and institutes concerned. This item also concerns bank charges and audit fees. Also the unspent funds (€16,000) for two projects that ended in 2015 are taken under this amount and will be refunded to contributor Turing Foundation.

III c. Notes to the Statement of Income and Expenses 2015

Amounts in Euros

5. Income

Each LRI partner has committed an annual contribution to the joint LRI research fund and contributes an equal share to the LRI running costs. In 2015 the current partners are: Netherlands Leprosy Relief (NLR), American Leprosy Missions (ALM), German Leprosy and Tuberculosis Relief Association (GLRA/DAHW), effect:hope (The Leprosy Mission Canada), The Leprosy Mission International (TLMI), Austrian Leprosy Relief Association (ALRA) and The Leprosy Mission Ireland (TLM Ireland). The amount mentioned under Others is the total amount from partners received in advance before 2015 and taken over from NLR at Januari 1st 2015.The breakdown of the total income is as follows:

		Realisation 2015	**Budget 2015**
		in €	in €
Income from contributors	ALM	187,920	188,000
	ALRA	59,129	0
	effect:hope	128,000	128,000
	GLRA/DAHW	180,000	178,000
	TLM International	130,000	128,000
	TLM Ireland	20,000	20,000
	NLR	390,000	400,000
	Others	222,587	100,000
Other income	Turing Foundation	23,118	25,000
		1,340,754	**1,167,000**

The total amount available for allocation in line with the objectives for 2015 arrived at: €1,340,754.

The realisation of the total income in 2015 was 15% higher than budgeted due to the outstanding balances from contributors and the income received in advance in 2014 for 2015. From the Turing Foundation we received a contribution for the running costs of the LRI to the amount of €23,118. This actual contribution was slightly lower than budgeted (€25,000) this is because the Turing Foundation contributes five percent of their actual co-funded allocated budget on project funding towards runnings costs as realised at the end of the year 2015. The total amount allocated to the research projects by the Turing Foundation was €457,502 in 2015.

6. Expenses

The expenses involves mainly the funding of (scientific) research project costs. A total of 12 new projects started in 2015. 5 projects were ongoing with start dates before 2015 under NLR. Please refer to the overview of research costs on page 11 for the specification of the project expenses. The LRI has spent a total of €923,559 on research funding and running costs in 2015.

	Realisation 2015	**Budget 2015**
Research	in €	in €
- Research projects funding	720,832	982,000
	720,832	**982,000**

The actual research project costs were 27% lower than budgeted due to the start-up of the LRI which was in the middle of the year and therefore several projects started later with their activities. However the budgets for the research projects are year budgets and also allocated yearly, and from the moment a proposal is granted the project should start within six months. The research project overview on page 11 specifies the granted funds per (scientific) research project.

Including the amount co-financed by Turing Foundation the total budget allocated under the LRI policy in 2015 sums up to €1,178,334.

	Realisation 2015	Budget 2015
Running costs	in €	in €
- Staff, housing and office costs	178,426	174,000
- Other operating expenses	24,301	11,000
	202,726	**185,000**

LRI has no staff members, all staff is employed by NLR. Due to this fact, NLR runs the LRI's secretariat, therefore the running costs mainly involves wages, salaries, pension costs (insured with Pensioenfonds Zorg en Welzijn), social security charges to the amount of €178,426 and other charged support costs for the LRI secretariat officers to the amount of €24,301. These costs are reimbursed by NLR. In 2015 on average equivalents 1.94 fte were employed via NLR in the LRI secretariat in Amsterdam. The LRI has no staff employed abroad during 2015. For the LRI secretariat officers the NLR standard terms, benefits and conditions of employment apply.

In 2015 there was a major increase of other operating expenses compared to the budget, this was due to the start-up costs of the LRI foundation, which mainly consist of legal fees. The other expenses involves the costs for translation of legal documents, audit fees, bank and postage costs and maintenance costs for the website.

