Evaluation of long-term health status and quality of life in adult survivors with Philadelphia-negative acute lymphoblastic leukemia/lymphoma treated with an intensive pediatric or pediatric-inspired protocol

EQUAALL01

MINIMAL RISKS AND CONSTRAINTS HUMAN RESEARCH STUDY

Version N° 4.0 of 03 April 2024
Protocol code number: P150969J / IDRCB no. 2019-A01443-54

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PROTOCOL SIGNATURE PAGE

MINIMAL RISKS AND CONSTRAINTS HUMAN RESEARCH STUDY

Protocol code number:
Title: Evaluation of long-term health status and quality of life in adult survivors with Philadelphia-negative acute lymphoblastic leukemia/lymphoma treated with an intensive pediatric or pediatric-inspired protocol
Version N° 4-0 of 03 April 2024

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Coordinating Investigator:
Pr Nicolas Boissel
Hematology Department
Saint Louis Hospital
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Date: ……4……/……06……/……2024……
Signature:

Sponsor

Assistance Publique-Hôpitaux de Paris
Clinical Research and Innovation Department
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06 JUIN 2024
Date: ……/……/……..
Signature:

The study was approved by the CPP of Nord Ouest IV on the 19th December 2019.

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1 SUMMARY

Full title	**Evaluation of long-term health status and quality of life in adult survivors with Philadelphia-negative acute lymphoblastic leukemia/lymphoma treated with an intensive pediatric or pediatric-inspired-inspired protocol.**
Acronym	EQUAALL01
Coordinating Investigator	*Pr Nicolas BOISSEL* *Hematology Department* *Saint-Louis Hospital* *+33142499643* *nicolas.boissel@aphp.fr*
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	The overall survival of adult patients (15-59y) with Philadelphia-negative acute lymphoblastic leukemia/lymphoma (ALL/LL) was dramatically improved by the use of full pediatric or pediatric-inspired protocols (GRAALL2003/05-LL03-FRALLE2000) that aimed to reduce the risk of relapse by adopting more intensive chemotherapeutical schedule. This approach led to a global improvement in overall survival (5y-OS, 57%) whatever patient age but was responsible for an excess of treatment-related mortality in patients older than 45 years (5y-TRM in patients > 45y, 19%). Pediatric longitudinal studies pointed out that long term leukemia survivors have an increased risk of developing specific adverse events like dysmetabolic syndrome, obesity, decreased fertility, organ dysfunction, osseous events, or impaired cognitive functions. This study aims to evaluate the impact in term of long-term events and QoL in adult patients that received an intensified therapeutic approach recently implemented in adult cooperative groups.
Main objective and primary endpoint	To evaluate the prevalence of late effects in adult patients treated 10 years ago for ALL/LL with an intensified pediatric-inspired protocol (GRAALL2003/05-LL03-FRALLE2000) that exposed patients to increased cumulative doses of chemotherapy, central nervous system irradiation or w/o allogeneic transplant after total body irradiation-based regimen w/o boost irradiation on central nevous system. The primary endpoint is thus defined by the prevalence of adverse events, including : - metabolic troubles (dysmetabolic syndrome, dyslipidemia, diabetes) - osseous events / osteoporosis - cardiac and vascular troubles - neurologic troubles - lung dysfunctions - endocrinal troubles - ophthalmological troubles - fertility disorders - secondary neoplasia
Secondary objectives and endpoints	- To evaluate the quality of life of these patients, - To correlate the prevalence of late effect or QoL status with previous social situation, previous medical condition to ALL. Treatment schemes including administration of protocols phases (delayed intensification, maintenance), central-nervous system irradiation, allogeneic SCT, graft-versus host disease occurrence. , - To elaborate risk-adapted recommendations for the long-term follow-up of adult patients treated for ALL with reinforced therapeutic strategies. The secondary endpoints are thus

