SENTINEL Lymphome

« Relevance of a Web-mediated Follow up in Patients Having a Lymphoma With a High Risk of Relapse in Complete or Partial Response»

ClinicalTrials.gov: NCT 03154710

Secondary ID: 2016-A01024-47
Sponsor Ref: ILC-1-2016

Coordinating investigator:

Dr Katell LE DU

Institut Inter-Régional de Cancérologie – Centre Jean Bernard
9 rue Beauverger – 72000 LE MANS

Scientific Commitee:

Dr Fabrice DENIS
Dr Katell LE DU
Dr Réda BOUABDALLAH
Dr Christophe FERME
Dr Corinne HAIOUN
Dr Philippe SOLAL-CELIGNY
Pr Hervé TILLY
Dr Olivier LALAUDE
Pr Olivier TOURNILHAC
Dr Pauline BRICE
Dr Olivier CASASNOVAS
Dr Laurence BRUGIERES

Sponsor:

WeproM

2 square Gaston Allard
49000 ANGERS
Tel: 02 41 68 29 40
Fax: 02 41 68 29 79
*H*ead Office : *9 rue Beauverger - 72000 LE MANS*

TABLE OF CONTENTS

1. STUDY RATIONALE

1.1. LYMPHOMA

Lymphomas are malignant hemopathies of lymphoid tissue, of ganglionic or extranodal origin. A classic distinction is made between Hodgkin's disease (MDH) and Non-Hodgkin's lymphomas (NHL).

Lymphoma is the 6th cancer in terms of incidence in France, where around 11,000 new cases are diagnosed each year. Most types of lymphoma are found at all ages with a predominance in the elderly.

The most common diagnostic circumstance is detection of malignant lymphoma in the form of a lymph node mass. When these lymphadenopathies are deep and voluminous, they can be revealed by the presence of various and non-specific symptoms: cough, pleural pain, vena cava depressive syndrome, abdominal pain, transit disorders, etc.

Since these tumors are highly chemo-sensitive, treatment is mainly based on chemotherapy: chemo-immunotherapy for NHL and radio-chemotherapy for Hodgkin's lymphoma.

For "aggressive" lymphomas, current chemotherapy regimens achieve a complete remission rate of 60 to 80% (1) and a 5-year survival rate of approximately 70%.

Thanks to the continuous improvement of diagnostic techniques and treatments, the prognosis of lymphomas is constantly improving. However, 20 to 40% of patients most often relapse within 2 or 3 years after the end of treatment (2, 3).

In the event of a relapse, the treatment regimen usually offered to patients consists of salvage chemotherapy followed by an autologous transplant.

1.2. PATIENT FOLLOW-UP

The objectives of post-treatment follow-up are to:
- detect local or remote recurrences,
- detect and manage late complications related to treatment as well as sequelae,
- organize the necessary supportive care,
- ensure the quality of life
- early detection of a second cancer.

The current monitoring framework includes a clinical examination and a biological assessment every 3 months for 2 years and then every 6 months up to 5 years and an imaging assessment every 6 months. However, the value of this systematic imaging surveillance is controversial (4-7) and no randomized study has been carried out on this subject. Several observational studies suggest that systematic imaging surveillance can detect patients with asymptomatic relapse, but none show earlier relapse detection (8, 9), nor any difference in survival.

According to Voss et al for patients (children or adolescents) followed for Hodgkin lymphoma in remission, the majority of relapses were detected by the appearance of symptoms, clinical manifestations or laboratory abnormalities (4, 10-13).

Another problem is the repeated exposure to radiation during each scan with a potentially increased risk of a second cancer (15, 16). These imaging tests can also generate anxiety in patients in asymptomatic remission, especially just before and while awaiting the results of these tests. Imaging

assessment can lead to the detection of false positives, which involves performing additional examinations, including biopsies that are also painful, expensive and anxiety-inducing (14).

These constraints would be acceptable if the relapse was detected before clinical manifestations and allowed patient survival to be increased.

Thompson et al recently published the results of a study regarding the utility of imaging surveillance in a large cohort study in patients with diffuse large B-cell lymphoma. Routine imaging surveillance allows detection of asymptomatic relapse in only 1.7% of patients (17, 18).

In this context, Huntington et al assessed the medico-economic impact of routine imaging surveillance. The results show that the clinical benefit of systematic imaging monitoring of asymptomatic patients in remission is very low or even zero compared to the substantial cost incurred (19).

1.3. MOOVECARE TOOL FOR LYMPHOMA RELAPSE DETECTION

We have developed a score based on the dynamics and the combination of clinical and biological signs to alert the doctor of a possible recurrence of lymphoma

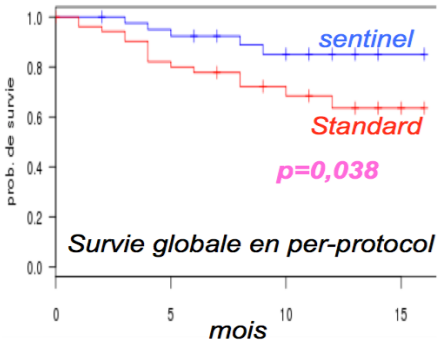
The considered clinical symptoms will be self-assessed (presence / absence or no problem / slight problem / medium problem / significant problem) by patients every 1 to 2 weeks, sent by their Smartphone or computer via the Internet, and will be analyzed by software that determines whether or not a relapse or significant complication is likely. The referring doctor will thus be alerted early and will summon the patient early for a check-up.

A similar application has been developed to detect relapse of lung cancer early (20, 21). The prospective study of this application showed interesting results in these patients with 100% sensitivity, 89% specificity, 81% PPV and 100% NPV with 11 symptoms studied. In the initial study to establish a detection algorithm based on only 6 symptoms, a NPV of 93% was already noted (20). In addition, relapses were detected on average 5 weeks before the scheduled date of the follow-up assessment (images every 3 months) (21).

An analysis of overall survival (monocentric and non-randomized) in our center also suggests a gain in survival of nearly 24% at 1 year ($p = 0.02$) (22). This gain in survival is most likely related to the early initiation of salvage treatment and supportive care.

