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Protocol

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Protocol for: Boumediene F, Cchour C, Chivorakoun P, et al. Community-based management of epilepsy in Southeast Asia: two intervention strategies in Lao PDR and Cambodia and Cambodia.

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ECLAIR - Epilepsy Cambodia LAos InteRvention

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- Field Team: 1 assistant, 1 provincial Coordinator, 3 neurologists, 4 qualified physicians, 17 employees Primary Health Centers (PHC), 30 local volunteers
- Principal investigator: Channara Chour

Laos team:

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- Principal investigator: Phetvongsinh Chivorakoun

Introduction

The **ECLAIR** research program is research aiming to improve access to healthcare for persons with epilepsy in South-East Asia, particularly in Cambodia and Laos. To do this, it draws on the concept of Domestic Health Visitors (DHV) developed in Prey Veng (Cambodia) in 2012 [1]. A response to a call for projects in August 2013 resulted in a reinforcement to the research program thanks to a contract covering of a very large part of the Laos program with Grand Challenges Canada (GCC). Thus, this program entails a comparative approach that is very relevant. ECLAIR therefore covers the coordination and the scientific objectives defined in this document in the two countries mentioned.

Context

The primary objective is to develop an intervention strategy to significantly improve the management of people with epilepsy in developing countries. In Cambodia and Laos, we have already observed that the barriers to diagnostic access as well as treatment (and clinical follow up) translate into a treatment gap of more than 90% in Laos and 66% in Cambodia. The baseline epilepsy prevalence in Cambodia is 5.8% [1] and 7.7% in Laos [2]; in other words, it is estimated that there are 86,000 persons with epilepsy in Cambodia and 51,000 in Laos, respectively. The stigma, in these relatively close socio-cultural contexts, is expressed in very diverse ways depending on the measurement of the stigma and/or discrimination or the segregationist attitude of the general population. The divergence in the results of recent surveys [1.2.3] shows the value of a comparative approach using identical indicators. The ECLAIR program therefore engages in a comparative approach that evaluates the efficiency of new territorial practices with an assumption. in the health access chain, the identification of people with epilepsy and the dispensing of treatment is optimized by the presence of DHV in villages. These DHV can be (i) local volunteers and/or (ii) a part of the Primary Health Care (PHC) staff.

Primary objective

The program's primary objective is to reduce the epilepsy treatment gap by 25% in the pilot area in comparison with the control area in each of the two countries: Laos and Cambodia

Primary evaluation criteria: increase in the number of patients receiving treatment.

Secondary objectives:

- 1- Reduce stigma
- 2- Increase adherence to treatment
- 3- Improve knowledge on epilepsy in key actors

Secondary evaluation criteria:

- 1- Stigma evolution according to Jacoby scale
- 2- Adherence evolution according to Morisky scale
- 3- Cost-effectiveness evaluation according to ICER (Incremental Cost-effectiveness Ratio)
- 4- Changes in knowledge and perception in each type of actors

General presentation

Our interventional research should help evaluate new strategies for access to epilepsy diagnosis and treatment adapted to the actual health care systems in place in the country (infrastructure and medical demographics, legislation, traditional practices, etc.):

(*) In the current health care system in Cambodia, an intervention including local volunteers (Voluntary Health Support Group – VHSG) allows for intervention through the mobilization of a permanent village stakeholder. These volunteers undergo training allowing them to obtain the DHV