The staff costs for the LRI officers arrived at €136,329 and can be specified as follows:

	Realisation 2015	Budget 2015
	in €	in €
Wages and salaries	105,255	105,000
Social security costs	16,630	17,000
Pension contributions	11,042	13,000
Other personnel costs	3,402	4,000
	136,329	**139,000**
Number of LRI employees on Dec. 31	2	3

In addition to these staff costs for the LRI officers, the running costs also consist of the housing and general office expenses that cannot be directly allocated to the research projects. The other charged support costs involves the housing and general office expenses at €42,098 in 2015. The total staff costs of the LRI amount to €178,426. This was slightly up by 2% compared to the budget. The expenditure on total running costs arrived at almost 10% higher than budgeted due to start-up costs of the LRI which mainly consist of legal fees. Due to lower expenditure in the first start-up year (27% lower than budgeted) to research projects, the running costs arrived at 22% of the realisation of total expenses, which is 6% higher than budgeted for 2015.

The Director of NLR and the Supervisory Board of the NLR and the Executive Group of the LRI, do their work on a voluntary basis and do not receive any remuneration for their activities.

pwc

Independent auditor's report

To: the director of Stichting Leprosy Research Initiative

Report on the financial statements 2015

Our opinion

In our opinion the accompanying financial statements give a true and fair view of the financial position of Stichting Leprosy Research Initiative as at 31 December 2015, and of its result for the year then ended in accordance with the Guideline for annual reporting 640 'Not-for-profit organisations' of the Dutch Accounting Standards Board.

What we have audited

We have audited the accompanying financial statements 2015 of Stichting Leprosy Research Initiative, Amsterdam ('the foundation').

The financial statements comprise:

- the balance sheet as at 31 December 2015;
- the statement of income and expenditure for the year then ended;
- the notes, comprising a summary of the accounting policies and other explanatory information.

The financial reporting framework that has been applied in the preparation of the financial statements is the Guideline for annual reporting 640 'Not-for-profit organisations' of the Dutch Accounting Standards Board.

The basis for our opinion

We conducted our audit in accordance with Dutch law, including the Dutch Standards on Auditing. Our responsibilities under those standards are further described in the section 'Our responsibilities for the audit of the financial statements' of our report.

We are independent of Stichting Leprosy Research Initiative in accordance with the 'Verordening inzake de onafhankelijkheid van accountants bij assurance-opdrachten' (ViO) and other relevant independence requirements in the Netherlands. Furthermore, we have complied with the 'Verordening gedrags- en beroepsregels accountants' (VGBA).

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Ref.: e0385369

PricewaterhouseCoopers Accountants N.V., Thomas R. Malthusstraat 5, 1066 JR Amsterdam, P.O. Box 90357, 1006 BJ Amsterdam, The Netherlands
T: +31 (0) 88 792 00 20, F: +31 (0) 88 792 96 40, www.pwc.nl

pwc

Unaudited corresponding figures

We have not audited the financial statements 2014. Consequently, we have not audited the corresponding figures included and the related notes.

Responsibilities of the director

The director is responsible for:

- the preparation and fair presentation of the financial statements in accordance with the Guideline for annual reporting 640 'Not-for-profit organisations' of the Dutch Accounting Standards Board; and for
- such internal control as the director determines is necessary to enable the preparation of the financial statements that are free from material misstatement, whether due to fraud or error.

As part of the preparation of the financial statements, the director is responsible for assessing the foundation's ability to continue as a going concern. Based on the financial reporting framework mentioned, the director should prepare the financial statements using the going-concern basis of accounting unless the director either intends to liquidate the foundation or to cease operations, or has no realistic alternative but to do so. The director should disclose events and circumstances that may cast significant doubt on the foundation's ability to continue as a going concern in the financial statements.

Our responsibilities for the audit of the financial statements

Our responsibility is to plan and perform an audit engagement to obtain sufficient and appropriate audit evidence to provide a basis for our opinion. Our audit opinion aims to provide reasonable assurance about whether the financial statements are free from material misstatement. Reasonable assurance is a high but not absolute level of assurance, which makes it possible that we may not detect all misstatements. Misstatements may arise due to fraud or error. They are considered to be material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of the financial statements.