In the follow-up of the patients, it appeared that the algorithm was more sensitive if the patients were not very symptomatic at inclusion and had an initial score of less than 7 (by adding the scores of 0 to 3 for the symptoms concerning cough, dyspnea, pain, anorexia and asthenia: no problem = 0, mild problem = 1, medium problem = 2, significant problem = 3). A phase 3 study comparing this computerized surveillance with surveillance according to the usual method is in progress.

The results of the interim study suggest a favorable trend in overall survival in user and compliant patients (use at least once a week): 62% in the standard arm versus 87% in the SENTINEL arm: p(logrank)=0,038 (23).



Results of the interim analysis of the phase 3 study
Per-protocol analysis of overall survival (p=0,038).

1.4. DESCRIPTION AND JUSTIFICATION OF THE INTERVENTION UNDER STUDY

As part of this study, we want to assess the value of web-application monitoring of patients treated for lymphoma in complete or partial response.

The underlying assumption is that the use of new information and communication technologies can improve the clinical follow-up of patients. To date, access to the Internet and to portable technologies is sufficiently wide and democratized to consider the use of this type of telemonitoring in the field of health; in particular to facilitate the dissemination of information between the patient and the doctor. It is thus possible to imagine using this flow of information to generate alerts, in the particular case of the application with the doctor, for example according to the symptoms felt and informed by the patient.

Strengthening clinical monitoring in this indication in which routine imaging has not demonstrated its value, in particular through the implementation of remote monitoring completed by the patient, may present an advantage in terms of efficiency and earliness. support. In fact, in this pathology, up to 40% of patients relapse early (within 2 to 3 years), in the vast majority of cases symptomatically (less than 2% of asymptomatic relapses discovered by imaging); and finally, the current follow-up by tomodensitometry every 6 months, which generates costs and radiation exposures for a benefit considered rather low, has been carried out in symptomatic patients for several weeks.

In addition, reinforced clinical follow-up can improve the early detection of relapses, and would also aim to improve the monitoring of all the significant clinical complications frequent in patients suffering from a serious pathology (sepsis, thromboembolism, late iatrogenias, etc.); if a survival benefit is to be hoped for, it will very probably be due on the one hand to the early detection of relapses and better control of the relapse through the implementation of early treatments, and on the other hand to the management and the early implementation of appropriate supportive care, if only through the management of depressive symptoms, or the management of iatrogenic or other complications.

However, in a context of increasing health needs and recourse to the health system, but also of medical shortage and strict control of health expenditure, strengthening the clinical monitoring of patients can only be considered by putting in place implement the means, if they prove to be effective, as efficient as possible, particularly in terms of time and costs. In this sense, involving the patient and implementing telemedicine solutions now appears very relevant by avoiding unnecessary travel and examinations.

1.5. BENEFITS ET RISKS

1.5.1. Benefits

1.5.1.1. Individual benefits

The expected benefit for patients using the Moovecare application will mainly be to have personalized follow-up, between 2 consultations. This strengthened clinical follow-up could allow earlier detection of a possible relapse or progression of lymphoma, promote early treatment and better control of the relapse. It could also improve the detection of possible complications related to treatment or the disease but also reduce the anxiety induced by routine surveillance examinations, and thus improve the quality of life of patients.

1.5.1.2. Collective benefits

Beyond the benefit for patients in terms of disease control and quality of life, the use of the Moovecare application makes it possible to space out the follow-up by imaging and thus reduce the stress and costs caused by the follow-up. standard of patients treated for lymphoma.

1.5.2. Risks

1.5.2.1. Individual risks

Constraints

The constraints are minimal and consist in competing:

- for all patients, a quality of life questionnaire and a questionnaire relating to depression at inclusion and then at follow-ups at 3, 6, 9 and 12 months
- for patients in the "web app follow up" arm, a satisfaction survey during the 6-month follow-up and at least every 14 days the specific questionnaire via a computer or a smartphone. The entry time is of the order of 1 to 2 minutes.

There is no further examination.

Risks associated with the disease

The risks of natural progression of the disease were not affected by this study.

1.5.2.2. Collective risks

None

1.5.3. Benefit/risk balance

As part of this study, we want to assess the value of web-application monitoring of patients treated for lymphoma in complete or partial response.

The web-application follow-up is a reinforced clinical follow-up with which it is unlikely that the events (complications or relapses) will be diagnosed later than during standard imaging follow-up. All

patients will be followed in consultation every 3 months. It is therefore expected that the use of the Moovcare app will only benefit patients.

The underlying hypothesis is that a strengthening of clinical monitoring, where the patient can regularly inform his doctor about his symptoms, would allow earlier discovery of relapses, and / or any other event requiring medical treatment.

A web-application follow-up could thus promote the earlier treatment of relapses and / or other medical events occurring during follow-up, and thus improve the survival of patients and their quality of life as suggested by the phase study. III in bronchial cancer.

Optimizing clinical follow-up could also favor the spacing out of systematic imaging follow-up, which has limitations. This reduction in the frequency of check-ups would benefit the patient by reducing his exposure to radiation, but also the benefit of society by reducing the overall cost of monitoring patients treated for lymphoma.

2. OBJECTIVES END ENDPOINT

2.1. OBJECTIF ET CRITERE D'EVALUATION PRINCIPAL

2.1.1. Primary objective

The main objective of the study is to show that follow-up via the Moovcare web-application could make it possible to better identify the significant complications occurring between two systematic follow-up consultations with the specialist in patients followed for high-risk lymphoma. relapse than with standard follow-up. The evaluation of the main objective will be carried out over 6 months of follow-up.

2.1.2. Primary endpoint

The primary endpoint is the appearance of a significant complication detected and confirmed by a medical consultation performed outside of standard follow-up.

The significant complications are:

- emergency hospitalization,
- a medical consultation without follow-up with medical prescription (imaging / drug prescription)
- a significant event at the classic follow-up consultation (very degraded PS, antibiotic therapy, supportive care with consultation, pulmonary embolism, sepsis, severe depression, etc.)