	- the prevalence of metabolic troubles (dysmetabolic syndrome, dyslipidemia, diabetes), - the prevalence of osseous events / osteoporosis, - the prevalence of cardiac and vascular troubles, - the prevalence of neurologic troubles, - the prevalence of lung dysfunctions, - the prevalence of endocrinal troubles, - the Quality of Life (SF-36) - the prevalence of ophthalmological troubles - the prevalence of fertility disorders - the prevalence of secondary neoplasia
Design of the study	This is a multicenter, cross-sectional, interventional minimal risks and constraints human research study
Population of study participants	Adult patients aged 15-59y at diagnosis treated ten years ago for a Ph1-negative acute lymphoblastic leukemia/lymphoma (ALL/LL)
Inclusion criteria	- Patient with Philadelphia-negative ALL or LL treated in or according to a pediatric-like or pediatric-inspired protocol (GRAALL or FRALLE) with or without allogeneic transplant. - Patients older than 15 years old and less than 60 years old at diagnosis - Patient with a follow-up from first complete remission of more than 10 years, - Patient who gave informed signed consent for baseline examination
Exclusion criteria	- Patient who experienced ALL/LL relapse within the 5 past years. - Philadelphia positive ALL patients
Interventions or product under investigation	None
Other interventions added by the study	- hormons tests - antral follicle count by US - Questionnaire
Expected benefits for the participants and for society	An expected individual benefit, since systematic reviews can be used to detect and take early care the late complications related to treatment
Minimal risks and constraints added by the study	None
Scope of the study	Risk minimal (A)
Number of participants included	300
Number of sites	Approximatively 36 centers of the GRAALL network
Schedule for the study	State: - inclusion period: 66 months - participation period: 9 months - total duration of the study : 75 months
Number of enrolments expected per site and per month	300 patients / 36 sites 66 months inclusion period = <1 patients/month/ site
Statistical analysis	The analysis will handle the left data truncation (given only patients who survive until 2016 are able to be included in the study). Approximately 1000 patients were included in the GRAALL-2003 and 2005, among them 630 before August 2009. Considering that 363/630 patients were alive at last follow-up, the opportunity to include patients treated according to these protocols, and a 80% inclusion success, approximately 300 patients will be recruited. This allows assessing the prevalence of troubles with a 95%CI width at 7% about assuming a 10% prevalence or to 0.10 assuming a 30% prevalence, and detection of OR at 2.5 or 2, respectively. This also allows reaching a statistical power of at least 80% for detecting OR at 2.
Sources of monetary support	Ministry of Health

2 SCIENTIFIC JUSTIFICATION FOR THE RESEARCH:

2.1 CURRENT KNOWLEDGE

2.1.1 About the condition under investigation

In the early 2000', the comparison of French adult and pediatric therapeutic approaches in adolescents aged 15-20 years old led to the conclusion that more intensive pediatric protocols could reduce the risk of relapse and improve long term survival rate in this population of young patients. This observation was confirmed by many other ALL cooperative groups in Europe and in the US.[1,2]

Based on these results, the French, Belgian, and Swiss Group of Research in Acute Lymphoblastic Leukemia (GRAALL) designed in 2003 a new pediatric-inspired approach protocol for adult patients aged 15-59 years old with Philadelphia-negative ALL.[3] The GRAALL-2003 trial aimed to reduce the risk of relapse by adopting more intensive chemotherapeutical schedules in patients non eligible for allogeneic stem cell transplantation (ASCT). When compared to previous therapeutic attitude in adult ALL in France, this protocol introduced a 5-drug including L-asparaginase induction, a dose-dense consolidation, a delayed intensification and 2-year maintenance with monthly vincristine and steroid pulses during the first year. Consequently, patients received 9 times more steroids, 3 times more vinca-alcaloids, 20 times more L-asparaginase, and 2 times more cytarabine than in the previous national LALA trial.[3] It is noticeable that, unlike contemporary pediatric trials, patients systematically received central nervous-system irradiation. Wide indications of allogeneic stem cell transplantation (SCT) were used with around 30% of patients actually transplanted in first complete remission.[4] Remaining not transplanted patients were thus planned to receive 7 to 8 months intensive phases of chemotherapy followed by a 2-year maintenance.This approach led to a global improvement in overall survival (5y-OS, 57%), whatever patient age, but was responsible for an excess of treatment-related mortality in patients older than 45 years (5y-TRM in patients > 45y, 19%).[3]

In parallel to the GRAALL trial, adult patients diagnosed at age 15-59 years with lymphoblastic leukemia were treated according to a very similar approach, the LL-03 trial. These pateints were exposed to the same dose-dense chemotherapy regimen than in the GRAALL-2003. In this trial, the 3-year survival was 69.1% (Lepretre, JCO 2016).