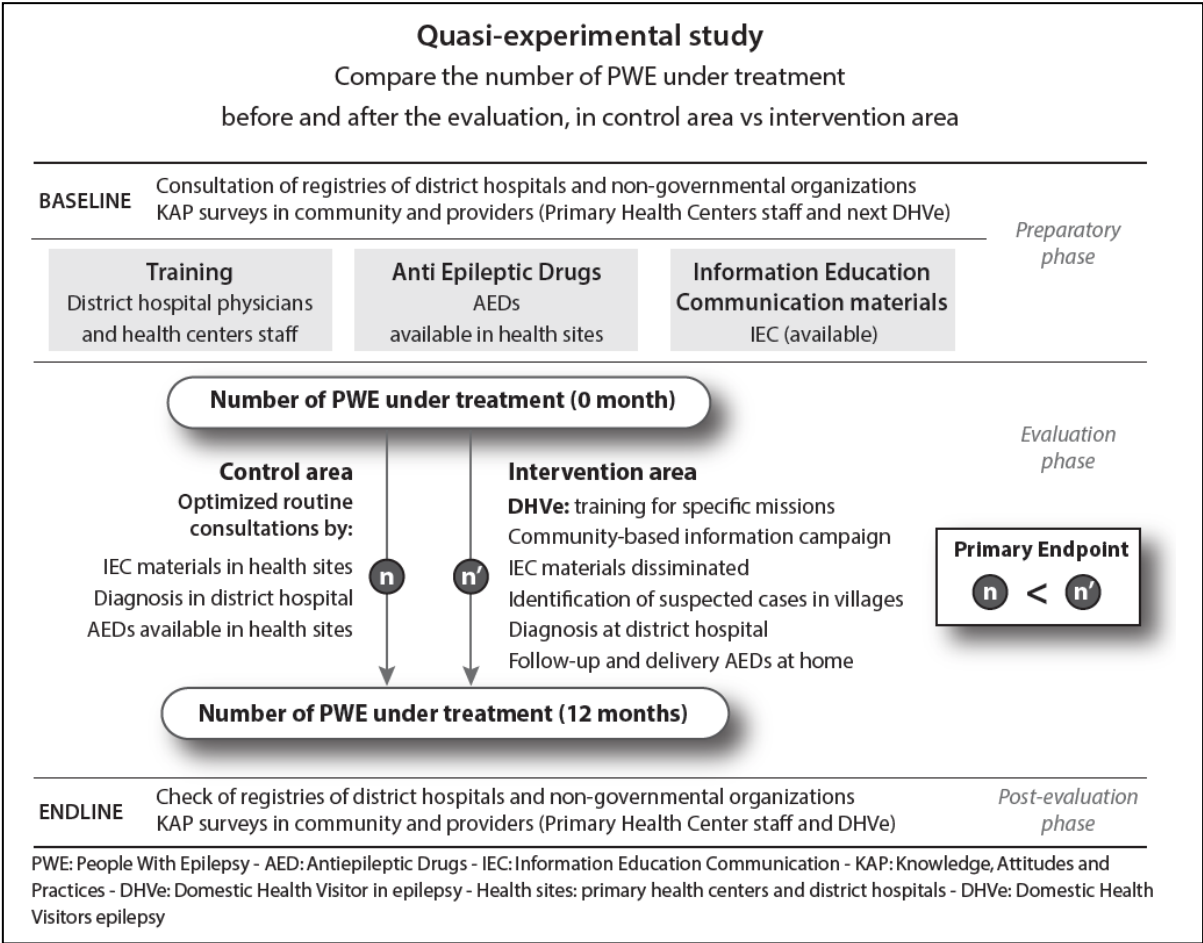
status. Once trained and provided with specific tools for Information, Education & Communication (IEC), they will carry out awareness programs and help with health care access in their respective villages. Over the course of this training, they will also acquire the skills to identify people that may have epilepsy. This patient identification process involves regular contact with qualified persons (village chiefs, religious leaders, teachers) and the local community. The summary of this activity is then periodically referred to staff working in the PHC.

(**) In Laos, the PHC staff undergoes this training in order to acquire the DHV status. Then, for a part of their work week (2 days per week), they periodically visit the villages in order to organize public meetings and to identify people who may have epilepsy.

With both intervention strategies, suspected cases will then benefit from a consultation with a trained physician (validated by a neurologist) in order to make a diagnosis and to provide them with a prescription. The DHV will then provide follow up for those people with epilepsy and will deliver their treatment to their homes.

General methodology

The DHV’s intervention (therefore after the necessary training to implement the program) is planned over a period of 12 months. The procedure being followed in each country is summarized in the following diagram:



The effectiveness of our intervention is measured using a **comparative approach** between an area where the intervention is implemented and another one where we only observe the current health