A more detailed description of our responsibilities is set out in the appendix to our report.

Amsterdam, 19 July 2016
PricewaterhouseCoopers Accountants N.V.

Original has been signed by J.L. Sebel RA

pwc

Appendix to our auditor's report on the financial statements 2015 of Stichting Leprosy Research Initiative

In addition to what is included in our auditor's report, we have further set out in this appendix our responsibilities for the audit of the financial statements and explained what an audit involves.

The auditor's responsibilities for the audit of the financial statements

We have exercised professional judgement and have maintained professional scepticism throughout the audit in accordance with Dutch Standards on Auditing, ethical requirements and independence requirements. Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error. Our audit consisted, among other things of the following:

- Identifying and assessing the risks of material misstatement of the financial statements, whether due to fraud or error, designing and performing audit procedures responsive to those risks, and obtaining audit evidence that is sufficient and appropriate to provide a basis for our opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the intentional override of internal control.
- Obtaining an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the foundation's internal control.
- Evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures made by the director.
- Concluding on the appropriateness of the director's use of the going concern basis of accounting, and based on the audit evidence obtained, concluding whether a material uncertainty exists related to events and/or conditions that may cast significant doubt on the foundation's ability to continue as a going concern. If we conclude that a material uncertainty exists, we are required to draw attention in our auditor's report to the related disclosures in the financial statements or, if such disclosures are inadequate, to modify our opinion. Our conclusions are based on the audit evidence obtained up to the date of our auditor's report and are made in the context of our opinion on the financial statements as a whole. However, future events or conditions may cause the foundation to cease to continue as a going concern.
- Evaluating the overall presentation, structure and content of the financial statements, including the disclosures, and evaluating whether the financial statements represent the underlying transactions and events in a manner that achieves fair presentation.

We communicate with the director regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant deficiencies in internal control that we identify during our audit.

Overview of research projects with budget comparison 2015

Amounts in Euros

Project number	1. Current research projects	Budget 2015	Allocation 2015	Realisation 2015*)	In % of the budget
709.00.22	DSiN/Stigma Assessment and Reduction of Impact, follow up (2010-2016)	25,030	25,030	22,452	
701.03.52	KIT/Treatment of Early Neuropathy in Leprosy Trial (2010-2016)	73,195	82,050	81,022	
701.05.20	LWM/Macro and micro epidemiology of leprosy in Cebu (2011-2016)	45,822	45,822	45,859	
702.02.72	LUMC/Immunopathology of leprosy, follow up (2011-2015)	18,750	18,750	19,805	
702.03.32	UM/How mycobacteria lyse phagosomal membrane (2011-2015)	55,976	55,976	59,399	
703.15.01	INF/Delays in diagnosis & treatment (April 2015-Jan 2018)	24,600	36,275	36,457	
703.15.10	TLMB/Contact cohorts (1 May 2015- Oct 2016)	55,000	27,689	27,689	
703.15.47	TLMB/Trial for effective plantar pressure (6 April 2015- March 2016)	21,600	21,384	21,384	
703.15.05	IDRI/Integration of rapid diagnostic tests to (1 May 2015- April 2019)	50,000	33,612	33,691	
703.15.50	DSiN/BRIDGES 1 July 2015 - June 2016	100,000	51,206	36,888	
703.15.07	EUR/Field evaluation of novel immunodiagn. (Jan 2015- Dec 2018), INDIGC	187,000	162,578	162,579	
703.15.25	GHI/Earlier detection of leprosy (1 June 2015 - March 2016)	26,000	19,771	19,838	
703.15.40	LSHTM/Developm. & validation severity scale ENL (May 2015 - April 2016)	40,000	59,128	59,129	
703.15.43	HSRA/Internat.collaboration for translation of Mleprae (July 2015- June 2018)	53,000	37,249	37,249	
703.15.15	TLM India/Comparison of 3 types targeted community (Sept 2015- Aug 2018)	27,000	28,775	25,992	
703.15.45	FIOCRUZ/Evaluation of the qPCR in household contact (Aug 2015- July 2018)	20,000	19,046	19,115	
703.15.41	TLM Nepal/Helminth influences in leprosy (sept 2015- Aug 2019)	50,000	5,561	5,561	
703.15.13	KIT/The neuropathic foot in Indonesia: (July 2015-July 2018)	50,000	0	0	
703.15.39	LEPRA/Health systems research (SPECDEL study)/2015	12,000	0	0	
703.15.14	ICDDRB/Breaking the barriers: Use ICT approaches (2015)	30,000	0	0	
709.00.20	Scientific Review Committee Spring & Autumn meeting	10,000	10,000	6,723	
709.99.99	LRI secretariat	7,027	0	0	
	Total research costs for current projects	**982,000**	**739,902**	**720,832**	-35%
	2. Running costs (staff, housing and office costs)	**174,000**	**164,000**	**178,426**	3%
	3. Other operating expenses	**11,000**	**25,000**	**24,301**	53%
	SUBTOTAL	1,167,000	928,902	923,559	-26%
	TOTAL	**1,167,000**	**928,902**	**923,559**	-26%

