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Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy, Placebo-controlled, in Infants With Moderate Acute Bronchiolitis.

Bronkiville

N° 2018-A00946-49

Version 4 - 30/01/2019

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1. Abstract

Design: This study is a randomized controlled multicentre triple-blind trial.

Investigators and centres: The sponsor of this study is the Réseau Kinésithérapie Bronchiolite Essonne, which is chaired by Mr. Thomas Baucher. The project manager and biostatistician is Mrs. Aurore Trébuchet. The co-investigators of the study are: Mr. Jeremy Cornuault, Mr. Tarek Hussein, Mrs. Audrey Rousselin, Mr. Bruno Tirel, Mr. Tony Roho, Dr. Benjamin Azémar and Dr. Sébastien Rouget. Dr. Sébastien Rouget is the coordinating physician of the project. The study will be conducted in the Department of Essonne (91) in two or three medical centres with general or paediatric medicine activity (coordinated poles in Appendix A). The managers of the medical centres are: Mr. Thomas Baucher, centre of Saint-Germain-lès-Arpajon; Mr. Tarek Hussein, centre of Corbeil-Essonne; Mr. Jan Litwin-Staszewski, centre of Athis-Mons.

Duration of the study: The study will begin in November 2019 and will be conducted on several sessions during winter periods from November 2019 to March 2022 (3 sessions per winter). Each session lasts 8 days.

Context: Bronchiolitis affects 460,000 children in France per year. The French Bronkilib 2 study found a positive effect of chest physiotherapy treatment. This study and the work done so far in chest physiotherapy [1,2,3,4,5,6,7] prompt us to recommend respiratory physiotherapy with slow passive expiratory handlings in the treatment of the moderate bronchiolitis of infants. But, further studies are still needed to corroborate these early findings. The Cochrane is recommending new high-level proof studies on passive expiratory techniques to conclude about their benefits [8].

Objectives: The aim of this study is to evaluate the effectiveness of the bronchial drainage procedure carried out during chest physiotherapy sessions, during episodes of moderate acute bronchiolitis in infants aged 3 to 24 months. Currently, the French High Authority for Health recommends performing physiotherapy sessions for the symptomatologic treatment of acute bronchiolitis in infants [9] - in cases where it could be described as moderate [10] - but few Studies have demonstrated the efficacy of this treatment: the only randomized trial on French techniques of chest physiotherapy concerning outpatients is Bronkilib 2 [11], pending publication. It is therefore the second such study in France that will corroborate or invalidate the results of the Bronkilib 2 study.

Methods: The study included infants with a first or second episode of bronchiolitis classified as moderate according to the Wang's Respiratory score [12] (3 <score <9). The treated group will receive chest physiotherapy treatment using slow extended and passive expiratory handlings. The control group will not receive physiotherapy treatment. To control parents' home care and ensure comparability of groups, a parents' education session to the rhinopharyngeal clearance procedure will be conducted in both groups. It is expected to treat 168 subjects that is to say 84 subjects per group, on the two medical centres. The results will be presented in descriptive statistics by diagrams and boxplots. The inferential statistics used will be the Chi2 test and the test of Logrank for discrete variables, the Smirnov test for continuous variables.

Outcomes criteria: The main outcome criterion is composite: it's the variation of the Wang's Respiratory score measured between T0 the day 1 and T30 day 4, and the evolution of the general health condition of the child between sessions. The main objective is to evaluate the medium-term effect of chest physiotherapy on the Wang's Respiratory score and the quality of life of the child (with the validated questionnaire QUALIN). Secondary outcomes are: the evolution of the oxygen saturation after a session and after four sessions of physiotherapy, and the variation of the Wang's Respiratory score between T0 day 1 and T30 day 4 according to the results of a RSV nasal swab test, and according to the "inflamed/ secreting status " of the children. The secondary aims are to assess: the effect of chest physiotherapy on the saturation and the impact of respiratory physiotherapy in children RVS positive versus RSV negative, and in children with 'inflammatory' versus 'secretant' status. This will also allow us to assess the number of children with RSV in our study.

2. Abbreviations and definitions

AFE slow: the increased expiratory flow technique is intended to increase the expiratory flow rates to help the secretions ascent to the upper airways. The slow AFE correspond to extended slow expirations.

Bronchiolitis: Inflammation of the bronchioles in infants, usually due to the presence of the human Respiratory Syncytial Virus.

RPC: Rhinopharynge Clearance.

Extended slow expiration: help to the thoraco-pulmonary deflation during exhalation, the movement accompanies the child.

Forced inspiration: use of the reflex of Hering-Breuer for inspiration of a large volume of air after a thoraco-pulmonary deflation, to achieve the expiratory reserve volume.

Parents: holders of parental authority are referred as 'parents' in this protocol.

RVS: human Respiratory Syncytial Virus.

3. Introduction and justification of the study

The Cochrane published a literature review on the impact of the techniques of slow expiration in 2016 [8] in the treatment of infant acute bronchiolitis. The low level of evidence of the analyzed studies (Webb 1985, Aviram 1992, Nicholas 1999, Lopez Galbany 2004, Bohemian 2004, 2008 in Córdoba, Gajdos 2010, Rochat 2010, Postiaux 2011, Sanchez Bayle 2012, Gomes 2012, Remondini 2014) and the presence of many bias lead to uncertain conclusions: these techniques are perhaps beneficial for a group of the population concerned.

Conclusion of the Cochrane review: postural drainage, percussion and vibration techniques are not recommended in the treatment of bronchiolitis. The increased expiratory flow technique is discouraged in the treatment of severe bronchiolitis in hospitalized infants. Increase in expiratory flow and slow extended expiration techniques have not been evaluated on low to moderate bronchiolitis, especially in outpatients (Cochrane 2016).

Deleterious effects of prolonged slow expiration technique (Postiaux 2011, Cochrane 2016) or RPC (Gomes 2016) [1,8,13] have not been reported. These techniques deserve to be explored.

This study is the second randomized controlled trial to be conducted in France on exhalation techniques in the management of moderate acute bronchiolitis in infants as outpatients.

The study Bronkilib 2 [11] suggests an improvement in the condition of the patient in 70.7% of patients in the treatment group compared to 9.76 % in the control group, that is to say an effect of the treatment for 60.94% of the patients. No aggravation was yet notified.

4. Study objectives

4.1 First Objective(s)

The main objective is composite. It is:

- To evaluate the medium-term (4 days) effect of chest physiotherapy on the Wang's Respiratory score. Therefore, the aim is to assess the effect of the gesture itself (long slow extended and passive exhalation) in the treatment of moderate acute bronchiolitis in infants.
- To evaluate the medium-term (4 days) effect of chest physiotherapy on the general health condition (quality of life) of the child. The aim is to evaluate the effect of the sessions of bronchial drainage on the clinical criteria used for the diagnosis of bronchiolitis.

4.2 Secondary Objective(s)

The secondary objectives are to assess the effect of physiotherapy on the oxygen saturation of the child, and the positive impact of chest physiotherapy in children RSV positive versus RSV negative, and in children with "inflamed status" versus "secreting status". In addition, this will allow us to assess the number of children with RSV in our study.

5. Study Plan

5.1 Administration of treatment and placebo

This study is a randomized controlled multicentre triple-blind trial (patients and parents, therapists administering the treatment, evaluating physicians, and biostatistician blind). The treatment group will receive a session of physiotherapy by slow extended and passive expiration for 10 minutes. The control group will not receive any physiotherapy session but receive a monitoring session. In both groups the children will be kept in session 15 minutes in total.

The administration of the treatment is the following: during sessions, the child is lying on the back, he should not have eaten within two hours prior to the sessions. An extended slow expiration handling is performed on 3 respiratory cycles consecutive, this session is repeated for 10 minutes. Breaks are made regularly during the treatment to have approximately 5 to 6 minutes of handlings and 4-5 minutes of rest on the total 10 minutes of treatment. Induced cough handlings will be conducted at five minutes and at ten minutes if the child has not coughed during the movements of chest physiotherapy. These are performed by a brief pressure above the jugular (suprasternal) notch of the patient. Only two consecutive trials of the induced cough handling are allowed, even if the handlings are unsuccessful: the physiotherapist does not insist. The following 5 minutes of the session are 5 minutes of rest. During the sessions the physiotherapist wears a mask and respects the usual rules of hygiene (washing hands, no jewellery...).

The administration of the placebo session procedure is as follows: 15 minutes of rest, without intervention of the physiotherapist. The physiotherapist is only watching over the child.

The children are therefore kept in session 15 minutes in both groups. The treatment is continued once daily for 4 days.

For both groups, at the first session, the handling of RPC is described to parents and an explanatory brochure is given. During this session, the physiotherapist will test the knowledge of the parents in a RPC practice test, in order to ensure that actions are carried out properly and wisely at home.

The RPC is taught as [14]: child in lateral decubitus on a plane inclined at 20 °, instillation of saline solution in the upper nostril, looking for a flow into the nostril opposite, until secretions are equivalent in colour and texture to the saline solution. The handling is performed in both nostrils. The handling is not insistent, it is stopped if the child is too agitated, and he is not instilled more than a pipette per nostril. Advice to parents is to perform this handling each morning and evening, and before each meal in case of meal difficulties.