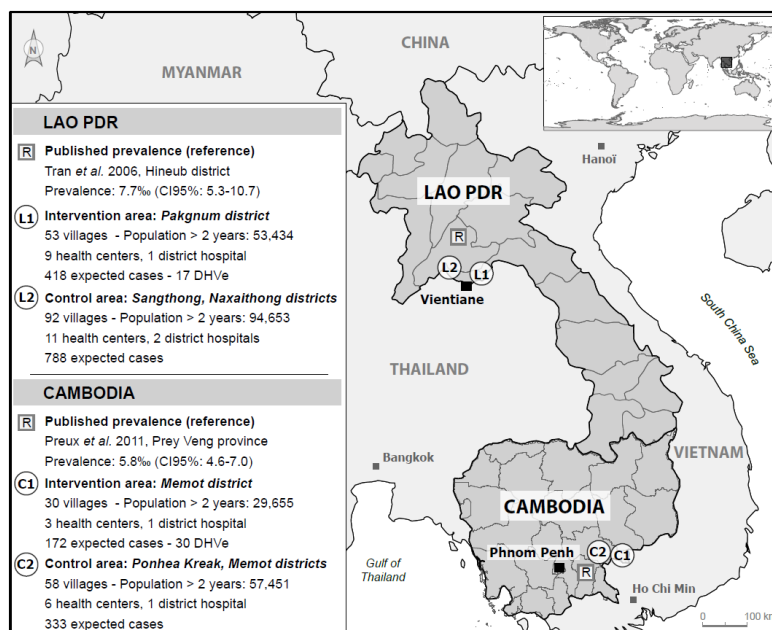
care system. Thus, in each country, the intervention is evaluated according to an **intervention area/control area** approach and on the program's global scale, we will measure the efficiency of our interventions by using a cost/effectiveness approach:

- of DHVs from PHC staff (PakNgum district, Laos)
- of DHVs from VHSG (Memot district, Cambodia)
- of the current operations in Laos (Naxaithong and Sangthong districts)
- of the current operations in Cambodia (Ponhea Kreak district)

The tools being implemented (training kits, IEC Materials, survey questionnaires, identification and follow up cards, treatment booklets, database for data collection, operating procedures) **are structurally identical for both countries**. The only differences are adaptations to better align with the local environment: training duration and frequency, target audience, translation, specific illustrations for the IEC materials, etc.

Presentation of investigated territories

In Laos, the three rural districts (1 intervention district and 2 control districts) are located on the opposite border of the Vientiane Capitale province. Directly to the west, there are 53,434 inhabitants in the intervention district (PakNgum) with 418 persons expected to have epilepsy. There are 1 district hospital and 8 PHCs including 53 villages in their jurisdiction. To the east of the province, there are 94,653 inhabitants in the two control districts (adjoining), Santhong and Naxaithong (with 788 persons expected to have epilepsy), for 2 district hospitals and 11 PHCs including 92 villages in their jurisdiction. In Cambodia, the rural districts are located in the Tboung Khmum province (formerly Kampong Cham) in the east of the country. The 30 intervention villages are located in the Memot district containing one district hospital and 10 PHCs. These 30 villages include 29,655 inhabitants with 172 people expected to have epilepsy. The control villages are located in the Ponhea Kreak and Memot districts containing one district hospital and 8 PHCs. The 58 selected villages (selected at random) include 57,451 inhabitants (with 333 persons expected to have epilepsy).



The number of needed subjects was estimated targeting a 25% relative reduction of the treatment gap in the intervention areas of each country. This estimation was based on expected numbers at baseline

of not treated PWE in intervention areas of each country, derived from the prevalence and treatment gap published in population-based studies in each country and the hypothesis of no change in the control area. In Cambodia, to reduce treatment gap from 66.0% to 49.5%, 69 new PWE should be treated during the intervention period; in Laos, to reduce treatment gap from 90.0% to 67.5%, 39 new PWE should be treated during the intervention period.

Intervention	Target Population	Evaluation criteria
IEC Actions, stigma reduced	General population in the study area	KAP survey pre-/post- intervention and between sites (<i>Appendix B1</i>)
Improve DHV KAPs	Staff being trained and active in the intervention districts	KAP survey pre-/post- training and at the end of the intervention and between sites (<i>Appendix B2</i>) – Results: suspected cases/diagnostic + (<i>Appendix B6</i>)
Identification	Intervention area populations	Results: epilepsy diagnosis/expected cases and between sites. (data transmitted by the primary physician and population census)
Prescription Treatment	Diagnosis + (individual more than 1 year old) in the study area	Number of cases diagnosed and receiving treatment (the prescribed dose at the time of evaluation) pre-/post-intervention and between sites (<i>Appendix B6, B8</i>)
Treatment access Follow-up	Patients receiving treatment in intervention districts	Number of withdrawals and/or bad practices during the treatment + reason and time of withdrawal/total being treated and between sites (<i>Appendix B8</i>)

All of these evaluation criteria, measuring the efficiency of new practices before and after intervention, will be established by comparing the control area and the intervention area.