We will identify in the web-app group, the absence of alert in the event of complications and in the standard arm, the absence of medical consultation (attending physician) in the event of complications.

Complications diagnosed during the follow-up consultation will be reviewed in the form of a list by the coordinator, who will rule on the significance of the complication.

2.2. SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1. Secondary objectives

The interest of web-application monitoring will also be assessed in terms of:

- progression-free survival,
- overall patient survival at 2 years,
- estimated time between the diagnosis of a complication, allowed by the application, and the theoretical date of the scheduled subsequent follow-up,
- proportion of hospitalization for life-threatening emergencies,
- total number of complications observed,
- quality of life of patients,
- the degree of patient compliance with the use of the web application
- the degree of satisfaction with the use of the web-application and the implementation of web-monitoring,
- number of significant complications whatever they may be (but defined above), which have arisen and not identified via the application (sensitivity calculation),
- number of significant complications whatever they may be (but defined above), which have arisen and identified in the systematic follow-up group, excluding systematic follow-up,
- Performance Status at relapse,
- description of health consumption in the 2 groups.

2.2.2. Secondary endpoints

Progression-free survival is defined as the time between the date of the first examination making the diagnosis of partial response or complete response and the date of consultation allowing the diagnosis of the relapse.

The diagnosis of partial or complete response, as well as relapse in this study follows the definition of the Cheson criteria.

The time between the date of diagnosis of the relapse and the nearest consultation date scheduled as part of the standard follow-up will be evaluated. The same will be done with the date of diagnosis of significant complications.

The time taken to set up a treatment will also be evaluated. Thus, the time between the date of diagnosis of each event and the date of implementation of the care (1st psychological consultation, date of D1 of treatment, etc.) will be evaluated.

Overall survival is defined as the time between the date of diagnosis of the complete or partial response as defined in chapter 2.1.2 and death from any cause within 2 years.

Quality of life will be studied using the QLQ-C30 and HUMEUR PhQ9 questionnaires at inclusion and then follow-up consultations at 3, 6, 9 and 12 months.

Patient compliance with the use of the web application will be assessed based on the number of assessments completed by patients; an evaluation every 14 days is expected. Patients who have completed less than 1 assessment per 42 days (6 weeks) will be considered non-compliant. An overall compliance rate over the entire period and a rate per 14-day period can then be presented.

The satisfaction and feelings of patients with regard to the web-monitoring and the use of the web-application will be assessed by a self-questionnaire during the follow-up visit in the 6th month.

The calculation of the application's sensitivity is based on the evaluation of the number of alerts triggered by the application against the results of systematic or alert-triggered imaging examinations.

The Performance Status will be assessed according to WHO recommendations.

The description of health consumption will be assessed by the number of consultations, imaging and laboratory tests performed by the patients in each group.

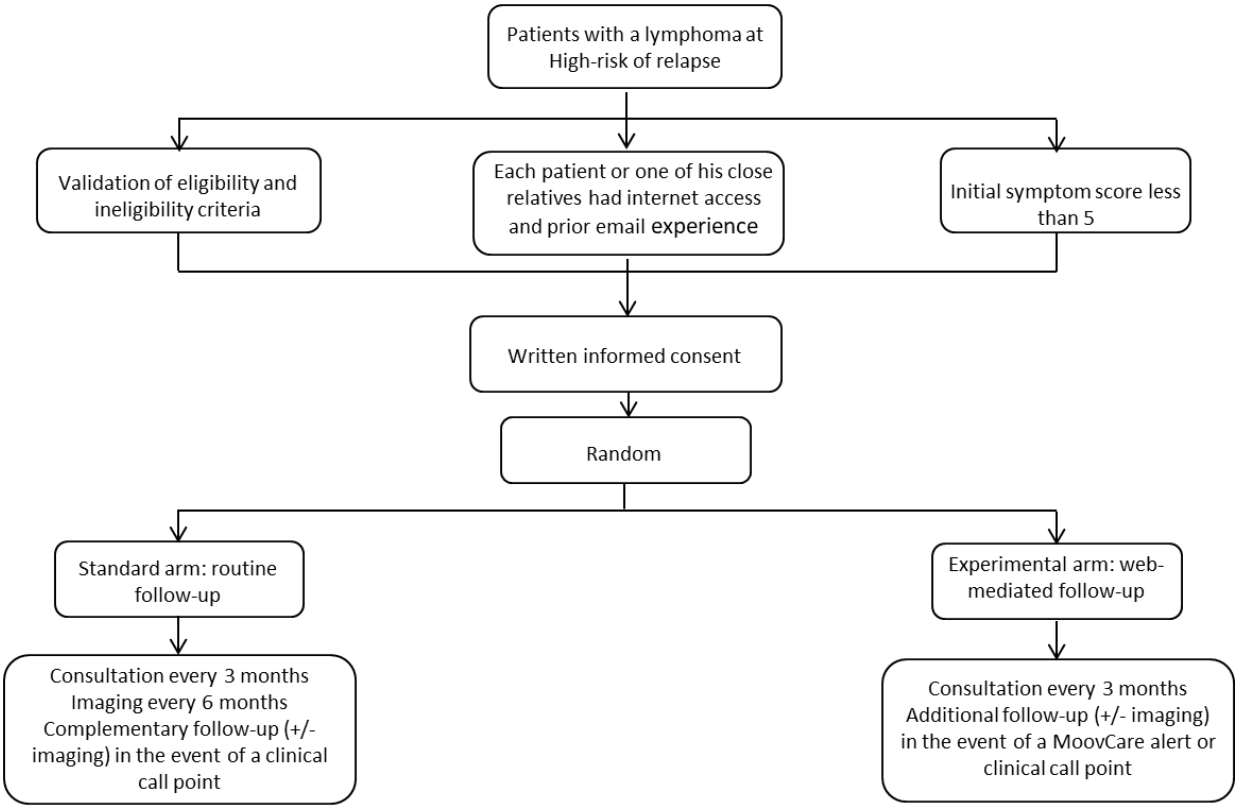
3. STUDY DESIGN

3.1. STUDY METHODOLOGY

This research is a cohort study, aimed at evaluating the value of web-application monitoring for the detection of relapses, and of any other event justifying medical treatment, in patients treated for partial response lymphoma. or complete.