Randomization will be made by a random computer draw by block of eight stratified by medical centre. If needed the procedure is detailed in paragraph 6.

All caregivers participating in the study (prescribing physicians, evaluating and physiotherapists) are trained to homogenize the practices within the study and ensure the respect of the protocol.

5.2 Population studied and criteria for the participants selection

The targeted population for this study includes all infant aged from 3 to 24 months suffering from infant moderate acute bronchiolitis, whom chest physiotherapy could help, without other specific diseases.

The inclusion criteria are the following:

- Acute bronchiolitis diagnosed during a medical consultation in one of the centres, and medical agreement: the prescription must be based on clinical diagnosis of bronchiolitis proposed by the Guideline of the Academy of Paediatrics (AAP), i.e. the presence of rhinorrhea, cough, wheezing or rales crackly, tachypnea, intercostal or chest indrawing, use of accessory muscles, flapping of the wings of the nose, expiratory grunting, lowest oxygen saturation (strictly less than 95%). The presence of three of these signs is enough to diagnose infant acute bronchiolitis.
- First or second episode of bronchiolitis: three episodes of bronchiolitis in the same winter suggest infant asthma, or the presence of other respiratory disease. To avoid any selection bias which might have a negative impact on the results of the study, only the first or second episodes of bronchiolitis will be included.
- 3 months \leq age \leq 24 months: children of less than three months have a very immature lung. To avoid any worsening of the health condition of the child related to potential side effects not considered of the treatment, the study will be conducted on children over 3 months old.
- 3 < Wang's Respiratory score < 9: bronchiolitis is considered light when Wang's Respiratory score is less than or equal to 3 and as severe when Wang's Respiratory score is greater than or equal to 9. The French Health Authority and the Cochrane discourage chest physiotherapy for the treatment of severe bronchiolitis. A hospital medical support is more adequate than a liberal support for this type of patient. They will not be included in the study.
- Informed written consent of the holders of parental authority: an information and consent form will be read and explained to the holders of parental authority before collecting their written consent during the interview with the prescribing physician. Consent will be collected by the physiotherapist on call of the investigative Centre, to let a cooling-off period for the holders of parental authority.

Exclusion criteria:

- Refusal of parents or holders of parental authority.
- No medical prescription: will only be included in the study children whose health can in no respect be endangered by their inclusion.
- Comorbidities: cardiac, pulmonary, neurological disease, immunodeficiency, congenital anomaly, other diseases explaining respiratory symptoms: the presence of comorbidities is likely to introduce a selection or a confusion bias in the results of the study. These patients will not be included.
- Wang's Respiratory score \leq 3 or \geq 9: a score \geq 9 requires a hospitalization.
- Status of the child requiring hospitalization.
- No affiliation to a social security scheme.

Appropriate recruitment of patients is insured by the inclusion guideline sent to prescribing physicians (Appendix C).

5.3 Number of centres and subjects

The study will be conducted on two or three liberal medical centres (general or paediatric medicine). The number of patients expected is 168, that is to say 84 patients per group. It is therefore expected from 56 to 84 patients by Centre. The involvement of several centres, beyond facilitating the recruitment of a large number of patients, will avoid potential selection bias (environmental and sociocultural mainly) and permit to

study a population representative of the targeted population of the study. There are few centres in rural areas, most centres being situated in urban or peri-urban areas.

5.4 Duration of the study

The study will be conducted from November 2019 to March 2022 on several sessions of 8 days. The number of session will be 3 by winter.

5.5 Outcomes criteria

The two components of the main outcome criterion are:

- The variation of the measured Wang's Respiratory score between T0 day 1 and T30 day 4. The Wang's Respiratory score (Appendix D) is measured on a daily basis, T0 corresponding to the time immediately preceding the session of physiotherapy, T30 measured 30 minutes after the beginning of the session of physiotherapy.
- The variation of the general health condition (quality of life) of the child after physiotherapy. It is measured by QUALIN (Appendix E) questionnaire completed by parents to T0 every day: it provides information on the general state of the child before physiotherapy support the first day, and on the state between sessions of physiotherapy during the following days. It measures food intake, the awakened state and the behavior of the child, among others [15]. Each item is quote -2 to + 2: for items 4, 6, 10, 14, 15, 17, 20, 23, 27, 30 the rating goes from -2 'absolutely true' + 2 'completely false', for other items the terms are listed in reverse. The score is range from -68 to 68. A child who has no item negatively quoted or positively quoted has a score equal to 0. It is estimated that a child has a good quality of life if his score is between 34 and 68 (not expressed by the authors).

We chose a composite outcome criterion because it is difficult to ignore one or the other of the two components: the Wang's Respiratory score is a score that is referenced in the evaluation of bronchiolitis, it is generally well known by the health profession and it has a good validity [12]. But the improvement of the quality of life of the child is the main goal of the parents, and it is in these terms that they speak when they describe the state of their child to the general practitioner. In addition, we assume that physiotherapy has a highest impact on the quality of life of the child than on the pathophysiology of bronchiolitis. We therefore chose to place these two components at the same level of importance in our study, as the composite primary outcome criterion.

The secondary criteria are:

- evolution of the oxygen saturation,
- "inflamed" or "secreting" children status, evaluated by a questionnaire (filled by the physiotherapist each day of treatment),
- and the results of a RVS test by nasal swab sampling performed at day 1, before the physiotherapy session.

5.6 Methodology

The study will be conducted as follow:

A study session begins on Friday of week 0, children may be included on Monday or Tuesday of the following week (week 1). The session ends the next Friday (week 1). Children entered on Monday are seen until Thursday, children entered on Tuesday are seen until Friday. Children can have a prescription dating back to Monday or Tuesday week 1, or Friday or Saturday Week 0.

Day 0 is the day when the child is greeted by the prescribing physician, general practitioner or paediatrician of the family. His role is to inform the parents of the child of the existence of the study. It so includes checking the criteria of inclusion and exclusion, including Wang's Respiratory score; explaining the course of the study; providing the patient with an information letter, a consent letter and a letter of no objection; giving them the treatment prescription; giving them the access information to the centre and the phone number of the physiotherapist (which they have to call without delay on the first next scheduled day); and answering their questions.

Parents are given some cooling-off (minimum 1 hour). Nevertheless, the entry in the study cannot take place later than Tuesday of the study week, and without prior consultation with other physiotherapists. Parents wishing to integrate the study are to call the physiotherapist indicated by the prescribing physician for an appointment.

Day 1 is a Monday or a Tuesday. The child is greeted by the physiotherapist who is expected to: schedule the appointments with the parents either by phone or in person, collect at least one consent letter, collect the letter of no objection, answer the questions of parents, remind that the consent of both legal guardians is required if not the case, inform them that they will be re-contacted by the project manager due to this missing written consent. Then the physiotherapist has to enter the child name in the database via the study website to receive the child code, which will be given to the parent. Thus, the child gets a code which will be then the only way to recognize him/her. The physiotherapist asks the evaluating physician to evaluate the Wang's Respiratory score of day 1.

The evaluating physician comes into the physiotherapy room to: check that the child meets the criteria for inclusion in the study (no worsening of the general condition and Wang's Respiratory score < 9), evaluate the first assessment by the Wang's Respiratory score. This evaluation is filled in on the study website with the identifiers of the physician and the child. Then the physician leaves the room.

Then, the physiotherapist performs the RSV nasal swab test. He has the parents perform the rhinopharyngeal clearance to verify that the procedure is known and correct. He hands the QUALIN questionnaire to the parents. He then asks the parents to leave the room for the session and asks via the website the randomization of the treatment. The treatment to be applied is then displayed on the screen. It is only visible on the page dedicated to physiotherapists. Physicians have no access to this information. Then the physiotherapist performs the treatment indicated by the randomization.

Randomization of treatment is performed only at this time to avoid an early randomization on children who would then get out of the study before the session of physiotherapy, which would risk creating an imbalance between groups.

During the physiotherapy session, parents in the waiting room fill in the QUALIN questionnaire and hand it over to the physiotherapist after the session. Parents are not present in the physiotherapy room during the sessions. The physiotherapist fills in balance sheets of saturation for all children, and the status of the child (inflamed / secreting) for children in the treatment group

Day 2, 3 and 4 the child is reviewed by the evaluating physician for a Wang's Respiratory score: prior to the session of physiotherapy or surveillance for days 2 and 3, 30 minutes after the session for day 4. The balance sheets of saturation (at T30 on day 4) and status of the child (inflamed / secreting) are again filled in by the physiotherapist. The parents fill in the questionnaire QUALIN in the waiting room during sessions.

Day 4, the study session is over. The evaluating physician suggests the continuation or cessation of sessions of chest physiotherapy, depending on the health state of the child during its last evaluation of the Wang's Respiratory score.

Evaluating physicians and physiotherapists are present from Monday to Friday (1 pm to 7 pm). Each centre has at least one physician every day during this period. Each centre has a physiotherapist on call every day during this period.