Diagnosis, prescription and treatment delivery rules to be followed

Considering the experimental protocol, following the rules should be emphasized, particularly regarding questions relative to diagnosis and prescription.

- Only neurologists and trained physicians can diagnose and confirm a case of epilepsy. From this point of view, the DHV project remains strictly limited to the identification of suspected cases and their accompaniment to a consultation.
- The first prescription is also solely reserved to neurologists and trained physicians. The provided treatment, given at the request of Cambodian and Lao neurologists, requires the availability of anti-epileptic drugs that are usually available and recommended by the authorities. Newly diagnosed cases (by physicians) are reviewed by the DHV a maximum of 30 days after the first prescription, and a maximum of 1 month for the neurologist (quality control), then every month by the DHV who will report their observations in the form corresponding to their projects (see appendices).
- Delivery of the first treatment is carried out the day of the consultation for the diagnosis, and the delivered quantity is equivalent to 1 month supply at the prescribed dosage (recommendation from local authorities). The DHV is then allowed to deliver treatment at home (renewal procedure) when following up with the patient.
- The program funding allows each DHV to contact a trained physician or neurologist by mobile phone during their identification and follow-up campaigns to obtain assistance and advice (as soon as necessary). Patients must report any adverse events to a doctor who should then follow the national adverse events alert procedure.

These precautionary measures are issued from discussions within the consortium. The program plans to measure the effectiveness of DHVs skills via the suspected/confirmed case analysis and to also allow for the consideration of recommendations related to possible developments in the diagnostic and prescription strategies stemming from the program.

Program sequences (10 items organized chronologically)

1. Mass information campaign

In rural areas, as printed press is very rarely consulted, we will favour radio communications, validated by health authorities, broadcasted on a daily basis all over the country (or almost) during the entire duration of the program. It will be an education message on epilepsy based on simple information such as: “this is a treatable disease,” “it is not contagious,” “it is not a mental illness, nor is it the result of an evil spirit,” “with treatment, people can lead a normal life, as much in their personal as their professional life,” etc.

2. KAP survey of the general population

The KAP survey includes a survey form composed of 52 items addressing Knowledge, Attitudes, Practices and perceptions of epilepsy (Appendix B1). It is conducted on the local population. We have planned to carry out this survey before and after the intervention in order to measure the changes.

The number of subjects needed (NSN) was calculated according to the objective of reducing the segregationist attitude by 60% at the local village level. In a survey conducted in 2006, Duc-SI [4] established that 21% of those surveyed believed that it was preferable that people with epilepsy be excluded from village activities. If we want this number to decrease by 8.4%, we must survey a minimum of 138 villagers in each group (5% of alpha - 80% of power - bilateral test). The survey also plans on surveying 150 people in the intervention district and 150 people in the control area. The villages were selected based on population size (number of people expected to have epilepsy) and access distance from the first health center in order to be representative of different situations present in the district. Considering 15 people per village, we will therefore survey 10 villages in the intervention area and 10 villages in the control area.

3. The KAP survey for people with epilepsy (PWEs)

As the program’s primary objective is to reduce the treatment gap by 25% – 80% of power and 5% of alpha: the NSN for Laos is 91 subjects/group (or 182 people with epilepsy in the study area in Lao) so that our analysis can observe whether the treatment gap drops from 90 to 67.5%.

Given the current diagnostic capabilities in these countries (very significant medical human resources deficit), it is not probable that these populations will be reached before the intervention. The recruitment for the baseline KAP is therefore exhaustive, based on a list of persons already identified with epilepsy by a district hospital, the PHCs and the possible research programs that have already been conducted in the studied areas.

To be noted for different KAP surveys: the only changes that will be made to the KAP questionnaire (Appendix B1) for a survey performed after an intervention will be additions related to knowledge of public meetings, IEC documents and the established relationship with DHV in order to measure our intervention’s role in the observed changes.

4. The generalized training on epilepsy and future DHV recruitment

Short term training is held at the beginning of the intervention for all PHC staff in the intervention area and the control area. The objective is to disseminate a minimum amount of knowledge (clinical signs,

current treatments and dosage, compliance problems, stigma, etc.) regarding epileptic patient care. These trainings will be held over two days and will be provided on a regular basis in Cambodia. In Laos, this training will occur once over three days.