It is a multicenter, prospective, longitudinal and randomized study.

3.2. STUDY SCHEMA



4. STUDY POPULATION

The population concerned includes all patients with lymphoma at high risk of relapse, in follow-up for this cancer and having access to the Internet.

We plan to include 80 patients over a 48-month period.

4.1. INCLUSION CRITERIA

1) Patient with either:
    a. T-cell lymphoma in first complete or partial response
    b. Hodgkin lymphoma in 2nd complete or partial response including after autograft
    c. c. Large B-cell diffuse lymphoma in 2nd complete or partial response including after autograft
2) End-of-treatment imaging in the last 4 weeks
3) Age ≥ 18 years
4) PS ≤2 (WHO)
5) Patient with an initial symptoms score less than or equal to 5
6) Patient with internet access and mailbox
7) Patient affiliated to a social security scheme
8) Patient with written consent prior to any procedure specific to the study

4.2. NON INCLUSION CRITERIA

1) Patient whose lymphoma progressed at the end of the specific treatment (evaluation <3 months after the end of the previous treatment)
2) Symptomatic brain or meninges localization
3) Presence or history of another cancer in the last 3 years, except skin cancers (other than melanoma), in situ cancers of the cervix or other cancers considered cured
4) Persons deprived of their liberty or under trusteeship
5) Dementia, mental impairment or psychiatric pathology that may compromise the informed consent of the patient and / or compliance with the protocol and follow-up of the study
6) Patients who cannot follow the protocol for psychological, social, family or geographical reasons,
7) Pregnancy or breast-feeding
8) Patient participating in another interventional study

5. STUDY DESCRIPTION

5.1. BASELINE

Patients eligible for the trial will be required to sign a consent to participate. A patient who has already been included in the study cannot be included a second time in the event of a new response to the treatment implemented.

For the initial inclusion assessment, certain examination results (extension assessment for a given pathology) carried out prior to signing the consent may be used if they were done within the time limits requested in the protocol.

5.1.1. Clinical assessment

It includes a complete clinical examination (within 2 weeks prior to inclusion) with:

- the history of the disease,
- the evaluation of weight and PS,
- the calculation of the initial score,
- completion of the QLQ-C30 and PhQ-9 quality of life questionnaires.

5.1.2. Imaging assessment

It should be less than 4 weeks old at the time of inclusion and start of surveillance and includes a thoraco-abdomino-pelvic (TAP) at least (cervical at best) and / or a PET scan.

5.2. STUDY EVALUATIONS

The type of follow-up the patient will benefit from will be assigned by randomization.

Patients will be able to benefit from the supportive care adapted to their situations. The need for this supportive care can be detected during consultations or through the application.

All patients will be seen in consultation every 3 months with a clinical examination including estimation of the PS and a biological assessment (according to the clinician's habits).

The questionnaires (QLQ-C30 and PhQ-9) will be completed again at the 3,6-,9- and 12-month follow-ups.

For patients randomized to the "standard" arm, a systematic imaging workup (minimum TAP CT (cervical at best)) will be performed every 6 months corresponding to standard follow-up.

Patients randomized to the "Web-application follow-up" arm will perform a self-assessment of symptoms via the Moovcare application with a maximum interval of 14 days between 2 seizures, and if necessary, each time symptoms appear.

In the event of a Moovcare alert (and telephone call to the patient) suggesting a relapse or a complication, a CT scan and / or other evaluation examination (PET, biopsies, etc.) will be scheduled within ideally less than 14 days depending on the type of alert.

To be able to connect to the application, included patients will receive personal access codes to the application by email with instructions for use:

- access to the application is via a username and password,
- the password is encrypted in the host's database,
- access to the application is via a secure SSL connection (https) which is a protocol for securing data exchanges between the client and the application server,
- a brute force intrusion detection system makes it possible, when too many connection attempts are detected, to deactivate the account in question.

A satisfaction questionnaire will be taken at the 6-month follow-up.

5.3. SCHEDULE OF THE STUDY

For patients randomized to the "standard" arm:

	Baseline	M3	M6	M9	M12	M15	M18	M21	M24
Eligibility criteria	X								
Study presentation / Written inform consent	X								
Cancer history	X								
Physical exam (PS, weight)	X (- 15 days)	X	X	X	X	X	X	X	X
Biology report (parameters at the discretion of the investigator)		X	X	X	X	X	X	X	X
Initial Symptom score	x								
Imaging assessment	X (- 4 weeks)		X		X		X		X
Quality of life questionnaires	X	X	X	X	X				

For patients randomized to the "web-application follow up" arm:

	Inclusion	M3	M6	M9	M12	M15	M18	M21	M24
Eligibility criteria	X								
Study presentation / Written inform consent	X								
Cancer history	X								
Physical exam (PS, weight)	X (- 15 days)	X	X	X	X	X	X	X	X
Biology report (parameters at the discretion of the investigator)		X	X	X	X	X	X	X	X
Initial Symptom score	x								
Self assessment	Every 14 days maximum for patients included in the "web application follow-up" arm								
Imaging assessment	X (- 4 weeks)	In the event of a Moovcare alert or clinical call point							
Satisfaction questionnaire			X						
Quality of life questionnaires	X	X	X	X	X				

5.4. MOOVCARE WEB-APPLICATION FOLLOW-UP MANAGEMENT

The investigator can regularly consult the history of the SENTINEL application.
In the event of a "suspected" relapse (depending on the answers to the questions), an alert email will be sent to the investigator.

In addition, an email will be systematically sent to the investigator if the free text window is filled in by the patient. If the symptoms appear not to be serious, the response will be optional, the patient being informed of this possibility. If there is any doubt, the investigator will call the patient or even summon him.