Side effects or the no-presentation of the child at the session can be reported at any time of the study by the evaluating physician or by the physiotherapist on the study website and via the dedicated tab. The information is then sent directly to the sponsor, the project manager and the coordinating physician. If there is a hospitalization, an emergency unblinding can be made by the sponsor, the project manager or the coordinating physician who will be notified by mail and phone: the guardians are informed by mail and/or phone of the treatment received and results of the assessments made.

If the child situation is getting worse: if Wang's Respiratory score ≥ 9 or if the child's condition becomes cause for concern during the assessment carried out by the evaluating physician (child unreceptive, amorphous, signs of respiratory distress associated with a frequency respiratory > 60 breaths / minutes, signs of cyanosis, saturation $\leq 94\%$), the child must be taken out of the study and sent to a hospital. If this takes place during the session of physiotherapy, the physiotherapist asks an assessment by the evaluating physician. An emergency unblinding is made by the sponsor, the project manager or coordinating physician.

These criteria of worsening are reminded of on the study website when filling out the balance sheet by therapists. If the criteria are met, the site visually alerts the therapist and suggests him to go to the tab 'side effects'. The physiotherapist and the evaluating physician can at any time report an adverse event.

If one of the guardians wishes to get out of the study, he informs the evaluating physician or the physiotherapist or some other official, who then reports it on the study website. The reason for getting out of the study will be sought by the project manager without pressure. Legal guardians have the right to wish not to report the reason why they get out of the study. If the child is not present at the scheduled appointments or during the day, this will be reported by the physiotherapist since it will take the child out of the study.

5.7 Statistical Analysis Plan

5.7.1 Risks and hypotheses

The α risk corresponds to the risk to treat patients mistakenly. It is not, in this study, the main risk. Since our study is not an assessment of the effectiveness of a drug with potentially toxic effects, the design had to be adapted [16,17]. Given the low risk of side effects of chest physiotherapy by extended and passive slow exhalation [1,3,6] and conversely the risk of worsening, or at least discomfort for the child if not taken in charge despite a real need - which would correspond to a type 2 error - it seems preferable to concentrate on a low β risk: this risk is therefore consented to 0.05.

The null hypotheses are always "the distribution of the random variable 'outcome criterion' evaluated is the same in both groups". Studying the distribution of the random variable boils down to study the distribution between the variables categories for the Chi² and Logrank tests, and studying the distribution function of the variables for the test of Smirnov.

The alternative hypotheses are "the distribution of the random variable "outcome criterion" assessed is different between the two groups".

The tests that can be made in bilateral or unilateral tails are all bilateral.

5.7.2 Number of subjects

Based on the consented risks and the validity conditions of the Chi2 tests, a minimum of 5 observations per box of the contingency table is needed (table 1).

The results of Bronkilib 2 conduct to an effect size estimated at 60%, corresponding to a change of category of bronchiolitis from moderate to light. . It is estimated a reduction of the Wang's Respiratory score of one point between day 1 and day 2 for at least 50% of the subjects. With $\beta = 0.05$, an effect size estimated at 50%, a test of the Chi2 at 7 degrees of freedom, and an α risk consented to 0.10, the study would require a total sample size of 75 subjects (3.1.9.2 GPower software).

However, we must take into account the distribution of the numbers in the contingency table to respect its conditions of validity.

Given the results of previous studies (Postiaux) [4], it is expected to observe a decrease in the score of 2.5 points Wang in the treated group and of 2 points in the untreated group. The treated group went from a score of [2.8 - 9.2] at [0.5 - 7.5] is at max 8.7 points and at least 1.7 points lost in 4 days of treatment, in the control group of [8.4 - 2.6] to [2-4] is at max 6.4 points and at least 0.6 points lost in 4 days. It is difficult to transpose these results in terms of percentages, nevertheless a decrease of 8 points is considered possible. The variable X: the Wang's Respiratory score observed between T0 day 1 and T30 dah 4, difference will probably take all its possible values in the interval [-8; 3]. The categories of the proposed variable will be: -8 to -6, -5-3, -2, -1, 0, +1, +2, +3. These data are insufficient to predict the number of observations in each category, especially as the number of children included in the study is low.

Table 1: planned analysis (analysis of the difference of Wang's Respiratory score between T150 to J4 and T0 to J1 and conditions of validity

	[-8 ; -6]	[-5 ; -3]	-2	-1	0	+1	+2	+3	Total
Treated group									5 ≤
Control group									5 ≤
Total	5 ≤	5 ≤	5 ≤	5 ≤	5 ≤	5 ≤	5 ≤	5 ≤	20 ≤

Based on the results of the Bronkilib study 2 [11], regarding the observed percentages of non-response and response to treatment by chest physiotherapy, we can forecast to observe as smaller percentage a percentage of 10% of response to treatment in the control group (table 2): in this scenario, and by consensus, we consider that we are likely to see a reduction in the Wang's Respiratory score of 2 or 1 point. Thus, we can divide the response to treatment (of 10%) in: decrease in the Wang's Respiratory score by 2 points (3%) and decrease in the Wang by 1 score point (7%). These percentages are arbitrary, but seem to be clinically plausible. We need minimum 5 subjects by box, so in order to have 3% be 5, the n(control) required would be 167 subjects. This would mean a total of 334 subjects (n (control) = n (treated)).

However, in the study Bronkilib 2 the evaluation was made on only one session. After 4 days and based on the results of Postiaux, we can assume that it is clinically consistent to multiply by 2 the planned percentages (6% minimum per box including in the box = 5) which brings back up to 84 subjects per group, that is to say 168 subjects. Indeed, it is more likely to get a reduction in the Wang's Respiratory score of 2 points on day 4 rather than on day 1, because the variable "evolution of the Wang's Respiratory score between sessions" follows a decreasing law on most subjects.

This leads to inclusion of 56 children per centre in 3 years. Either 19 children per centre and per year on average for three investigation centres, or 28 per year and by centre for two investigation centres.

Table 2: preliminary results of the study Bronkilib 2 and correspondence with the planned analysis

	Decrease of the Wang's Respiratory score	Stagnation of the Wang's Respiratory score	Aggravation of the Wang's Respiratory score
Correspondence	-8 /.../-3 / -2 / -1	0	+1 / +2 / +3
Treated group	70 %	30 %	0 %
Control group	10 %	90 %	0 %

These computation are approximate due to the small number of studies conducted on the subject and the lack of exploratory studies. It is not possible to estimate the number of patients needed for the analysis of the quality of life of the infant because it is the first time, to our knowledge, that it is studied in the context of the treatment by chest physiotherapy in infant bronchiolitis.

Nevertheless with a number of children of 168, we take into account the risks in this study and insure a good power to be able to demonstrate a significant effect of chest physiotherapy. So with a 0.05 β risk, a 0.1 α risk, and a sample of 168 subjects, we can highlight an effect size estimated a priori at 0.344 (GPower software.).

5.7.3 Descriptive statistics

Tables will allow to represent demographic and socio-economic data to indicate the initial characteristics of the two samples: age (months), sex, parents' smoking status.

The descriptive statistics of the variables studied will be made by diagrams, set aside for the saturation which will be represented by a boxplot.

5.7.4 Inferential statistics

Inferential statistics will be carried out as described below:

- Intensity of the variation of Wang's Respiratory score between T0 day 1 and T30 day 4: the Chi² test and the Logrank test. The effect of the RVS test results and the child "inflamed / secreting status" will be tested with stratified analyses. If the validity conditions of the Chi² tests are not respected in stratified analyses, the categories will be grouped thus: [-8; -1], 0, [+ 1; + 3]. Concerning the Logrank test, the endpoint is defined as "when the Wang score become ≤ 3 ".
- Variation of the score QUALIN between T0 day 1, day 2, day 3, day 4: the Logrank test: evaluates if and when a change of the general health condition of the child appears, this change is defined by an increase of 10 points from the score compared to the initial score.
- Variation of saturation between T0 day 1 and T0 day 2, and between T0 day 1 and T30 day 4: the Smirnov test.

We don't consider stratification by centre in the analyses, because it is assumed that the evaluated populations is relatively similar with regard to the results of treatment with physiotherapy. Moreover, any bias of selection and confusion is controlled by the block randomization, stratified by centre.

Concerning the qualitative variables, we have no interest in using tests on averages: this would be a loss of information and would not be clinically coherent, as it would make the results more difficult to communicate.

From the existing literature, there is no reason to consider that the variable "saturation variation between T0 day 1 and T0 day 2" follows a normal distribution. That's why we choose a nonparametric test analysis of the empirical distribution functions.

5.7.5 Exploratory analyses

A Principal Components Analysis (PCA) focused on the variation of the questionnaire QUALIN score will be conducted with, as explanatory variables, the change in ratings of each item of the questionnaire. This will permit to highlight the potential impact of treatment on some somatic connotation items such as the item 1: in effect the QUALIN questionnaire aims to cover the overall quality of life of the infant, and its usual use is broader than that made in this study, although it is validated as a research tool. This questionnaire includes behavioural and environmental dimensions, and the treatment by physiotherapy is more likely to impact somatic items and, perhaps, behavioural items. These items could be blended among other items : they could well be improved despite the fact that no significant improvement would be statistically and/or clinically detected in the overall score, or vice versa. This analysis will allow additional information to feed discussion about the interest of chest physiotherapy in infant bronchiolitis concerning the quality of life of the infant.