In these trials, it was not planned to monitor neither late effects, nor quality of life (QoL), nor psychosocial impact in these patients. More generally, long-term impact of pediatric-like therapeutic attitudes in adult patients with ALL has not been comprehensively investigated, mostly because these reinforced strategies were recently implemented in adult cooperative groups.

a) Adult survivors after childhood ALL

The outcome of children and adolescents treated for ALL has also dramatically improved over the last decades and led pediatricians to address the question of long-term morbidity and how this morbidity is associated with the different therapeutic options.[5,6] Longitudinal studies of long-term survivors showed that these patients are at risk of developing specific adverse events like metabolic syndrome, obesity, decreased fertility, organ dysfunction, osseous events, or impaired cognitive functions.[7,8] All of these adverse events may not only disturb patient QoL but also impair social outcome.[9,10]

The long-term toxicity profile is tightly related to some therapeutic options including prophylactic central nervous system (CNS) irradiation and hematopoietic stem cell transplantation (HSCT), which indications have considerably decreased in the most recent protocols. For example, both secondary neoplasms and neurocognitive sequelae have been correlated to the use of CNS irradiation.[11,12] In the French childhood acute leukemia LEA cohort, the risk to develop one sequela ore more is five time higher in transplanted patients than in patients treated by chemotherapy alone.[13]

b) Adult survivors after HSCT

The number of patients that received HSCT as part of their therapy increase with time and some patients have a post-transplant follow-up of more than two decades. In hematologic malignancy survivors, many of long-term effects have been linked to HSCT procedure and the occurrence of acute and chronic graft-versus host disease that may directly damage some organs or indirectly cause toxicity through prolonged exposition to immunosuppressive drugs including corticosteroids.[14,15]

These long-term medical issues after HSCT in children and adults have been extensively studied and reviewed. Due to these late effects, survivors after HSCT are exposed to a more elevated age-adjusted risk of mortality.[16] In patients transplanted in adulthood, most studies have been conducted whatever the underlying hematological disease and pre-transplant therapy. The risk to develop late effects depend on many factors including the age of the patient at HSCT, the presence of comorbidity before transplant, the type of conditioning regimen, the type of donor, the occurrence and the grade of GVHD, the type of immunosuppressive drug used.[17–20] Recommendations for the screening and the prevention in HSCT survivors have been published in 2006 and updated in 2012.[21,22]

Quality of life (QoL) has also been widely evaluated in adult patients after HSCT.[14,23] As expected, QoL is strongly correlated to the time from HSCT to evaluation, the type of transplant, the presence of chronic GVHD. Once again, these studies were mostly conducted in heterogeneous cohort of patients in term of underlying disease, pre-transplant therapy and time from transplant to evaluation. Few studies were interested in comparing patients with acute leukemia whether they received HSCT or conventional therapy.[13,24,25]

c) Expected patient and public health benefit

As mentioned above, there are actually no guidelines for the long-term follow-up of adult patients with ALL treated with intensive chemotherapeutic approaches. Patients are frequently seen as outpatients up to 5 years after complete remission in the tertiary Hematology centers. Subsequent follow-up is often ensured by general practitioner with few specific recommendations nowadays.

The originality of our cohort of patients consist in the homogeneity of the treatment received, in term of chemotherapy, CNS irradiation but also conditioning regimen in transplanted patients. Based on our findings, recommendations for such a follow-up could be provided, as well as designing specific studies attempting to prevent or shorten time to diagnosis of these long-term troubles. This will also help hematologists to design strategy trials aiming to prevent or decrease such health troubles. Finally, each patient included in the present EQUAALL study will potentially benefit from the early diagnosis of health trouble and may benefit for a specific medical care.

3 OBJECTIVES OF THE RESEARCH

3.1 Main objective of the research

The primary objective of the EQUAALL study is to evaluate the global prevalence of late effects in adult patients treated 10 years ago with an intensified pediatric-inspired protocol (GRAALL2003/05-LL03-FRAALL2000) that exposed patients to increased cumulative doses of chemotherapy, central nervous system irradiation or without allogeneic transplant after total body irradiation-based regimen w/o boost irradiation on central nevous system.

3.2 Secondary objectives

The secondary objectives of the EQUAALL study are:

- to evaluate the quality of life of these patients,
- to correlate the prevalence of late effect or QoL status with previous or current social situation and previous medical condition to ALL. Treatment schemes including administration of protocols phases (delayed intensification, maintenance), central-nervous system irradiation, graft-versus host disease occurrence, allogeneic SCT.
- to elaborate risk-adapted recommendations for the long-term follow-up of adult patients treated for ALL with reinforced therapeutic strategies.