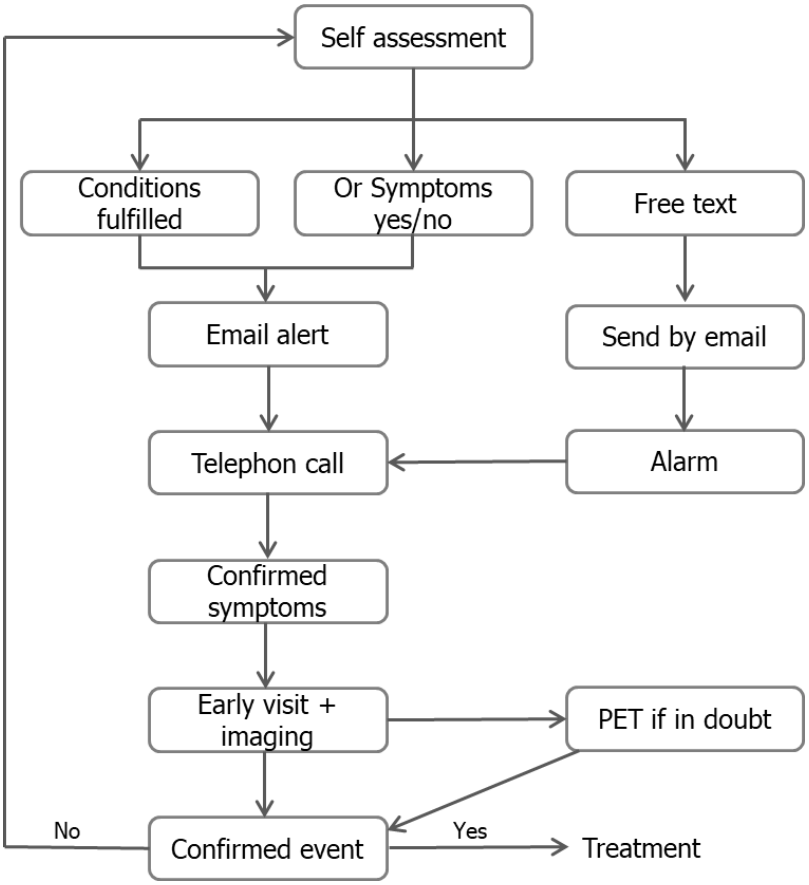
In the event of a SENTINEL alert, the investigator should:

1) consult the history of symptoms,
2) call the patient to verify the absence of entry errors, the absence of a low-calorie diet in case of weight loss, and ask the patient about his symptoms
3) if the doubt is confirmed, summon the patient as soon as possible (ideally <14 days) with an initial TAP CT (and cerebral if suggestive clinical signs).

For the most significant symptoms, supportive care may be offered, for example:

- if persistent pain: consultation of algology,
- if weight loss of 3 kg or more and / or anorexia: dietician advice,
- if dyspnea: pneumologic opinion
- if depression: psychologist / psychiatrist advice / psychotropic treatment.

Decision-making tree for Moovcare web -application alerts



In the event of a relapse or complication, the treatments will be left to the discretion of the investigators. The application will be used during the treatment of the relapse or complication at the same rate.

5.5. IDENTIFICATION OF ALL SOURCE DATA NOT APPEARING IN THE RECORDS

The satisfaction and quality of life questionnaires will not be in the patient's source record. They will be made available in a pocket per patient in the investigator file so that they can be transcribed in the e-CRFs. On the other hand, the self-assessments carried out by the patients will not be in the source file, they will be carried out directly on the Moovcare web application.

The other data relating to the patient and necessary for his follow-up outside the trial, will be collected in his medical file.

5.6. RULES FOR SUBJECT WITHDRAWAL

5.6.1. Criteria for a study subject's early withdrawal

Patients can withdraw their consent and request to withdraw from the trial at any time and for any reason, without losing the right to be treated by their doctor. The investigator may also prematurely discontinue a patient's participation in the trial for any reason that would serve the best interests of the patient, including the case of an intercurrent disease or an adverse event. In the event of premature discharge, at any time and for any reason, the investigator should notify the patient, if necessary, and document the reasons as fully as possible.
Test exits must be reported in particular for the following possible reasons:

- Death,
- Withdrawal of consent with the patient's request not to use the data already collected,
- Wrongly included,
- Choice of investigator,
- Patient choice,
- No seizure in the application for 6 consecutive weeks apart from a pathology or relapse preventing seizure,
- Lost view.

5.6.2. Procedure for a study subject's early withdrawal

The terms of medical care and follow-up in the event of premature discontinuation of the study for a given patient will be identical to those usual outside the protocol.

5.6.3. Study termination criteria (excluding biostatistics considerations)

The end of the research will be defined as the last follow-up visit (at 24 months) of the last patient included.

In addition, the study may be interrupted for administrative reasons, and / or by decision of the promoter. If the study is terminated prematurely or suspended, the study leader will immediately inform the Ethics Committee of the reason for the termination or suspension. In all cases, the patients included will be followed as part of the study until the 24-month follow-up visit by the investigator.

6. DATA MANAGEMENT ET STATISTICS

6.1. STUDY DATA COLLECTION AND PROCESSING

6.1.1. Data collection

An electronic observation log (e-CRF) (ENNOV Clincal®, Cenon, France) will be created per patient. All the information required by the protocol will be collected in the e-CRF. It will include the data necessary to confirm compliance with the protocol and detect major deviations from the protocol, as well as all the data necessary for statistical analyzes.

The person (s) responsible for filling in the e-CRFs (investigator, CRA, etc.) must be defined and identified in the table of delegations of responsibilities for each center (kept in the investigative workbook).

6.1.2. Data coding

By signing this protocol, the principal investigator and all investigators agree to keep confidential the identities of the patients who participated in the study.

The information required by the protocol will be collected without mentioning the first and last name in the e-CRF with an identification number for the center and a patient number. Only the first letters of the patient's first and last name will appear.

This code will be the only information that will appear in the observation notebook (e-CRF) and which will allow the e-CRF to be linked to the patient posteriori.