The correlation between the evolution of the Wang's Respiratory score and the evolution of the QUALIN score will be studied by the Kendall correlation coefficient: indeed, no reason to assume that these variables follow normal laws, and this test is robust to the equally-ranked.

5.7.6 Missing data management

The project manager gets as many reasons as possible for censorship, in order to manage at best the missing data in the statistical analyses. Lost subjects will be treated as follows:

- If the child gets out of the study for hospitalization due to respiratory decompensation: Wang's Respiratory score will be considered equal to 9 at Day + 1, the response to the questionnaire for the general condition will be considered as minimum, the saturation as equal to 92%.
- If the child gets out of the study for non-related respiratory problems, hospitalization or side effects: the last known value will be retained for the missing data.
- If the child gets out of the study because parents found that it was not necessary to continue the treatment: Wang's Respiratory score will be considered equal to 3, the response to the questionnaire for the general state as maximum, with a normal saturation (98%).
- If no reason can be identified: two scenarios will be tested: scenario 1 missing data treated as equal to 12 for Wang's Respiratory score, minimum score for the questionnaire, equal to 92% saturation. Scenario 2 missing data treated as equal to 0 for the Wang's Respiratory score, notes maximum for the questionnaire, saturation equal to 98%. The probabilities of the two scenarios will be calculated conditionally to non-missing data in the sample. This will facilitate conclusions, whatever may be the impact of the missing data.
- Day 1 missing data will be reported but will not be considered in the analysis.
- Missing data on quality of life questionnaires QUALIN will be: attributed according to the latest data received regarding the Wang's Respiratory score, assuming that there is correlation between the Wang's Respiratory score and the quality of life of the infant, such as specified above. Censored data for which no value can be estimated will be handled by the two aforementioned scenarios.
- Missing data on other variables will be deleted, but the number of missing data and valuable data will be specified ("inflamed / secreting" status, state of RSV).

5.8 Adjuvants and adverse events

Adjuvant: the RPC will be made with physiological serum available in the centres providing physiotherapy.

Notifications of adverse events:

- Side effect (effect harmful or unwanted): petechiae, cyanosis, vomiting.

- Serious adverse event: hospitalization, death, disability, malaise or fractured ribs.
- Unexpected side effect.
- New fact.

Serious adverse events require the exit of the study. Side effects will all be reported via the website, registered with the child code. They will be visible by the entitled persons (sponsor, project manager, coordinating physician). If there is hospitalization, emergency unblinding procedure will be requested by notification to these three officials by phone and e-mail. If serious adverse events reach 10 percent of the subjects, that is to say occur on 16 children, the study is stopped.

The exit criteria are:

- Withdrawal of consent,
- Worsening of the condition of the child: if the Wang's Respiratory score ≥ 9 or if the evaluating physician considers the state of the child is concerning (unreceptive, amorphous, signs of respiratory distress associated with a frequency respiratory > 60 breaths / minute, signs of cyanosis, saturation $\leq 94\%$). A request for hospitalization will follow,
- Serious adverse event: hospitalization, death, disability and fractured ribs.

6 Data protection

The demographic and socio-economic data collection is done by answering questions on filling out the questionnaire QUALIN on day 1. The data concerning the studied variables will be collected on paper and delivered to the project manager. They will then be processed by computer. They are encoded by the procedure blind (child code). (Annex E)

Procedure for blinding: the draw is made via a secured website that emits a random draw by block of eight at the request of the physiotherapist. The child is then assigned to a group A/B. The child is recognizable by a reference number and registered on the site as being linked to a group. So, it is possible for physiotherapists to know which group the child is assigned to. Only the number of the child and his Group treated/control are known to the physiotherapist. The data are therefore encoded at their collection. Evaluators do not know the group to which belongs the child. Physiotherapists have no knowledge of the results of the assessments carried out on the child.

Only the website knows the link between the patient's code and the associated treatment group. This information is available to the coordinating physician and the project manager via the website of the study in order to raise the blinding if needed. The biostatistician being the project manager, the lifting of blinding is also possible for her if a quick answer is needed, which cannot be supplied by the above-mentioned persons; in that case, she will have the opportunity to provide main information (name of the child, treatment received, results of balance sheets, etc.) without having to raise the blinding. That information will be sent by e-mail to the parents / the physician in charge of the follow-up of the child. If it is impossible to use the procedure above, she could have access of the overall information except the coding of treated/control group (she won't know in which Group A/B was the child, but she will know whether he received physiotherapy treatment).

If the patient's code is lost while a lifting of blinding is needed for medical reasons, the project manager can ask the centre manager for the patient's code. In this context, the centre manager can use the patient's code-name matrix. This request must be limited as an exception and must be recorded on the provided form. The encoded data will be used as part of the study for research and publication purposes.

The collection of the consent of the parents' patients is presented in Appendix B.

People with direct access, according to the legislative and regulatory provisions in force, including items 1121-3 and R. 5121-13 of the public health code (for example, those responsible for control of quality including monitors, clinical research assistants and unregistered students, as well as all persons called to collaborate in the research), take all necessary precautions to ensure the confidentiality of information related to experimental drugs used, trials, persons concerned, particularly in regard to their identity, as well as the results obtained. The data collected by these persons during quality controls or audits are then coded.

The knowledge of these data is subject to the respect of privacy in the context of professional secrecy to which the rights of access, rectification and opposition will apply.

7 Ethical and legal considerations

7.1 Regulatory framework of the study

During the study, the patient will be assigned either to a group control without specific treatment, or to a group receiving treatment by chest physiotherapy. The conduct of the study is described earlier.

Only the similar study Bronkilib 2 has been conducted in France on French bronchial drainage techniques. The French recommendations are to offer patients with infant moderate acute bronchiolitis a treatment by chest physiotherapy by exhalation techniques like AFE techniques. The American recommendations are to not practice physiotherapy in infant bronchiolitis.

In this study, the articles of the code of public health corresponding to the Jardé law, the rules of practice of the European Union and the Declaration of Helsinki ethical principles are respected.

7.2 Responsibility and insurance of the sponsor and the investigator

The sponsor has subscribed an insurance covering the responsibility of the investigator (and his team) for the damages that may be suffered by those involved in the study (Appendix G).

7.3 Submission of the protocol and the study contract

Before the start of the study, the protocol and the information letter, the informed consent form, the dates of study and information about the selected centres are submitted to the opinion of the French Committee for the Protection of Persons (CPP). The study can begin only after a favourable opinion of the CPP, submission of the protocol to the French National Commission for Information Technology and Civil Liberties (CNIL), and after submission for information to the French Health Authority for Medication and Biomedical Research (ANSM).

The conditions of remuneration of researchers and collaborators are specified in the Appendix H.

7.4 Amendments to the protocol and approval of amendments

Any significant change in the protocol is applicable only after agreement between the sponsor and the investigator, and following the opinion of the CPP or other competent authority (ANSM, CNIL)... depending on the nature of the amendment.

Parents/holders of parental authority of included patients will be informed.

7.5 Information and collection of free, express and informed consent

The patient's parents are informed by the prescribing physician of the protocol of the study. The prescribing physician and the physiotherapists are entitled to answer their questions about the study. Holders of parental authority have the right to cooling-off period and are told so. The consent of at least one of the holder of parental authority is collected via the consent letter, which is handed back to the physiotherapist on their first appointment. The second consent, if it has not been collected on the first appointment, is asked by phone and/or by e-mail or post. Consent search certificates will be filled for attest. The project manager collects these documents at each session and verify their compliance (Appendix B).

This search for the second holder of parental consent is delayed because:

- Our research has only negligible constraints and risks, and has no influence on the medical care of the minor;
- the search is performed on the occasion of acts of care, which are routine care, usually offered by a number of general practitioners and paediatricians in this disease,
- the other holder of parental authority cannot give his authorization within a time compatible with the duration of the study and disease,

Article L1122-2, II of the code of Public Health.

7.6 Delegation of tasks by the investigator

The coordinating physician's role is to coordinate the study, assist the principal investigator in the study (as consultant) in logistic and the safety of patients.

Prescribing physicians have to prescribe physiotherapy and to include patients in the study. They give to the parents the information letter, the consent letters and the letters of no objection, as well as practical information collection.

Evaluating physicians have to assess the Wang's Respiratory score each day of the study (T0 day1 to day3, T30 day 4), and to ensure the security of the patient (serious side effects, contraindications or anything involving the exit of the study). They must also guide the parents at the end of the study concerning the continuation of the treatment.