4 DESCRIPTION OF THE RESEARCH

4.1 Primary endpoint

This is a binary, composite, endpoint, defined by the Prevalence of adverse events, including any of the following adverse events:

- metabolic troubles (dysmetabolic syndrome, dyslipidemia, diabetes)
- osseous events /osteoporosis
- cardiac and vascular troubles
- neurologic troubles
- lung dysfunctions
- endocrinal troubles
- ophthalmological troubles
- fertility disorders
- secondary neoplasia

4.2 Secondary endpoints

- Prevalence of metabolic troubles (dysmetabolic syndrome, dyslipidemia, diabetes)
- Prevalence of osseous events / osteoporosis
- Prevalence of cardiac and vascular troubles
- Prevalence of neurologic troubles
- Prevalence of lung dysfunctions
- Prevalence of endocrinal troubles
- Quality of Life (SF-36)
- Prevalence of ophthalmological troubles
- Prevalence of fertility disorders
- Prevalence of secondary neoplasia

5 RESEARCH METHODOLOGY

5.1 Design of the study

This is a multicentre, cross-sectional, interventional study. All patients with Philadelphia negative ALL treated in according to the GRAALL2003/05-LL03-FRAALL2000 trials will be invited to participate to the study.

All patients previously included in the GRAALL03/05 trials but also all patients treated according to these protocols will be considered for inclusion. Actually, these trials included 225 and 730 patients, respectively, with 94 and 276 patients who died during the study (Table 1).

Table 1: Sample sizes and outcomes of patients included in the GRAALL03/05 trials

Trial	GRAALL03 Participating subset /Overall	GRAALL05 Pts included <AUG2009 /Overall	Total Participating subset /Overall
Number of enrolled pts	225	405/730	630/955
Number of deaths	94	173/276	267/370
Total number of potentially eligible patients	131	232/454	**363**/585

Representativeness: The sample should be recruited so that the final proportions in each of these GRAALL network trials match the original trials. No attempt should be made to balance exactly across cross-stratifications, such as centre. Thus, a representative sampling to estimate potential accrual by phone call will be performed among the participating centres.

Such a cross-sectional design is commonly used in epidemiologic studies. The advantage of such a design is that information on the whole patient history can be obtained at the time of the study, and that it

does not require expensive follow-up of a cohort, especially for rare diseases. Moreover, as the patients have been included in standardized protocols, most of the exposure variables (including treatment exposures and potential confounders) are already available from the original trials, thus mostly avoiding recall bias. Note that, in such a clinical epidemiology setting, each patient from the study will benefit from the early diagnosis of health troubles that may benefit for a medical care.

However, it is important to be aware of data truncation, as it distorts the data set and has potential to cause large biases. Indeed, in such a cross-sectional survey, both right and left truncation can occur, due to selection of patients at a random time after treatment. In particular, individuals with longer lifetimes are favoured by the sampling process. Thus, on one hand, patients who died from adverse events will not be sampled (left truncation), and on the other hand, patients with very late adverse events will be under-represented (right truncation). There is a way of avoiding truncation bias in the design of the study, which apply to cross-sectional studies. One is to collect data from patients who are old enough to have no more late adverse events, but this requires long-term recall. Alternatively, the bias can be handled in the analysis, by using statistical modelling. This will be used in this project (see Statistical Methods section).

5.2 Number of participating sites

This study will be conducted among centers of the cooperative GRAALL network in which patients were initially treated. This network is used to federate clinical and translational, academic and industrial research programs. It includes 36 centers.

5.3 Avoiding and reducing bias

5.3.1 Participant identification

For this research, the subjects will be identified as follows:
Centre No. (3 numerical positions) - Selection order No. of the person in the center (4 numerical positions) - surname initial - first name initial
This reference is unique and will be retained for the entire research period.

6 PROCEDURE FOR THE RESEARCH

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
Patients treated in or according to pediatric or pediatric-like protocols (GRAALL-2003/2005, LL03, FRALLE-2000) trials still regularly seen in consultation at the center	Investigator of hematologic department	Routine and inclusion visit	After time reflexion during inclusion visit
Patients treated in or according to pediatric or pediatric-like protocols (GRAALL-2003/2005, LL03, FRALLE-2000) trials no more seen in consultation at the center (expected to be the most frequent situation)	Investigator of hematologic department	The patients will be contacted in each center either by phone or by mail to be proposed to participate to the study. And at inclusion visit	After time reflexion during inclusion visit

6.1 Schedule for the study

- Enrolment period: 66 months
- Duration of participation by each patient: 9 months
- Total study duration: 75 months

6.1.1 Inclusion /Baseline visit

- ✓ Once a patient is selected and informed, and if the patient agreed for participation to the protocol, the patient will be contacted for inclusion visit. During this visit the patient eligibility will be evaluated from inclusion and non-inclusion criteria. Once the consent will be signed by the patient and investigator, the patient will be included by connecting the eCRF.
- ✓ Selected patients who are unable to visit the site due to distance or relocation will be informed of the research by telephone.
  If the patient agrees to take part in the protocol, he or she will then receive the written information and consent form by post at his or her address and will be asked to sign and return it.
  Once the investigator has received this form, he will send a duplicate signed by both parties to the patient, and an appointment will then be made for the teleconsultation.
  The quality of life questionnaire (SF-36), and a stamped letter, will be sent to the patient for completion and return.