*) The realisation is including co-financing from Turing Foundation (€457,502) and ALRA (€59,129)

LEPROSY RESEARCH INITIATIVE

Budget Stichting Leprosy Research Initiative (LRI) 2016

Amounts x €1,000/ in Euro thousands

Main Group	Specification	Budget 2016	Realisation 2015	Budget 2015
Income:				
-Income from contributors *)	ALM	266	188	188
	GLRA/DAHW	176	180	178
	NLR	390	390	400
	effect:hope	126	128	128
	TLM International	126	130	128
	TLM Ireland	20	20	20
	ALRA	0	59	0
	Others	0	223	100
- Other income	Turing Foundation	25	23	25
Sum of income		**1,129**	**1,341**	**1,167**

Expenses:	Budget 2016	Realisation 2015	Budget 2015
Expenses on the Objectives:			
-Research project costs	1,338	721	982
TOTAL RESEARCH PROJECTS BUDGET	1,338	721	982
	1,338	**721**	**982**
-Running costs (via NLR) and other operating expenses	192	203	185
	192	**203**	**185**
Sum of expenses	**1,530**	**924**	**1,167**
Result	**(401)**	**417**	**0**

Accumulated joint fund balance 2015	**0**
Accumulated joint fund balance 2016	**417**

*) Turing Foundation has cofinanced a total of €457,502 to research projects in 2015. The total allocated funding, including cofinancing by Turing Foundation via the LRI is €1,575,502 in 2015.

Multi Annual Budget Stichting Leprosy Research Initiative (LRI) 2016-2018

Amounts x €1,000/ in Euro thousands

This overview shows the budget and projection for the upcoming three years:

	Budget 2016	Projection 2017	Projection 2018
Income:			
Income from contributors	1,129	1,165	1,165
Sum of income	**1,129**	**1,165**	**1,165**
Expenses:			
Expenses on the Objectives:			
- Approved Leprosy research projects (ongoing)	1,338	856	605
- Funding of new research projects		97	348
	1,338	**953**	**953**
Running costs	**192**	**212**	**212**
	192	**212**	**212**
Sum of expenses	**1,530**	**1,165**	**1,165**
Result	**(401)**	**0**	**0**

Leprosy Research Initiative (LRI)

Management Board	**From**
Netherlands Leprosy Relief (NLR)	1-6-2015

Executives Group

The LRI Executives Group (EG) consists of the executive directors of the LRI partners.

Mr B. Simmons
Chief Executive Officer; American Leprosy Missions

Mr B. Kömm
Chief Executive Officer; German Leprosy Relief Association

Mr P. Derrick
Chief Executive Officer; effect:hope The Leprosy Mission Canada

Mr G. Warne
Chief Executive Officer; The Leprosy Mission International

Mr J. van Berkel
Chair; Netherlands Leprosy Relief