The on-call physiotherapists are responsible for collecting the consents of legal guardians. They must realize the day 0 RVS nasal swab and the saturation assessments, and the "inflamed/secreting child status" test each day. They must then carry out care within the study protocol and the group to which the patient is admitted. They must inform the coordinating physician and the principal investigator if any adverse event occurs or for any event requiring the exit of the study. They are responsible to collect the quality of life questionnaire from the child's parents (after the session), to ensure that there are no missing data, and transmit it to the principal investigator.

These roles will be confirmed by signing a contract (Appendice I).

7.7 Archiving

Study participants' last names, first names and emails are not recorded in the database. The patients' code, the results of the medical evaluations and tests, the treatment group and the dates of participation are the only data recorded in the database. The centre managers and the sponsor must store the study documents during the legal period of 15 years, as the following conditions:

The database will be activated during the study sessions. It will be frozen and stored on a PDF format at the end of the study by the project manager, Ms. Aurore Trébuchet, to be used for publication(s).

The consent of the patients' parents with last names, first names and contact details (emails, address, phone numbers) will be stored by the centre managers for each centre. The centre manager will not have any access to the database. An envelope will be used at each study session for the storage of these documents.

The matrix patients' code-name will be on a paper format, stored in a specific envelope. An envelope will be used at each study session for the storage of these documents.

Each centre's consents and matrix will be stored by the centre manager during the legal period of 15 years, following the rules of sensitive data protection: in a secured and sealed envelope, in a locked room only accessible by the centre manager. The access to the envelope must be limited to legal or medical reasons. This access must be recorded in the provided form, stored with the envelope following the same archiving rules. The documents must be securely destroyed at the end of the legal period of archiving.

The managers of the centres are: Mr. Thomas Baucher, centre of Saint-Germain-lès-Arpajon; Mr. Tarek Hussein, centre of Corbeil-Essonne; Mr. Jan Litwin-Staszewski, centre of Athis-Mons.

7.8 Premature stop of the study

The sponsor and/or the project manager are entitled to stop the study at any time; the CCP, the ANSM and the CNIL will be kept informed.

8 Documentation and use of the results of the study

8.1 Documentation of the results of the study

The sponsor provides an observations notebook of by subject, available on the website of the study. They will so be computerized.

All data collected in the context of the protocol will have to be transcribed into the observations notebook by the investigator or a designated representative: evaluating physicians and physiotherapists. The wording, filling and correction of the observations notebooks will be explained by the investigator. If the investigator delegate to some people the right to transcribe data in the observations notebook, he will have to provide the sponsor with the list of the persons authorized with their names, functions, signatures and initials.

The investigator or the designated representative will have to complete the notebook for comments as soon as possible after the collection of the information, preferably the very day of the visit for a clinical examination or any other procedure of the study. All pending data will be recorded immediately after the final visit. An explanation will be provided for any missing data.

The observations notebook will be reviewed and signed by the investigator responsible for the protocol, or by a designated co-investigator. The originals of all the observations notebooks will be retained by the sponsor. The investigator will keep a copy of all the filled observations notebooks.

8.2 Use of the results of the study

Information relating to the functioning of the sponsor, or the scientific data provided by the sponsor, and not yet published, are confidential and remain the sole property of the sponsor. The principal investigator commits to use that information only for the conduct of the study and for no other use unless prior written agreement of the sponsor.

Observations notebooks filled in the study are the property of the sponsor.

By signing the protocol, the investigator accepts that the results of the study will be used for purposes of publication and information of medical and pharmaceutical professionals. If necessary, the names, addresses, qualifications and roles in the study of the investigator will be notified to the authorities.

The sponsor will prepare a final report of the study (annex J).

9 Duration of the study and calendar

The duration of the study is 3 years, the recruitment of subjects should begin in November 2019 and end in March 2022. 3 sessions of 8 days of study are planned to be conducted per winter.

10 Engagement of sponsor and the investigator

The protocol has been reviewed and approved by the appropriate reading Committee and the sponsor. The information is consistent with the moral, ethical and scientific principles defined in the declaration of Helsinki, and in the French laws and regulations.

The investigator will be informed of all new or significant data, and of any new element concerning the study.

11 Budget

Estimated budget for two medical centres knowing that it is planned to recruit 168 patients on 9 sessions of 8 days (including 4 days of treatment by child):

	<i>Categories</i>	<i>Computation</i>	<i>Total</i>
Physicians			10,080 €
	Prescribing physicians	20€/consultation x 168 subjects	3,360 €
	Evaluating physicians	10€/ evaluation x 168 subjects x 4	6,720 €
Physiotherapists			18,800 €
		200€/day on call x 5 days x 2 centres x 3 sessions x 3 years	18,800 €
Administrative cost			31,700 €
	Tests RVS	Test + Transport + Analysis	14,935 €
	Study website		3,000 €
	Miscellaneous administrative expenses		4,000€
	Administrative expenses		3,000€
	Publication expenses		3,000 €
	Miscellaneous logistic expenses		3,765 €
TOTAL			60,580 €*

*Estimated budget for three medical centres: 68,780 €.

12 References

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13 Appendices

Appendice A : Contact information for investigative sites

Appendice B : Information notice, consent letter and no-objection

Appendice C : Record inclusion helps prescribing physicians

Appendice D : Wang's Respiratory score

Appendice E : Questionnaire about general health condition of the child

Appendice F : Blind procedure

Appendice G : Insurance underwritten by the sponsor

Appendice H : Planned compensation for participant to the study

Appendice I : Contract sponsor-investigator

Appendice J : Publication contract

Appendice A: Contact information for investigative sites

Centre 1

Docteur MARIN Catherine, paediatrician

Docteur REGNIER NGUYEN Hélène, paediatrician

Docteur NZONZILA LUZAMBA Joséphine, paediatrician

Address :

Cabinet libéral - Pédiatrie

3 bis rue des Closeaux

91180 Saint-Germain-lès-Arpajon

01 60 82 56 92

Centre 2

Docteur SELSELET Amina, paediatrician

Docteur COLIN Anne-Marie, paediatrician

Docteur BOUTAOUS Brahim, general practitioner

Docteur MEDDAHI M'hammed, general practitioner

Address:

Maison de Santé Pluri professionnelle Les allées

18 avenue Carnot

91100 Corbeil-Essonnes

01 85 76 01 01

Centre 3 (on going)

Docteur SALDANHA GOMES Cécilia, médecin généraliste

Docteur LANFRANCHI Michel, médecin généraliste

Docteur DUBOIS Pierre, médecin généraliste

Maison de Santé Léonie Chaptal

4 rue de l'entente

91200 Athis-Mons

01 85 74 29 90

Appendice B: Information notice, consent letter and no-objection

Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy, Placebo-controlled, on Infants With Moderate Acute Bronchiolitis.

N° ID-RCB 2018-A00946-49

Version n°4 - 30/01/2019

INFORMATION NOTICE FOR LEGAL REPRESENTATIVES

Madam, Sir,

➤ Your child suffers from infant moderate bronchiolitis. This disease due to a virus has currently no specific treatment. Your physician may propose a symptomatic treatment: bronchodilators, antipyretics. He can also propose chest physiotherapy. Chest physiotherapy in bronchiolitis is designed to bring your child to breathe in a wider way, by helping him to expectorate secretions present in his lungs. This will allow him to breathe better. There are no known side effects of these techniques, but their effectiveness in bronchiolitis is not for the time being fully demonstrated.

Study objective

➤ Chest physiotherapy by slow techniques of inspiration and expiration at high volume has for goal to help your child to move secretions from his lungs to facilitate their expectoration. This technique seems to have the advantage of having no known side effects while encouraging short-term effects in improving the comfort of the children and their parents. It is possible that these techniques could also reduce the duration of symptoms. That's what we want to check by doing this study, which is expected to include 168 patients.

Progress

➤ This study starts Friday... /... / 20... You can enter the study by Monday /... / 20 or by Tuesday... /... / 20... You are entitled to a cooling-off period until this Tuesday... /... / 20...

➤ If you agree to participate in this study, you will be included, according to the result of a draw, in one of the following two groups:

- in the first group called treated, you will have to come to the medical centre where your child will receive a physiotherapy session, which will consist of handlings of bronchial clearance such as above, and each day of the study.
- in the second group called control, you will have to come to the medical centre where your child will receive a physiotherapy session which will consist of monitoring of his respiratory and general states, each day of the study.

Your child should not eat anything within two hours before the consultation at the medical centre. He must not have received chest physiotherapy treatment during the cooling-off period.

➤ Whichever group in which your child will be assigned, a nasal swab test will be completed the first day of the study to know if your child bronchiolitis is caused by a virus. A respiratory assessment will be carried out each day of the study. Saturation (oxygen in the blood) will be measured through a device every day, just before or after the session. You will be asked to complete a questionnaire of quality of life concerning your child each day, during the session of physiotherapy. This questionnaire is a multiple choice that can be fill out in less than 2 minutes.

- The presence of your child in the study lasts four days. If your child shows a worsening of his symptoms at any time, he will automatically be taken out of study and you will be sent back to your referring physician or specialist for any necessary care. You can leave the study at any time without justification. Whatever the case, if you get out of the study, you are free to consult any physician or health professional you want if you need it.
- Your child cannot participate simultaneously in another research and, at the study end, you will have to wait until the end of the study until he could participate in another research. Similarly, if your child requires any physician or other health professional intervention other than those provided by the study, you are requested to inform the coordinating physician and the project manager, in which case your child will be taken out of the study. Indeed, the co-administration of several treatments can skew the results of the study.