The patient identification number will be allocated. The detailed data collection would be vital to characterize participants' clinical and functional status, assess their current health, and identify cases of prevalent diseases. Actually, different measures will be performed if not realized in the year before except blood tests concerning the metabolic syndrom (< 6 months) within three months of study inclusion according to center's policy. The antral follicle count US, AMH (in non menopausal females) and Questionnaires (QoL(SF-36) will be assess in investigator center during the inclusion visit because they are procedures added by the research.
For measures and exams that will be performed outside of center the investigator will give a prescription to the patient. Then he or she will report or send the results to the investigator center.

6.1.1.1 Clinical history and examination

- Report of disease and therapy administrated
- Medical history from the diagnosis of ALL
- Quantification of tobacco use and alcohol consumption
- Menopausal status including date of menopause
- Examination :
  - OMS grade,
  - size, weight,
  - blood pressure, pulse, Sp02, abdominal circumference,
  - search for peripheral neuropathy, bone pain…

6.1.1.2 Blood tests

- complete blood bount (CBC),
- fasting glucose,
- triglycerides,
- HDL/LDL-cholesterol,
- Kidney function tests : creatinine, urea, urine protein screening,
- Liver function tests : Gamma-GT, ALP, ASAT, ALAT, total serum bilirubin,
- Serum ferritin, transferrin saturation coefficient,
- calcium, phosphor,
- Thyroid function tests : TSHus, T4l,
- Sexual hormone serum levels : FSH, LH, testosterone in males; FSH, LH, AMH, in females,

6.1.1.3 Morphological evaluation

- Bone mineral density (BMD) test: T-score and Z-score,
- Chest X-ray,
- Cardiac and vascular evaluation: electrocardiogram, cardiac US with LVEF evaluation and carotid US/Doppler,
- Ophthalmologic exam: clinical evaluation, visual acuity, oculus fundus exam,
- Gynecologic examinations, antral follicle count US.

6.1.1.4 Psychosocial evaluation

- Sociodemographic and socioeconomic data,
- Scholar trajectory: time taken to return-to-school since the start of sick leave, educational cursus.
- Professional trajectory : time taken to return-to-work since the start of sick leave, history of occupation since the start of sick leave, partial time work, occupational category,
- Questionnaires: QoL(SF-36).

6.1.1.5 Centralized proofreading of reports

Centers will anonymise, scan, send the following reports (see below § 10) :

- ✓ ultrasound echography (ovarian, cardiovascular, thyroid)
- ✓ osteodensitometry
- ✓ Chest X Ray conclusion
- ✓ Spermogram interpretation
- ✓ Ophltalmological report

6.1.1.6 Additional clinically driven exploration

According to symptoms and clinical evaluation, additional explorations could be prescribed by the investigator. Following examples are nonrestrictive:

- Electromyogram and nerve conduction studies in case of peripheral neuropathy,
- Bone MRI in case of avascular osteonecrosis suspicion,
- Liver MRI and HFE screening in case of iron overload,
- Chest CT-scan in case of abnormal X-ray or PFTs,
- Dental assessment…

All these findings will be recorded in a standardized case report form (CRF).

6.1.1.7 Considerations about "personal data"

- Social Health Inegalities

These questions (ethnical roots of the patient), combined with others in this study, will be useful for studying health inequalities in the post-cancer era. (i.e access to bank loans, access to a stable job...). The study of these inequalities will be usefull for clarifications on the social profile.

- Toxicity profile

These questions (ethnical roots of the patient) will be also usefull for clarifications on potential toxicities profil according to ethnic groups (i.e patient with asian origin have a specific polymorphisms and metabolize the drugs differently)

- Zip code

The question of the zip code is asked in order to follow the movements of the patients on the French territory.

Research end date:

The participation of the patient ends at the end of the outpatient visits and investigations 9 months maximum after study inclusion.