The sponsor is also required to encode the patient data on all documents he may have in his possession (reports of imaging examinations, biology, etc.) which would be attached to the e-CRF.

6.1.3. Data processing

For each patient, all the data will be collected in the e-CRF. The latter will be completed by the investigator and / or the CRA designated for this task.

The processing of the trial data is carried out by the sponsor; the data being the property of WeproM, promoter of the research.

The data processing software are ENNOV Clinical® (Cenon, France) and SAS 9.3 (SAS Institute Inc. Cary, NC, USA) software.

In accordance with the revision of the Data Protection Act of August 6, 2004 and its implementing decree, WeproM has undertaken to follow the MR001 reference methodology of the National Commission for Computing and Liberties.

6.2. STATISTICS

6.2.1. Description of planned statistical methods

This study should allow us to evaluate the functioning of the application in a follow-up context in patients with lymphoma at high risk of relapse.

The patient sample for this analysis will consist of all patients, included in the study and meeting all the eligibility criteria described in Chapter 4, who have signed a consent.

The initial characteristics of the analysis population (demographic data, disease, previous and concomitant treatments, prognostic factors, etc.) and all the evaluation criteria described in paragraph 2 will be presented globally

For the qualitative variables, we will present the number as well as the percentage. For quantitative variables, we will present the median or the mean plus or minus the standard deviation depending on the normality of the variable, the minimums and maximums will also be indicated.

Events, as defined in chapter 2.1.2. (apart from relapse) will be described in terms of frequency by etiological type (HLT or HLGT according to the MedDRA classification) and by severity according to NCI CTCAE v4.02.

For the analysis of the censored data (overall survival and other timeframes of events), the survival curves will be plotted according to the Kaplan-Meier estimates, the medians of survival will be presented as well as their 95% confidence intervals.

For performing multivariate survival analyzes, the semi-parametric Cox model will be used to calculate the odds ratios which will be presented with their 95% confidence interval.

The sensitivity of the application to detect a relapse and / or significant complications will be calculated.

Quality of life scores will be calculated according to EORTC guidelines for the QLQ-C30. The quality of life will be described at each measurement time and compared to inclusion and then studied longitudinally using mixed analysis of variance models for repeated measures.
PHQ9 scores will be calculated according to the recommendations, described at each measurement time and compared to inclusion. The classes proposed in the literature (<= 4; 5-14;> 14) will be used to describe the state of depression of patients.

The analyzes will be carried out with SAS 9.3 software (SAS Institute Inc. Cary, NC, USA).

6.2.1. Sample size determination

The main objective of the study is to show that follow-up via the SENTINEL Lymphoma web-application could make it possible to better identify the significant complications occurring between two systematic follow-up consultations with the specialist in patients followed for high-risk lymphoma. relapse than with standard follow-up. The evaluation of the main objective will be carried out over 6 months of follow-up.

This study is based on a pooled triangle test analysis (24, 25, 26). Two groups will be composed, one will be monitored via the web-application, the other will be monitored in a standard way (consultation and imaging).

A 1: 1 randomization will assign the treatment group to the patient. Stratification on center, autologous transplant, PS, relapse and lymphoma type will be performed to ensure the comparability of our two populations at inclusion.

This sequential method will make it possible to evaluate during recruitment the diagnostic efficiency of significant complications outside systematic consultations while controlling the power (risk of accepting our null hypothesis wrongly) and the type I error (risk of rejecting our wrongly null hypothesis). This design allows us to consider stopping the trial as soon as the information gathered is sufficient to conclude. We will be able to conclude that the web-application is diagnostic efficiently or, on the contrary, that it is lacking in interest.

We set the risk of the first species alpha at 5%, the potency at 90%, we envisage that monitoring via the web-application allows us to identify significant complications between two systematic follow-ups in 90% of patients (i.e. 10% of patient presenting an event not identified early) against 60% (i.e. 40% of patient presenting an event not identified early) in the group followed in a standard way (i.e. a difference of 30%).

The early unidentified event is defined:

- in the web application follow up group by the absence of an alert in the following cases:
  - emergency hospitalization,
  - a medical consultation without follow-up with medical prescription (imaging / drug prescription)
  - a significant event at the classic follow-up consultation (very degraded PS, antibiotic therapy, supportive care with consultation, pulmonary embolism, sepsis, severe depression, etc.)

- ¬ in the standard group in the following cases:
  - emergency hospitalization, without medical consultation justifying this hospitalization,
  - a significant event at the classic follow-up consultation (very degraded PS, antibiotic therapy, supportive care with consultation, pulmonary embolism, sepsis, severe depression, etc.).

The events diagnosed during the follow-up consultation will be reviewed, in the form of a list (pooled data from the web-application follow-up and standard groups), by the coordinator, who will rule on the significance of the event.

- The hypotheses are written:

H0: The proportion of patients without an undiagnosed event outside the systematic consultation (follow-up visit and systematic imaging) is not different between the two groups.

H1: The proportion of patients without an undiagnosed event excluding systematic consultation (follow-up visit and systematic imaging) is higher with the web-application (by 30%) compared to standard follow-up (90% against 60%).

With 2 scheduled analyzes, it is necessary to include a maximum of 40 patients per group. The analyzes will be carried out every 2x20 patients included (20 in the control group and 20 in the group followed by web-application)

As the inclusions progress, two statistics will be calculated, one reflecting the efficiency and the other the amount of information accumulated. The whole will make it possible to draw a decisional graph, leaving the area thus drawn a conclusion will be possible. If we find ourselves above the zone we will conclude that H0 has been rejected, if we find ourselves below the zone we will conclude with an acceptance of H0 and therefore ineffective monitoring via the web-application.

6.2.3 Randomization

Randomization 1: 1 will be performed following minimization with stratification on the center, autologous transplant, PS, relapse and type of lymphoma. Randomization will be carried out by the investigator directly via the electronic CRF developed with ENNOV Clinical® software (Cenon, France).