Regulatory information.

As part of biomedical research to which the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne invites you to participate, a processing of your personal data will be implemented. This will allow to analyse the results of the research towards the objectives of the study, as they have been presented to you. For this reason, medical data and data relating to your lifestyle will be transmitted to the sponsor of the research or to persons acting on his account (biostatisticians), in France or abroad. These data will be identified by a code number and your initials. These data will be recorded during the legal period of 15 years by the medical centre, following the rules of data protection. These data may also, under conditions ensuring their confidentiality, be sent to health authorities, French or foreign, to other entities of the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne.

In accordance to the provisions of law relating to computing, files and freedoms, you have a right of access and rectification. You have a right of opposition to the transmission of data covered by professional secrecy which may be used or treated as part of this research. You can also access all of your health information in accordance with the provisions of article L1111-7 of the Code of public health directly or through a doctor of your choice. These rights are exercised with the physician who follows you as part of the research and who knows your identity.

You are free to refuse or suspend your participation in this study at any time without any liability nor prejudiced thereby and without having to explain. This will not alter the quality of care which will be proposed to you and will not affect your relationship with all of the health care team. If you get out of the study, information about you will be retained unless opposition from your side.

This study has received the approval of the French Committee for Protection of Persons of Paris VI the October 9, 2018, repeated the March 27, 2019. It is covered by an insurance contract subscribed by the sponsor of this study, the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne, with BiomedicInsure (SHAM n ° 144.942).

For the duration of the protocol, a viral study of a nasal swab sample will be made and this is the reason why we ask you a specific consent (see page 3) in accordance with the law of August 6, 2004. You are free to consent or not to this viral study and your refusal does not need to be justified. At the end of the study, if the conservation of your pre-authorized appears useful for continuation of the research, we will ask again your permission to keep those samples. In any case, no conservation of samples taken during this intervention will be made beyond the duration of this study, for research purposes, without your authorization.

Contact details of the study managers

➤ Manager of the data management and delegate to the data protection:

Aurore Trébuchet, 31 rue du Pont Cagé, 91790 Boissy-sous-Saint-Yon. 06.17.05.4.6.88

➤ Representative of the manager of the data management:

Thomas Baucher, 10 rue Van Gogh, 91600 Savigny-sur-Orge. 06.83.22.25.58

**Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy,
Placebo-controlled, in Infants With Moderate Acute Bronchiolitis.**

N° ID-RCB 2018-A00946-49

Version n°4 - 30/01/2019

CONSENT LETTER FOR LEGAL REPRESENTATIVES

Infant (Last Name, First name)

Born the / /

Adress

.....

The physician has proposed that my child participate in a clinical trial organized by the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne, 10 rue Van Gogh, 91600 Savigny-sur-Orge, for assessing the effects of chest physiotherapy versus placebo in infants suffering from moderate acute bronchiolitis.

He told me that I am free to accept or to refuse, and to withdraw at any time. This will not change our relationship for my treatment.

I had got the right to a cooling-off period before signing the consent letter. I received and I understand the following information:

- The purpose of this research is to assess the impact of chest physiotherapy as bronchial clearance on the evolution of the disease, evaluated by the Wang's Respiratory score (respiratory assessment), and other parameters (quality of life, oxygen saturation).
- The examinations and treatments include a session of chest physiotherapy including bronchial clearance techniques or a monitoring of the child, an assessment by questionnaire of the quality of life of the child once a day, the oxygen saturation of the child will be measured every day, and an assessment of the child's symptoms (respiratory assessment the Wang's Respiratory score) will be carried out every day of the study. A nasal swab test will also be realized the first day.

I agree to participate in this research under the conditions specified in the notice.

My consent does not absolve the research organizers of their responsibilities. I keep all my rights guaranteed by law. If I want, I'll be free at any time to stop my participation. I will then inform the coordinating physician Sébastien Rouget and the project manager Aurore Trébuchet (contact information provided on the entry form).

I agree that data recorded on this research can undergo an automated processing by the sponsor on his behalf. I have noted that the right of access under the law of January 6, 1978, relative to computers, files and liberties (article 39) is carried out at any time with the physician who follows me in the research and who knows my identity. I can exercise my right to rectification and opposition with this same physician who will contact the sponsor of the research.

I can at any time ask Dr. for more information by calling the.....

Made in, in triplicate, one of which is given to the person concerned.

Last name and first name of the holder of parental authority 1:

Address:

.....

Phone number:

Email:

Signature of the holder of parental authority 1

Last name and first name of the holder of parental authority 2:

Address:

.....

Phone number:

Email :

Signature of the holder of parental authority 2

Last name of the prescribing physician.....

Last name of the on call physiotherapist who had collected the consent letter.....

Signature of the physiotherapist

.....

**Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy,
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N° ID-RCB 2018-A00946-49

Version n°4 - 30/01/2019

LETTER OF NO OBJECTION

Madam, Miss, Sir,

In this study, we want to collect a nasal swab sample of your child to detect the presence of human Respiratory Syncytial Virus in his body. This virus is sometimes involved in infant bronchiolitis.

In this context we ask your consent:

- a) To allow us to do a study on the impact of the treatment with chest physiotherapy in children with this virus in their body. Medical data are data processing. You have rights of access or correction to the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne, 10 rue Van Gogh, 91600 Savigny-sur-Orge.
- b) To allow us to keep the samples data. These will be destroyed at the end of the study. The collected data will remain strictly confidential. They may be consulted only by the medical team, the duly mandated persons and possibly by representatives of health and judicial authorities empowered.

Made in, in triplicate, one of which is given to the person concerned.

Last name and first name of the holder of parental authority 1:

Address:

.....

Phone number:

Email:

Signature of the holder of parental authority 1

Last name and first name of the holder of parental authority 2:

Address:

.....

Phone number:

Email :

Signature of the holder of parental authority 2

Last name of the on call physiotherapist who had collected the consent letter.....

Signature of the physiotherapist

**Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy,
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Version n°4 - 30/01/2019

TESTIMONY OF SEARCH FOR CONSENT

Madam Trebuchet Aurore, project manager, certify on honour have actively searched the consent of dear Madam/Sir.....living at the following address :

.....,
second parent of the infant born the/...../.....,

for his participation of the study n°2018-A00946-49 entitled « Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy, Placebo-controlled, in Infants With Moderate Acute Bronchiolitis », realized by the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne.

The research was made by:

- ☐ Call to the phone number
- ☐ Email to the mail address
- ☐ A letter sent to the second parent's address if no answer was obtained within three days to previous contact attempts

Made the/...../.....,

In,

Appendice C: Memo for prescribing physicians

Inclusion data sheet

This sheet is meant as a guideline for the inclusion of patients. Following this sheet will ensure that you don't forget exclusion criteria and you include all patients with infant moderate bronchiolitis.

Clinical criteria for diagnosis of infant bronchiolitis (AAP)

Viral infection of the upper airways, cough or rhinorrhea, exposure to a person with a viral infection of the upper airways. Clinical signs and symptoms of bronchiolitis consist of:

- ☐ rhinorrhea,
- ☐ cough,
- ☐ tachypnea,
- ☐ wheezing, rales,
- ☐ grunting,
- ☐ nasal flaring, and
- ☐ intercostal and/or subcostal retractions
- ☐ oxygen saturation under 95%

Diagnosis :

Exclusion criteria

- ☐ Refusal of parents or holders of parental authority
- ☐ No medical prescription
- ☐ Comorbidities: cardiac, pulmonary, neurological disease, immunodeficiency, congenital anomaly, other diseases explaining respiratory symptoms
- ☐ ≥ 9 : a score ≥ 9 requires a hospitalization
- ☐ Status of the child requiring hospitalization
- ☐ No affiliation to a social security scheme

Inclusion criteria

- ☐ Acute bronchiolitis diagnosed during a medical consultation in one of the centres and medical agreement
- ☐ First episode of bronchiolitis
- ☐ $3 \leq \text{age} \leq 12 \text{ mois}$
- ☐ $3 < \text{Wang's Respiratory score} < 9$
- ☐ Informed written consent of the holders of parental authority

Wang's Respiratory score

	0	1	2	3	Child's score
Respiratory rate (breaths/minutes)	< 30/min	30 à 45 /min	45 à 60/min	> 60/min	
Wheezing	None	Terminal expiratory or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope	
Retraction	None	Intercostal only	Tracheosternal	Severe with nasal flaring	
General condition	Normal			Irritable, lethargic, poor feeding	
Total score					

Appendix D: Wang's Respiratory score

Each item is rated from 0 to 3. The total score is rated from 0 to 12. The infant bronchiolitis is considered as benign for a score less than or equal to 3, moderate for a score of 4 to 8, severe for a score greater than or equal to 12.