6.2 Distinction between standard care and research

TABLE: "Standard care" vs. "Added interventions" required specifically for the research

Procedures and treatments carried out as part of the research	Procedures and treatments associated with care	Procedures and treatments added because of the research
Consultations	▪ Clinical visit ▪ Ophthalmologic exam (clinical evaluation, visual acuity, oculus fundus exam)	
Blood samples	• complete blood count (CBC), • fasting glucose, • triglycerides, • HDL/LDL-cholesterol, • Kidney function tests : creatinine, urea, • Liver function tests : Gamma-GT, ALP, ASAT, ALAT, total serum bilirubin, • Serum ferritin, transferrin saturation coefficient, • calcium, phosphor, • Thyroid function tests : TSHus, T4l, • Sexual hormone serum levels: FSH, LH, testosterone in males; FSH, LH, in females.	• AMH, in non menopausal females
Imaging, etc.	• Bone mineral density (BMD) test: T-score and Z-score, • Cardiac and vascular evaluation: electrocardiogram, cardiac US with LVEF evaluation and carotid US/Doppler,	• antral follicle count US.
Other		• Questionnaire

7 ELIGIBILITY CRITERIA

All patients will be included once all the eligibility criteria (all inclusion criteria and none of the exclusion criteria must be fulfilled) have been checked.

7.1 Inclusion criteria

All persons who

- had Philadelphia negative ALL or LL treated in or according to a pediatric-like or a pediatric-inspired protocol (GRAALL or FRALLE) with or without allogeneic transplant
- were older than 15 years old and less than 60 years old at diagnosis (ALL)
- had a follow-up from first complete remission of more than 10 years
- Patient who gave informed signed consent for baseline examination

7.2 Exclusion criteria

- Patient who experienced ALL/LL relapse within the 5 past years.
- Philadelphia positive ALL patients

7.3 Enrolment procedure

This study will be conducted among centers of the cooperative GRAALL network in which patients were initially treated or near from their present place of residence. This network is used to federate clinical and translational, academic and industrial research programs.

The GRAALL network comprises 33 French centers involved in the treatment of acute leukemia. Each center will be responsible for the recruitment, the inclusion and the measurements performed in each enrolled patient.

	Number of participants
Total number of participants to be included	*300*
Number of sites	*36*
Enrolment period (months)	*66*
Number of participants/site/month	**<1**

8 TERMINATION AND EXIT RULES

8.1 Criteria and procedure for premature withdrawals and exits from the study

- Participants may exit the study at any time and for any reason.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- If a participant exits the study prematurely, all data about that participant may be used until consent is withdrawn.
- If a participant exits the study prematurely, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment). State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

The case report form must list the various reasons why the participant exited or was withdrawn from the study:

- ☐ Medical problem
- ☐ Subject's personal reasons
- ☐ Explicit withdrawal of consent

8.1.1 Full or partial cancellation of the study

AP-HP, as sponsor reserves the right to permanently suspend inclusions at any time if it appears that the inclusion objectives are not met.

9 VIGILANCE

"During this research, adverse events (serious and otherwise) do not need to be reported to the sponsor. The report must instead be made as part of the vigilance procedure applicable to the product or intervention under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device, etc.).

10 SPECIFIC COMMITTEES FOR THE STUDY

10.1 Steering Committee

The steering committee, composed by the Coordinating Investigator and the member of the 4 participating teams (F. Huguet –Toulouse ; M. Hunault –Angers; T. Leguay –Bordeaux ; M. Balsat – Lyon) a member of the Clinical research Unit and the head office project advisor, will:

- develop and modify study protocol and policies,
- review Coordinating Center reports of study progress and recommend corrective action as needed

10.2 Centralized reports review committees

Centers will anonymise, scan, send the following reports via Case report forms (eCRF) specific to EQUAALL:

- ✓ ultrasound echography (ovarian, cardiovascular, thyroid)
- ✓ osteodensitometry
- ✓ Chest X Ray conclusion
- ✓ Spermogram interpretation
- ✓ Ophltalmological report

We choose to collect all this reports because we do not have experience in the field of long term sequela. T

The goal of this centralized proofreading is to overlook any detail that could be of interest.

The central review committee, composed of specialists of each specific orrgan will review the reports at the end of study.
A centyralised assessement of the reports will be filled in a dedicated section of the e-CRF.

11 DATA MANAGEMENT

11.1 Data collection

Data will be collected in an electronic case report form (e-CRF), devised by the study coordinator in collaboration with URC-St Louis.

11.2 Identification of data recorded directly in the CRF which will be considered as source data

The data recorded directly in the CRF which will be considered as source data are those reporting on section 6.1.1.

11.3 Right to access source data and documents

11.3.1 Data access

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the research and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force

11.3.2 Source documents

The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the study. Source documents will be kept by the investigator, or by the hospital in the case of hospital medical records, for 15 years.