Randomization will only be possible after the main data has been recorded on the e-CRF (date of signature of consent, stratification criteria, inclusion and non-inclusion criteria).

The patient's home group will be instantly displayed on the e-CRF after performing the randomization. A randomization confirmation email will also be sent to the investigator.

7. SAFETY EVALUATION

7.1. DEFINITIONS

7.1.1. Adverse event

An adverse event is defined as any untoward medical occurrence, in a patient or clinical trial subject treated by a medicinal product and which does not necessarily have a causal relationship with this treatment.

Severity will be assessed by a qualified physician (Investigator) using the NCI CTCAE version 5.0. The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

- **Grade 1**: **Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**: **Moderate**, minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- **Grade 3**: **Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4**: **Life-threatening** consequences; urgent intervention indicated.
- **Grade 5**: **Death** related to the event.

7.1.2. Unexpected side effect

An unexpected side effect is an effect the nature, severity, frequency or course of which does not match the information on the procedures performed and methods used during the trial.

As part of this research, no AE is expected from the use of the Moovcare application. The AEs expected during this study are those related to the disease, to the treatments offered or to the injection of contrast product during CT (allergic, cardiovascular, neurosensory, digestive, respiratory, renal, thyroid or local effects) reactions.

7.1.3. Serious adverse event

A serious adverse event is defined as any untoward medical occurrence or effect that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth effect.

Will not be considered as SAE:

- hospitalizations for the management of a history,
- outpatient hospitalizations not leading to hospital admission,
- relapse or progression of lymphoma
- deaths linked to the progression of the disease.

7.2. SERIOUS ADVERSE EVENTS REPORTING

7.2.1. SAE notification

Any SAE (except exception specified in the previous paragraph) requires the completion of an SAE occurrence report (available in the e-CRF), it was expected or not expected. The investigator must check that the information provided on this form is precise and clear (do not use an abbreviation ...).

The SAE must be reported immediately (within 24 hours of its discovery by the investigator) to the sponsor via e-CRF and then by fax.
After receiving the notification of an SUSAR, the promoter declares to the supervisory authorities. Once a year, it draws up an annual safety report.

7.2.2. Independent data monitoring committee

As the patients were not exposed to any additional risk, it was therefore not considered necessary to use an independent monitoring committee in the context of this study.

7.3. MODALITIES AND DURATION OF THE FOLLOW-UP OF PERSONS FOLLOWING THE OCCURRENCE OF ADVERSE EVENTS

All the patients included in the study are followed for 2 years (24 months).

8. ADMINISTRATIVE AND REGULATORY ASPECTS

8.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

The medical data concerning each patient will only be sent to the Sponsor or any person duly authorised thereby, and where applicable to the authorised health authorities, under conditions guaranteeing the confidentiality of the data.

The Sponsor and the supervisory authorities may request direct access to medical records to verify the clinical trial procedures and/or data, without breaching confidentiality and to the extent permitted by the laws and regulations.

Data collected during the trial may be subject to computer processing in accordance with the CNIL requirements (MR001).

8.2. TRIAL MONITORING

Monitoring will be provided by WeproM (study sponsor). A Clinical Research Associate (CRA) will visit each site regularly to carry out quality control of the data reported in the observation books.

The Protocol has been classified as Risk D (High Risk) according to the definition of the level of monitoring based on patient risk and the “LI” score.

Monitoring will be done as follows.

Each site will be visited at least once, with collection of the following data:

1) The existence of the patients included

2) The collection of signed informed consents and their archiving

3) Compliance with the eligibility criteria (inclusion and non-inclusion)

4) The presence of the primary judgment criterion

5) The declaration and monitoring of Adverse Events

   a) Serious Adverse Events (SAEs)

   b) Notion of a new fact

6) according to the "level of risk" table: for 20% of patients, the files will be monitored at 100%.

The investigator should devote the necessary time to these visits. He must also ensure that the monitor has free access to the source documents (that is to say the patient's clinical file, original biological and radiological examinations, etc.) which support the data contained in the observation book.

8.3. INSPECTION / AUDIT

As part of this study, an inspection or audit may take place. The promoter will be in charge of preparing this audit or inspection, and ensuring access to all research data and verification of all source data.

8.4. ETHICAL CONSIDERATIONS

8.4.1. Written Inform Consent

The investigator undertakes to inform the patient in a clear and fair manner of the protocol and to ask him for informed and written consent (information letter and consent collection form attached). They will give the patient a copy of the information letter and a consent form. The patient can only be included in the study after having read the information letter and having signed and dated the consent form. The investigator must also sign and date the consent collection form. The investigator's original will be filed in the investigator binder.

8.4.2. Ethics Committee

The study project must first be submitted for authorization by an Ethics Committee. The information communicated relates, on the one hand, to the methods and nature of the research and, on the other, to the guarantees provided for the patients participating in this trial.

The CPP Ouest II of Angers issued a favorable opinion on this research on 08/11/2016.

8.5. COMPETENTE AUTHORITY

The ANSM gave its authorization for this research to be carried out on 11/22/2016.

8.6. CHANGES TO THE PROTOCOL

Requests for substantial modifications will be sent by the promoter for authorization or information to the ANSM and / or to the Ethics Committee concerned in accordance with Law 2004-806 of August 9, 2004 and its implementing decrees.

The amended protocol should be the subject of a dated updated version.
Patient information and consent forms should be amended if necessary.

8.7. FUNDING AND INSURANCE

Sponsor provides financing for the study and takes out an insurance policy with BiomedicInsure (policy n ° 01005345-14058-160056-10005) guaranteeing the pecuniary consequences of its civil liability, in accordance with the regulations.

8.8. PUBLICATION RULES

A copy of the publication will be given to WeproM, the sponsor of the study, which will necessarily be cited. The authors will be determined in proportion to the number of evaluable patients included. The coordinating investigator will establish the list of authors.

9. REFERENCES

1 - Elis A, Blickstein D, Klein O, Eliav-Ronen R, Manor Y, Lishner M. **Detection of relapse in non-Hodgkin's lymphoma: role of routine follow-up studies.** Am J Hematol. 2002 Jan; 69(1):41-4.