We will perform a KAP evaluation (*Appendix B2*) specific to PHC staff before and after the training. We will make use of this first occurrence to identify (previously designated by the local health care system) the future central program stakeholders:

- 30 DHVs and 10 PHC employees and 1 pharmacist for the training(s) organized in Cambodia in the intervention area and 8 PHC employees in the control area
- 17 DHVs for the training organized in Laos (2 people per PHC in the intervention area) and 19 PHC employees (one “data collection” point of contact per PHC in the control area).

5. The specific training needed to become a DHV

A “long-term” training is provided for future health visitors in order to provide them with the necessary skills for IEC activities, the key knowledge for identification of people with epilepsy, for their regular follow-up, as well as for home delivery of treatment. This training is composed of 50% on the theoretical aspects of epilepsy (class room training), 25% practical (trainees observe consultations in small groups, meet and talk to persons with epilepsy who are already receiving treatment) to optimize the identification of suspected cases in villages; and finally, 25% of the training time is dedicated to using the program tool (IEC brochures, forms to be completed, organizing and hosting public information meetings, procedures and activity planning, etc.).

As the VHSGs in Cambodia are volunteers who are seeking a part-time activity, the training is concentrated over 6 days. Their field activity is therefore important as they can dedicate several days of the week to it. Health care workers in Laos must work, so the 6 days of training will be performed over a 1 month period. Each PHC’s human resources department will record the availability of these professionals to schedule their village visits. The 17 DHVs visit the villages one day a week; the schedule is therefore designed so that each village is visited every month and that each DHV includes a maximum of 4 villages in their jurisdiction.

A new KAP survey is carried out after the long training (*Appendix B2*).

6. Routing and treatment availability

This will be done so that sufficient quantities of anti-epileptic drugs are made available in the intervention areas and control areas. The available quantity corresponds to the amount needed to treat the number of persons with epilepsy set via the program objectives. This amount therefore enables the treatment of the expected number of people with epilepsy (calculated according to the reference prevalence) over 18 months. In control districts, the inventory is stored by the district hospital’s pharmacy so that the supply is organized according to the country’s regular process. In intervention districts, the inventory is stored by the district hospital’s pharmaceutical inventory manager who then ensures its distribution to each PHC. The latter is responsible for (under the coordination of the hospital point-of-contact) making the necessary amounts of drugs available progressively as the DHVs carry out their village visits. In the context of the program, treatment is made accessible at cost (+45% of the recovery fees) for all identified persons with epilepsy in the study area.

7. DHV interventions in the regions

DHVs have a “DHV Guide” that reminds them of the best practices, procedures, advice, etc. In the 30 villages covered by the intervention in Cambodia, each DHV lives in the village where they work and therefore provide a kind of “round the clock medical service” in the village.

In Laos, each DHV has 2 to 4 villages in their jurisdiction that they must each visit at least once per month (one entire day).

- Hosting public IEC meetings: after obtaining authorization from the head of the village, the DHV organizes their public IEC meetings every month. To carry this out, they are provided with a range of IEC tools supporting their interaction with the public. The number of participants will be systematically reported.
- Dissemination of IEC materials: the IEC materials used for public awareness that do not require assistance have also been created (comic books, posters, quizzes). The DHV's goal is to ensure the dissemination of these materials during their public meetings and to leave them in reference points in the village (schools, pagodas, etc.)
- Identification of suspected epilepsy cases: Identifying suspected cases is carried out using the skills acquired from their long training (and through the experience they progressively acquire in the field during the program). They are provided with referential documents (types of seizures, frequency, etc.) in order to ascertain whether a diagnostic exam from a specialist is necessary. If need be, they should systematically record the judgement criterion/criteria that they used to arrive at this conclusion (Appendix B6).
- A diagnostic exam performed by a trained physician and verified by a neurologist: Consultations are performed by a trained physician at the district hospital. The DHV should keep suspected cases informed of potential options, and in case of difficulties, they must accompany the patient until a diagnosis has been made. Logistical support is considered to ensure the transportation of villagers to the district hospital. As said earlier, a prescription may be written over the course of this diagnostic exam and the patient therefore will be provided with their treatment for one month. Quality control can be made in hospital district or in village.
- Follow-up and drug delivery: During their monthly village visits, the DHV ensures patient follow-up (they record the development of clinical signs, the regular administration [or not] of treatment, the proper recording of information in the follow-up booklet, etc.). After a fixed deadline of 15 days for the first visit, each patient undergoing treatment should be seen a minimum of once a month (Appendix B8).