The list of source documents relevant to the study (medical files, original laboratory test results, medical imaging reports, etc.) are reporting on 6.1.1

11.3.3 Data protection

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the Code de la Santé Publique - CSP (French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the research, the participants and in particular their identity and the results obtained.

These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).

During and after the research, all data collected about the participants and sent to the sponsor by the investigators (or any other specialized collaborators) will be anonymized.

Under no circumstances will the names and addresses of the participants be shown.

Only the participant's initials will be recorded, along with an identification code specific to the study indicating the order of enrolment.

The sponsor will ensure that each participant has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the person responsible and the location for data processing

Data management and statistical analysis will be performed by Pr Sylvie CHEVRET in the « Service de Biostatistique et Information Médicale (SBIM), hôpital Saint-Louis, Paris ».

11.4.2 . Data entry

Data entry will be carried out on electronic media via a web browser by staff dedicated to this task in each center with a restricted access to investigators.

11.5 Ownership of the data

AP-HP is the owners of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Planned statistical methods

A cross-sectional survey collects data to make inferences about a population of interest (universe) at one point in time. The analysis will handle the data truncation (given only patients who survive and free of relapse until 2016 are able to be included in the study, and only adverse events that occur within the first years after the end of the protocol could be observed yet).

The most common method of modelling binomial health data such as that related on the observation of any adverse event in cross-sectional studies has long been logistic analysis. We will model and estimate prevalence ratios with the 95% confidence interval (95%CI), instead of odds ratios, and search for potential risk factors using log-binomial models, as previously recommended in cross-sectional studies when diseases or injuries are not rare [Barros 2003; Petersen 2008].

However, due to the cross-sectional sampling, included patients, by virtue of having survived to the time of enrolment, could not have died between diagnosis and study enrolment, and therefore they should be removed from the risk set between those two time points. To leave them in the risk set would bias the survival estimates resulting in so-called left data truncation; in other words, if we were to estimate incidence of those adverse events from the time of first trial enrolment, we would observe a survival bias. Thus, nonparametric maximum likelihood estimator (NPMLE) of the distribution function observed under truncation will be used [Efron 1999]. Finally, inverse probability weighting (IPW) approach will be used to causal inference purposes [Robins1999].

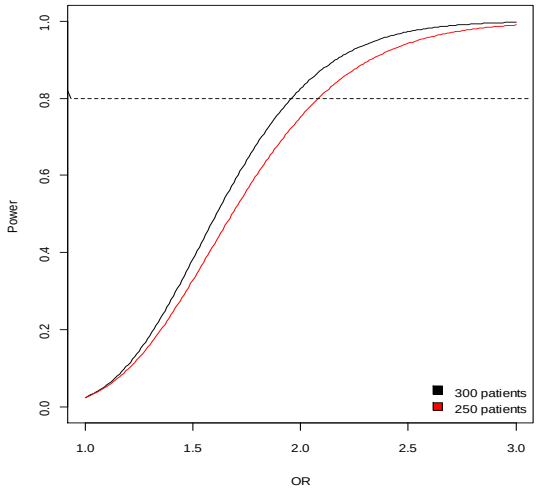
Analysis will be based on R software (http://www.R-project.org/), with packages survival [Therneau 2014], DTDA [Moreira 2010].

12.2 Calculation hypotheses for the number of subjects required and the result

Approximately 1000 patients were included in the Ph1-negative ALL GRAALL-2003 and 2005, among them 630 before August 2009, who will reach 10 year follow-up during inclusion period (see Table 1).

Considering that 363/630 patients were alive at last follow-up, the opportunity to include patients treated according to these protocols, the LL-03 trials, and pediatric protocols (mostly during inter-protocol phases), and a 80% inclusion success (loss of follow-up, refusal…), approximately 300 patients will be recruited in the EQUAALL01 study.

This allows assessing the prevalence of troubles with a 95%CI width at 7% about assuming a 10% prevalence or to 0.10 assuming a 30% prevalence, and detection of OR at 2.5 or 2, respectively. This also allows reaching a statistical power of at least 80% for detecting OR at 2 (Figure below).



12.3 Statistical References

Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol 2003; 3: 21.

Efron B, Petrosian V (1999). Nonparametric Methods for Doubly Truncated Data. Journal of the American Statistical Association, 94, 824-834.