Variables	Scores			
	0	1	2	3
Respiratory rate, breaths/min=RR	<30	31-45	46-60	>60
Wheezing=WH	None	Terminal expiratory or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Retraction=RE	None	Intercostal only	Tracheosternal	Severe with nasal flaring
General condition=GC	Normal			Irritable, lethargic, poor feeding

Questionnaire d'évaluation de l'état général du nourrisson

Sex: ☐ masculin ☐ féminin

To assess the possible impact of smoking on infant bronchiolitis, it would be useful to clarify your smoking habits:

☐ The nanny smokes ☐ One parent smokes ☐ Both parents smoke Non-☐ smokers

It is important that you answer all items so that we can calculate his score. This will allow us to have appropriate results to reflect the actual state of your baby. In order to share all necessary information to be able to answer accurately, please remember to exchange all appropriate about your child's state with your spouse (husband) if she or he was absent any time of the day, in particular with regard to meals. This will ensure that the person who has to answer to the questionnaire will have all the needed information.

[illegible]

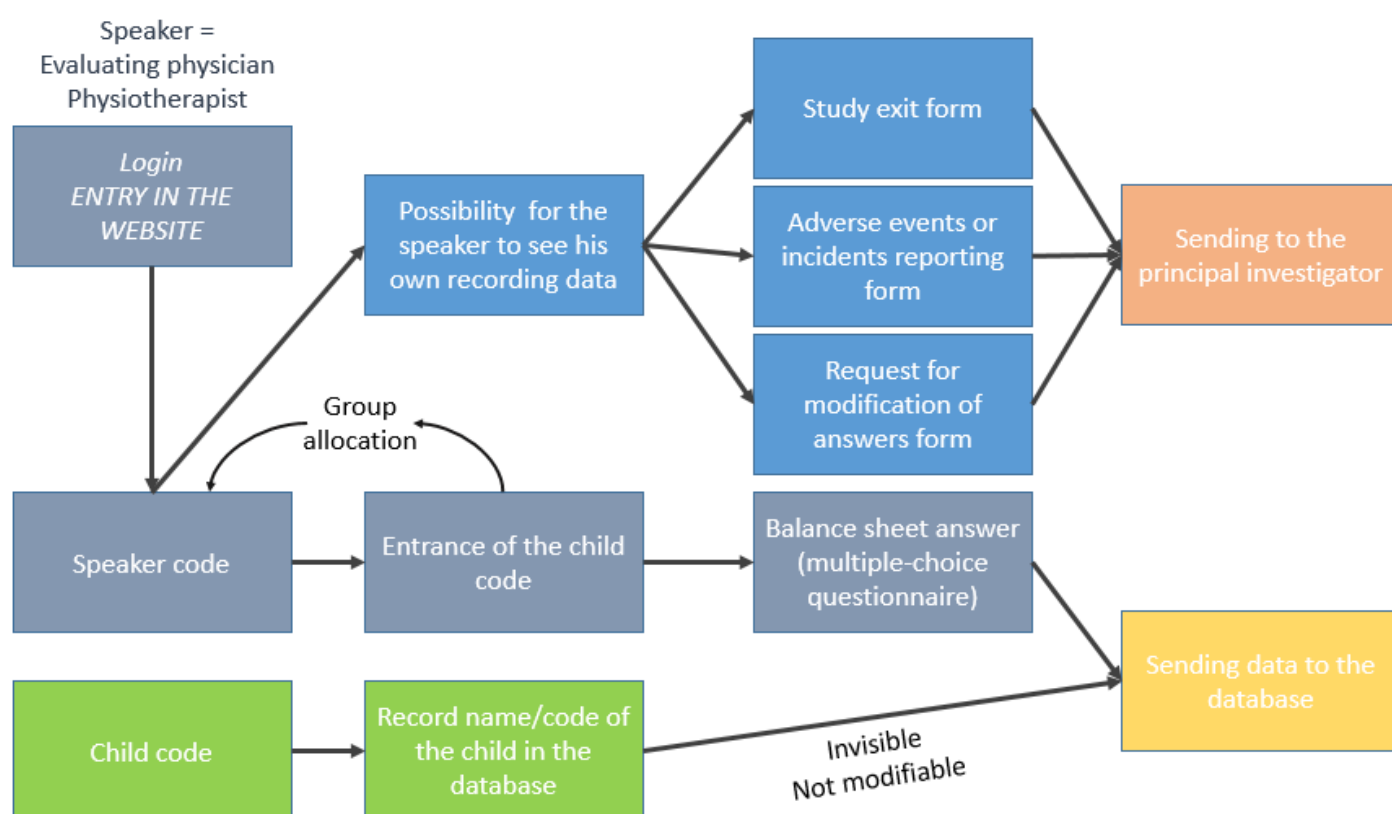
26. Il y a une bonne entente entre ses parents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Il est souvent malade	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. il dort bien	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Il a un rythme de vie équilibré	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. Il pleure souvent	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. Son mode de garde est satisfaisant	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. Il est câlin, affectueux	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33. Quand il pleure, on comprend bien pourquoi	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Il n'est pas sauvage	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

As part of biomedical research to which the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne invites you to participate, a processing of your personal data will be implemented. This will allow to analyze the results of the research towards the objectives of the study, as they have been presented to you. For this reason, medical data and data relating to your lifestyle will be transmitted to the sponsor of the research or to persons acting on his account, in France or abroad. These data will be identified by a code number and your initials. These data may also, under conditions ensuring their confidentiality, be sent to health authorities, French or foreign, to other entities of the physiotherapy network Réseau Kinésithérapie Bronchiolite Essonne.

In accordance to the provisions of law relating to computing, files and freedoms, you have a right of access and rectification. You have a right of opposition to the transmission of data covered by professional secrecy which may be used or treated as part of this research. You can also access all of your health information in accordance with the provisions of article L1111-7 of the Code of public health directly or through a doctor of your choice. These rights are exercised with the physician who follows you as part of the research and who knows your identity.

[Translation of the items of the score (not validated): 1. He eats well - 2. He looks good - 3. He's awake - 4. He is always in pain - 5. He plays well - 6. He's nervous - 7. He likes that we take care of him - 8. He's happy, he smiles easily - 9. He lets people come near to him easily - 10. He is always needing that we take care of him - 11. He has got a good family circle - 12. He's growing well, healthily - 13. He's playful, cheeky - 14. He often looks worried - 15. He tries to get noticed - 16. He's lively - 17. He cries as soon as he is alone - 18. He likes to play - 19. He's able to adapt easily to change - 20. He is impossible - 21. He chirps - 22. He's curious, interested, and open to his environment - 23. He often asks to be carried - 24. He's graceful - 25. He likes to see people - 26. There is a good relationship between his parents - 27. He's often sick - 28. He sleeps well - 29. He has a balanced rhythm of life - 30. He's often crying - 31. The chosen childcare seems satisfied - 32. He's cuddly, affectionate - 33. When he cries, we easily understand why - 34. He's not savage.]

Appendice F: Blind procedure



The physiotherapists only had got access to the information of the group code: treated / control.

Database: automatic recording

Child code	Wang's score J1	Wang's score J4	QUALIN score	QUALIN score by items (34 columns)	Oxygen saturation (per day = 4 columns)	RVS (0 = négative, 1 = positive)	Status (0 = inflamed, 1 = secretant)	Adverse events	Study exit

Score QUALIN, adverse effects, data outputs of studies reasons will be returned in the database by the project manager via the web site of the study with his ID (non-exhaustive list).

Appendice G : Insurance underwritten by the sponsor (translation below)



HDI Global SE
Tour Opus 12 – Défense 9
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92914 PARIS LA DEFENSE CEDEX
478 913 882 RCS Nanterre
N° SIRET : 478 913 882 000 54

COURTIER EN ASSURANCES
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biomail@biomedic-insure.com



ATTESTATION D'ASSURANCE RESPONSABILITE CIVILE PROMOTEUR DE RECHERCHES IMPLIQUANT LA PERSONNE HUMAINE

CONTRAT N° 0100534514058 180042

Nous, soussignés **HDI GLOBAL SE** - Direction pour la France - TOUR OPUS 12, 77, Esplanade de la Défense 92914 PARIS LA DEFENSE agissant en qualité d'assureur, attestons par la présente que :

RESEAU KINESITHERAPIE BRONCHIOLITE ESSONE
10 RUE VAN GOGH
91600 SAVIGNY SUR ORGE

a souscrit un contrat de Responsabilité Promoteur de recherche impliquant la personne humaine sous le numéro ci-dessus référencé.

Ce contrat est conforme aux dispositions légales et réglementaires Françaises sur les recherches impliquant la personne humaine et notamment aux dispositions de la loi 88.1138 du 20/12/1988, modifiée par les textes subséquents notamment la Loi n°2012-300 du 5 Mars 2012 et son décret d'application n°2016-1537 du 16 Novembre 2016, pour la recherche dénommée ci-après :

Nom du promoteur : RESEAU KINESITHERAPIE BRONCHIOLITE ESSONE

Numéro d'enregistrement : 2018-A00946-49
(EUDRACT ou n° fourni par l'ANSM)

Titre de la recherche :

Essai contrôlé randomisé multicentrique : Evaluation des effets de la kinésithérapie respiratoire versus placebo chez le nourrisson atteint de bronchiolite aigüe modérée.