8. Operating principle in the control districts

The goal of the program is to evaluate the effectiveness of new territorial practices. The operations in the control districts should therefore be differentiated according to specific points. Thus, we guarantee the availability of IEC documents and treatments in district hospitals without any particular instructions (other than the training program and generalized information provided during the 3 day general training). Then, every 2 months, we will collect the number of incidents and the information regarding dispensed anti-epileptic drugs (new script and renewal) at the district hospital and we will visit the health care centers.

9. Data Collection System

A system is organized every month to collect the forms completed by the DHVs (public meeting minutes, identification forms [Appendix B1], follow-up forms [Appendix B1], report of a full day of visits, etc. At this time, a visit to the PHCs will allow to record the inventory of treatments that is still available and the IEC public documents. The forms are entered by the program assistant in the secured data base. Each person involved in the program has an individual digital ID (ID_ind) that is automatically incremented and associated to a particular status (DHV, patient, etc.). Part of the recorded information is then given to the relevant DHVs (depending on the villages that they are

responsible for) so that they have the information that they have already collected and that are necessary for the follow-up of people with epilepsy. See paragraph *Consent, Ethics Committees and Data Confidentiality*.

10. Intervention and results valorization

The valorization of the results should be done on several levels during the final meetings by systematically combining presentation of the results with a round table discussion with the targeted public:

- Public Health employees in the districts (doctors and pharmacists in the district hospital, PHC employees, village volunteers) over the entire study area: the goal is to collect the opinions/suggestions from the principal stakeholders after the intervention experiment.
- Ministry authorities and provincial coordinators: the goal is to think in terms of costs/effectiveness and reflect on the most effective methods and those most suitable to the health care system that is already in place in order to design an efficient national model.
- The scientific community: the goal is to provide proof to other Public Health researchers and/or program initiators of our findings as they relate to the intervention methods. The targeted scientific audience will be primarily centered around researchers working in developing countries.
- 5 publications in the indexed reviews are planned based on the expected findings.

Ministry authorizations

In Laos, the program authorization, sent on December 15, 2013, was finally approved on April 18, 2014. In Cambodia, the application will be sent in October 2014. The time required to obtain these authorizations is, in large part, explained by the interservice and interministerial consultations (Ministry of Health and Ministry of Foreign Affairs).

Consent, Ethics Committees and Data Confidentiality

- For all of the conducted surveys (general population, persons with epilepsy and their caregivers; DHV) a consent will be routinely requested from the interviewee and the questionnaire will be transmitted once consent is obtained via a signature, and, in the event of illiteracy, via the signature of a witness with the consent of the patient.

- This protocol will be submitted (November 2014) for an opinion from the Committee for the Protection of People [*Comité de Protection des Personnes*] (CPP) in the Limousin Region, meeting in the configuration of the Ethics Committee. A version presenting the intervention in Laos was submitted to the Lao Ethics Committee in December 2013 and was approved. A version presenting the intervention in Cambodia was submitted to the Cambodia Ethics Committee in November 2014 for approval.

- The information collection databases are created in SQL format using the Microsoft Access software. These databases are installed locally (one in Vientiane and the other in Phnom Penh) requiring a password to open and under the management of the local coordinator. Anonymized exports are sent to program coordination (IENT, Limoges) once a month (data conservation and analysis). A unique identifier is assigned to each patient, interviewee and DHV. Thus, researchers will conduct their analyses using exports in Excel formats with anonymized registries. The only people who can link individual identifiers (ID_ind: non-modifiable number automatically incremented during entry into the database) with their name are the local program coordinators and the health care staff performing the patient diagnostics and follow-ups: all are bound to confidentiality and professional secrecy.

References

- [1] Bhalla *et al.*, *Comprehensive evaluation of the psychosocial parameters of epilepsy: a representative population-based study in Prey Veng (Cambodia)*. *Epilepsia*. 2013 Aug;54(8):1342-51.
- [2] Duc-Si *et al.*, *Epilepsy in Laos: Knowledge, attitudes, and practices in the community*. *Epilepsy & Behavior* 10 (2007) 565–570
- [3] Harimanana *et al.*, *Is insufficient knowledge of epilepsy the reason for low levels of healthcare in the Lao PDR ?*. *BMC Health Services Research* 2013, 13:41
- [4] Duc-Si *et al.*, *Prevalence of Epilepsy in a Rural District of Central Lao PDR*, *Neuroepidemiology* 2006;26:199–206