2 - Salles G, Shipp MA, Coiffier B.**Chemotherapy of non-Hodgkin's aggressive lymphomas.**SeminHematol. 1994 Jan; 31(1):46-69.

3 - Armitage JO.**Treatment of non-Hodgkin's lymphoma.**N Engl J Med. 1993 Apr 8; 328(14):1023-30.

4 - Edelman MJ, Meyers FJ, Siegel D. **The utility of follow-up testing after curative cancer therapy.A critical review and economic analysis.**J Gen Intern Med. 1997 May; 12(5):318-31.

5 - Abel GA.**Does surveillance imaging after treatment for diffuse large B-cell lymphoma really work?**J ClinOncol. 2015 May 1; 33(13):1427-9.

6 - Weeks JC, Yeap BY, Canellos GP, Shipp MA.**Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete remission.**J ClinOncol. 1991 Jul; 9(7):1196-203.

7 - Armitage JO, Loberiza FR. **Is there a place for routine imaging for patients in complete remission from aggressive lymphoma?** Ann Oncol. 2006 Jun;17(6):883-4.

8 - Abel GA, Vanderplas A, Rodriguez MA, Crosby AL, Czuczman MS, Niland JC, Gordon LI, Millenson M, Zelenetz AD, Friedberg JW, LaCasce AS.**High rates of surveillance imaging for treated diffuse large B-cell lymphoma: findings from a large national database.** Leuk Lymphoma. 2012 Jun; 53(6):1113-6.

9 - Guppy AE, Tebbutt NC, Norman A, Cunningham D. **The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma.** Leuk Lymphoma. 2003 Jan; 44(1):123-5.

10 - Voss SD, Chen L, Constine LS, Chauvenet A, Fitzgerald TJ, Kaste SC, Slovis T, Schwartz CL. **Surveillance computed tomography imaging and detection of relapse in intermediate- and advanced-stage pediatric Hodgkin's lymphoma: a report from the Children's Oncology Group.**J Clin Oncol. 2012 Jul 20; 30(21):2635-40.

11 - Dryver ET, Jernström H, Tompkins K, Buckstein R, Imrie KR.**Follow-up of patients with Hodgkin's disease following curative treatment: the routine CT scan is of little value.**Br J Cancer. 2003 Aug 4; 89(3):482-6.

12 – Xavier MF, Schuster SJ, Andreadis C et al. **Detection of relapse in diffuse large B-cell lymphoma (DLBCL) and Hodgkin's lymphoma (HL) : observations and implications for post-remission radiologic surveillance**. Blood (ASH Annual Meeting Abstracts) 2006 ; 108 :2428

13 - Lynda M. Foltz, MD, Kevin W. Song, MD and Joseph M. Connors, MD **Who Actually Detects Relapse in Hodgkin Lymphoma: Patient or Physician?** Blood (ASH Annual Meeting Abstracts) 2004 104: Abstract 3124

14 **-** Seam P, Juweid ME, Cheson BD. **The role of FDG-PET scans in patients with lymphoma.** Blood. 2007 Nov 15; 110(10):3507-16.

15 - Brenner DJ, Hall EJ.**Computed tomography--an increasing source of radiation exposure.**N Engl J Med. 2007 Nov 29; 357(22):2277-84.

16 - Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, Shah ND, Nasir K, Einstein AJ, Nallamothu BK.**Exposure to low-dose ionizing radiation from medical imaging procedures.**N Engl J Med. 2009 Aug 27; 361(9):849-57.

17- Thompson CA, Charlson ME, Schenkein E, Wells MT, Furman RR, Elstrom R, Ruan J, Martin P, Leonard JP. **Surveillance CT scans are a source of anxiety and fear of recurrence in long-term lymphoma survivors.** Ann Oncol. 2010 Nov;21(11):2262-6.

18 - Armitage JO. **Who benefits from surveillance imaging?** J ClinOncol. 2012 Jul 20; 30(21):2579-80.

19 - Huntington SF, Svoboda J, Doshi JA.**Cost-effectiveness analysis of routine surveillance imaging of patients with diffuse large B-cell lymphoma in first remission.**J ClinOncol. 2015 May 1; 33(13):1467-74.

20 - Denis F, Viger L, Charron A, Voog E, Letellier C. **Detecting lung cancer relapse using self-evaluation forms weekly filled at home: the sentinel follow-up.** Support Care Cancer. 2014 Jan; 22(1):79-85.

21 - Denis F, Viger L, Charron A, Voog E, Dupuis O, Pointreau Y, Letellier C. **Detection of lung cancer relapse using self-reported symptoms transmitted via an internet web-application: pilot study of the sentinel follow-up.** Support Care Cancer. 2014 Jun;22(6):1467-73.

22 - Denis F, Yossi S, Septans AL, Charron A, Voog E, Dupuis O, Ganem G, Pointreau Y, Letellier C.**Improving Survival in Patients Treated for a Lung Cancer Using Self-Evaluated Symptoms Reported Through a Web Application.**Am J ClinOncol. 2015 Mar 24. [Epub ahead of print]

23 - Denis F, Trémolières P, Lizée T et al. **Application clinique de la théorie du chaos en oncologie. Résultats intermédiaires de l'essai randomisé multicentrique de phase 3 "SENTINEL" de surveillance post-thérapeutique par web-application de patients suivis pour un cancer bronchique**. Congrès SFRO 2015

24 - Ranque S[1], Badiaga S, Delmont J, Brouqui P. **Triangular test applied to the clinical trial of azithromycin against relapses in Plasmodium vivax infections.** Malar J. 2002 Nov 12;1:13. Epub 2002 Nov 12.

25 - Bellissant E, Benichou J,Chastang C. **Application of the triangular test to phase II cancer clinical trials.**Stat Med. 1990 Aug;9(8):907-17.

26 - Bellissant E, Benichou J,Chastang C. **Design and analysis of phase II trials in oncology with a group sequential method, the triangular test].**Therapie. 1991 Jan-Feb;46(1):21-7. French.