Nombre de patients : 168

Début et fin prévisionnels : du 01/12/0018 au 28/02/2021

La garantie est conforme à l'obligation d'assurance instituée par les textes de la loi précitée, article L 1121-10 du Code de la Santé Publique et articles R 1121-4 à R 1121-9 à la charge du promoteur, tant pour sa responsabilité que pour celle des intervenants.

La présente attestation est valable pour la durée de la recherche concernée et sa présentation vaut présomption de garantie à la charge de l'assureur.

Fait, le 17/04/2018


Le Courtier
BIOMEDIC INSURE
COURTIER EN ASSURANCES
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L'Assureur
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Executive Board: Dr. Christian Hirsch (Chairman),
Dr. Joachim ten Eicken, Frank Harting, Dr. Edgar Puls,
Dr. Stefan Sigulla, Jens Wohlthat, Ulrich Wollschläger

The start and end dates of the insurance contract will be updated as needed prior to the launch of the study

Translation of the Insurance Contract

INSURANCE CERTIFICATE

CIVIL RESPONSIBILITY FOR SPONSOR OF RESEARCH INVOLVING THE HUMAN PERSON

We undersigned HDI GLOBAL SE - Direction pour la France - TOUR OPUS 12, 77, Esplanade de la Défense 92914 PARIS LA DEFENSE acting as an insurer, attest hereby that:

RESEAU KINESITHERAPIE BRONCHIOLITE ESSONE
10 RUE VAN GOGH
91600 SAVIGNY SUR ORGE

signed a contract of responsibility for sponsor of research involving human under the above referenced number.

This contract is in accordance with French legal and regulatory provisions on researches involving human and including the provisions of the Act 88.1138 of 20/12/1988, amended by the subsequent texts including the law n ° 2012-300 March 5 2012 and its implementing Decree No. 2016-1537 of November 16, 2016, for the referred search:

Sponsor name: RESEAU KINESITHERAPIE BRONCHIOLITE ESSONNE

Registered number: 2018-A00946-49

(EDRACT or n° provided by the ANSM)

Title of the study:

Multicentre Randomized Controlled Trial: Evaluation of the Effects of Respiratory Physiotherapy, Placebo-controlled, in Infants with Moderate Acute Bronchiolitis.

Patients number: 168

Forecasted start and end: du 01/12/2018 au 28/02/2021

The warranty is consistent with the obligation of insurance set up by the texts of the above law, article L 1121-10 of the Code of public health and R 1121-4-R 1121-9 at the expense of the sponsor, both for its responsibility and that of others stakeholders.

This certificate is valid for the duration of the concerned research and its presentation is a presumption of guarantee from the insurer.

Appendice H: Planned compensation for participant to the study

Remuneration of the physicians

A added remuneration of 20 euros per medical consultation is provided for the prescribing physicians. A remuneration of 10 euros per evaluation (Wang's Respiratory score) is provided for the evaluating physicians.

Remuneration of the physiotherapists

A remuneration of 200 euros per on-call day is provided for the physiotherapists.

Funding constraint

In case of difficulty in finding full project financing, the remuneration may be partially reduced. Stakeholders have been warned and the possibility of voluntary interventions in the context of the study has been discussed with them.

Patient compensation for participating in a study

The costs related to the care carried out as part of the study (medical assessments, respiratory physiotherapy sessions) are fully covered by the sponsor via the remuneration specified below. Patients only pay for consultation with the prescribing physician, whether or not they enter the study.

Appendice I: Sponsor-Investigator contract

PARTICIPATION CONTRACT FOR AN INTERVENTIONAL STUDY

Between the undersigned

Réseau Kinésithérapie Bronchiolite Essonne, 10 rue Van Gogh, 91600 Savigny-sur-Orge

hereinafter referred to as "the promoter"

et

..... Prescribing physician/evaluating physician/physiotherapist,

Address

Phone number

Registered on the board of the County Council of the order of..... under the number

With the ADELI number

hereinafter referred to as "the speaker"

Article 1 – Object:

The signatory has decided to exercise his profession with the patient included in the study on the basis of a contract of participation in an interventional clinical trial as a speaker with the sponsor.

Article 2 – Obligations of the parties:

Signatory obligations:

The signatory prescribes/evaluates/exercises with the patients included in the study and ensures the achievement of the task entrusted to him such as described in the study protocol. The signatory practices in his usual workplace or on premises proposed by the sponsor. He practices in respect of his usual professional obligations.

The signatory reports to the sponsor any incident that can be defined as an adverse event, serious or not, through the online form on the site of the study. The signatory respects professional secrecy on his activities concerning the patients and concerning the study until the end of the full study. In particular, the login provided to the signatory should not be disclosed to a third party, or be used for other purposes than those included in the framework of the study.

The signatory provides the documents related to the study exclusively to the sponsor or to the project manager. These documents may not be disclosed to a third party.

Sponsor obligation:

The sponsor will notify to the signatories the end of the study and inform them of the final results.

Article 3 – Training:

The signatory is committed to participate in short trainings for the homogenisation of practices within the study.

Article 4 – Duration of the contract:

This agreement covers the period going from the / / to the / /

Article 5 - Respect of the professional rules:

Signatories commit themselves to respect the legislative provisions and regulations relating to the exercise of their profession, including the code of ethics and to maintain their activity within limits so that the patients receive conscientious, bright, attentive and careful care, consistent with acquired science data.

They must refrain from any action that would impede the free choice of the practitioner by the patient.

Furthermore, they respect the will of the patient to leave the study at any time without justification and must inform the sponsor.

Article 6 – Insurance:

Any incident that could be considered as undesirable is reported by the signatory to the sponsor through the online form on the web site of the study. The sponsor insurance cover incidents involved in the study.

Nevertheless, the signatory must be insured for its professional acts to be admitted as a participant in the study, and must provide proof of this insurance.

Article 7 – Benefits:

The signatory is compensated by:

- 20 euros by included child in addition to the price of the consultation for prescribing physicians,
- 10 euros for evaluating physicians for each check-up carried out,
- 200 euros per on-call day for physiotherapists,

These compensations are subject to obtaining the planned financing. Details on the distribution of funding by post in the study can be sent on request.

The expenses related to the operation of the premises, to physiotherapists technical installation and material provided by the study is the responsibility of the sponsor, in case premises, installation or equipment relating to the study are different from those of the signatory.

Costs related to the movement of the signatory on the place of exercise and meals are the responsibility of the signatory.

Article 8 – Taxes and charges:

The signatory declares being registered as independent worker from the URSSAF under n° or employee with the SIRET (VAT number property) n°

The signatory and sponsor pay all the taxes and charges arising from their own professional practice. Property tax remains the responsibility of the owner of the premises.

Article 9 – Adjournment of the contract:

Should the signatory be absent, especially on account of illness, he will inform as early as possible the sponsor in order to be replaced. It is up to the sponsor to ensure the replacement of the signatory.

Article 10 – Termination of the contract:

Each party may terminate this agreement at any time without having to justify any reason, with a notice period of two weeks.

The notice must be brought to the knowledge of the other party by registered letter with acknowledgement of receipt.

The respect of this notice period is not imposed upon termination for conviction of a serious breach from one or the other party to the professional and ethical rules, when the breach has been sanctioned by a final decision prohibiting to exercise or deliver care, or in breach of the rules of professional secrecy regarding the study.

Article 11 - Conciliation:

In case of problems raised by the application or the interpretation of this Act, and in accordance with article R.4321 - 99 (2) of the code of public health, the parties undertake, prior to any court action, and without sacrificing to the time limits for introduction and / or continuance of suit, to submit their dispute to an attempt of reconciliation assigned as needed to the County Council of the order of the physiotherapists or the order of physicians.

The conciliation procedure organised pursuant to article R.4321 - 99 (2) of the code of public health differs from prior conciliation to disciplinary action on complaint.

Article 12 - Litigation:

In the event of failure of conciliation, litigation or disputes concerning the validity, interpretation, execution of the present contract will be submitted to the competent court.

Made the/..../.....,

In,

In duplicate:

Signatures preceded by the words "*read and approved*":

Appendice J: Publication contract

Publication contract between the co-writers

This agreement is intended to establish the order of the names of the various authors appearing in publications of the results of the study.

The criteria for the appearance as authors are:

- participation in the implementation of the study (method, design, data collection, analysis of the results),
- participation in the writing of the article,
- endorsing the overall content of the article.

The order of appearance of the authors will be the following:

1. Thomas Baucher
2. Aurore Trébuchet
3. Tarek Hussein
4. Bruno Tirel
5. Jeremy Cornuault
6. Audrey Rousselin
7. Tony Roho
8. Nadia Demayer
9. Cheikh Sidate Diouf
10. Benjamin Azémar
11. Sebastien Rouget

Made in: The

Name of the author : Signature:

Name of the author : Signature:

Name of the author : Signature:

Name of the author : Signature:

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