Attachments in appendices: KAP survey forms, Case Report Form (suspicious case identification) and CRF follow-up (follow-up form for patients undergoing treatment)

Summary of changes to the protocol approved by the ethics Committee

1. The documents mentioned in the appendix to this document are available in appendix 3 and 5 in supplementary appendix of the paper.
2. In Cambodia, the duration of the PHC staff training was 2 days, and 3 days for DHVs with the same pedagogical objectives.
3. The secondary objective of assessing the cost-effectiveness of the strategies was achieved (a posteriori) according to expenditures during 12-month period. Cost-effectiveness evaluation was estimated according to ICER (Incremental Cost-effectiveness Ratio, see appendix 10 of the paper).
4. The secondary objective of reducing *the segregationist attitude* by 60% at the local village level was complicated because of the lack of reliability of responses (due to the socio-cultural context and face-to-face data collect). We focused only on knowledge and perception changes (not Attitudes and Practices).

Original statistical analysis plan

Overview

ECLAIR is a quasi-experimental study, i. e. a "here/elsewhere" and "before/ after" comparison between an area where DHVs are involved and an area without DHVs.

The statistical tests were used:

- to compare data (e.g. status) between intervention and control areas.
- to compare the same area, before and after 12-month period; demonstrating whether the situation after the experimentation was significantly different from the baseline situation.
- to compare evolutions between intervention and control areas; demonstrating whether evolution of the area of intervention was significantly different from the control area.

Two types of tests were used:

- for unmatched samples: chi-square test or Fisher exact test depending on the expected values
- for matched samples: Mac Nemar test or Mac Nemar test with Yates correction depending on the number of discordant pairs.

All descriptive analysis: qualitative variables will be described using numbers and percentages, and quantitative variables using means and standard deviation or medians and interquartile ranges depending on their distribution.

All statistical comparisons will be done using a 5% significance level.

Focus on primary endpoint (Table 2)

Main outcome: test of the difference of treatment gap between intervention and control areas. Use of chi-square test or Fisher exact test. Proportions of treated numbers of PWE will be estimated using previously published prevalence.

Focus on secondary endpoints (Table 3)

Use of Mac Nemar test or Mac Nemar test with Yates correction to compare evolution between first and last visit concerning the number of PWEs adherent, the number of seizures and the reporting stigma.

- For adherence: Use of Morisky scale (Morisky et al., 1986). It consists of a score based on the answers to four questions, in 2 terms (each response has a score 0 or 1). The final score therefore ranges from 0 to 4. We considered the PWE was compliant with a score = 4, and no compliant when it is different from 4.
- For seizures number: it was self-reporting, validated by the health diary consultation.
- For stigma: Use of Jacoby scale (Jacoby et al., 1994). It consists of a score based on the answers to three questions, in 4 terms (each response has a score of 0 to 3). The final score therefore ranges from 0 to 9. We considered that PWE did not suffer from stigma when the score was 0.

For adherence and stigma, Appendix 8 showed results before and after intervention with intermediate levels (only descriptive analysis).

We used Fisher exact test to compare the evolution between intervention and control area.

Focus on other results (Supplementary appendix)

All these statistical principles are applicable to the results presented in the Supplementary appendix.

Statistical analysis was performed using Stata software 11, and XLS stats. GIS software used is QGIS 2.10. The optimization of the maps was created with Adobe Illustrator CS6.

Summary of changes to the original statistical analysis plan

The only analysis not provided in the original statistical plan concerns the cost-effectiveness analysis. Following is an extract of the appendix 10 (see this appendix for more details on total direct costs).

Regarding economic evaluation, the cost-effectiveness of the strategy was assessed from a governmental perspective by the Incremental Cost-Effectiveness Ratio (ICER), defined as the difference in costs between intervention and control areas, divided by the difference in treatment gap reductions. The reference value in the absence of DHVe was estimated by the ratio of the cost (per 10,000 inhabitants) divided by the treatment gap evolution in the control area. **ICER represents the average incremental cost associated with one percent of treatment gap reduction.**

Incremental Cost-Effectiveness Ratio (ICER):

$$\frac{[\text{total cost (per 10,000 inhabitants) in intervention area}] - [\text{total cost (per 10,000 inhabitants) in control area}]}{[\text{Treatment gap reduction in intervention area}] - [\text{treatment gap reduction in control area}]}$$

Nota: the number of Inhabitants concerned should be the same between intervention and control areas.