Carla Moreira, Jacobo de Uña-Álvarez, Rosa Crujeiras. DTDA: An R Package to Analyze Randomly Truncated Data. Journal of Statistical Software, 2010;37(7):1-20. URL http://www.jstatsoft.org/v37/i07/

Petersen MR, Deddens JA. A comparison of two methods for estimating prevalence ratios. BMC Med Research Methodol 2008;8: 9. doi:10.1186/1471-2288-8-9

Robins JM. Marginal structural models versus structural nested models as tools for causal inference. In: Halloran ME, Berry D, eds. Statistical Models in Epidemiology, the Environment, and Clinical Trials. New York, NY: Springer-Verlag New York;1999:95–134.

Therneau T (2014). A Package for Survival Analysis in S. R package version 2.37-7, <URL: http://CRAN.R-project.org/package=survival>.

13 QUALITY CONTROL AND ASSURANCE

13.1 General organization

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study.
The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centers.
The sponsor will establish a system for opening the research centers and may also implement a data quality control system.

13.1.1 Strategy for site opening

The strategy for opening the centers established for this research is determined using the appropriate monitoring plan.

13.1.2 Data quality control

For this Minimal Risk and constraints research study, the appropriate quality control level has been determined based on the impact and the budget of the research. The sponsor, working in liaison with the coordinating investigator, will determine this level before the research begins.

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI.
The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate.

13.2 Case report forms

The case report forms should only contain the data needed to analyze the study and publish the results. All other data needed to monitor the participants during and after the study are recorded in the medical file.

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and must be written clearly and legibly. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.
Centers will anonymise, scan, send the reports listed on section 10.2.,via secure eCRF web, for proofreading by the centralized proofreading committee.
Using on-line case report forms means the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data. In addition, there are consistency checks to ensure the data are verified immediately upon being entered. The investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the research. The sponsor will keep the original. The investigator must keep a copy.

13.3 Management of non-compliances

Any events that occur as a result the investigator or any other individual involved in conducting the study failing to comply with the protocol, standard operating procedures or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

The sponsor has its own procedures for managing these non-compliances.

13.4 Audits

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's audit requirements.
The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

13.5 Principal Investigator's declaration of responsibility

Before starting the study, each investigator will give the sponsor’s representative a signed and dated copy of his/her most recent curriculum vitæ, produced within the past year, and RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must describe any previous participation in clinical research and related training.

Each investigator will agree to comply with legislation and to conduct the study in line with regulations, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their co-workers will sign a delegation form specifying each person's role and must supply their CV.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of said Code.

The person's will be first informed of the study during their usual follow-up (if they still regularly seen in consultation at the center) or contacted either by phone or by mail (if no more seen in consultation at the center (expected to be the most frequent situation). Then he or she will receive oral and written information (note of information) by Investigator of hematologic department and another consultation will be planned for inclusion

The person will be granted a reflection period between the time when the subject receives the information and the time when he or she signs the consent form at inclusion visit

The person's free and informed written consent will be obtained by the principal investigator, a doctor representing the investigator or a qualified person, before the person is enrolled on the study at inclusion visit.

The information sheet and one copy of the consent form, signed and dated by the research participant and by the investigator the doctor representing the investigator or a qualified person, are given to the individual prior to being enrolled on the study.

In addition, the investigator will specify in the research participant's medical file the methods used for obtaining their consent [or the consent of any other person, in the cases described in Articles L.1122-1-1 to L.1122-2 CSP] as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

14.2 Compensation for participants

Patients will not paid in compensation for the inconveniences relating to the research.

14.3 Legal obligations

Assistance Publique-Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique-Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.4 Request for approval from the CPP

Prior to starting the study, AP-HP, as sponsor, must obtain approval from the CPP (Research Ethics Committee) for its Minimal Risks and Burden research study, within the scope of the committee's authority and in accordance with in force legislation and regulatory requirements.

14.5 Informing the ANSM

AP-HP will send the approval from the CPP (Research Ethics Committee) and the summary of the protocol to the ANSM for information.

14.6 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Request for authorisation by the CNIL (French Data Protection Agency)

This research is not governed by the CNIL "Reference Method" (MR-001) because some personals data (specify in 6.1.1.6 Considerations about "personal data") are collected and will be very helpful to analyze the results.

The sponsor must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research.

14.7 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.8 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the Code de la Santé Publique (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study

14.9 Archiving

Specific documents for a research involving human participants with Minimal Risks and Burden are to be archived by the investigator and the sponsor for 15 years following the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- Study binders for the investigator and the sponsor, including (non-exhaustive list):
    - the successive versions of the protocol (identified by the version number and its date), and any appendices
    - decisions of the CPP (Research Ethics Committee)
    - any correspondence
    - the enrolment list or register
    - the appendices specific to the research
    - final study report

Data collection documents

15 FUNDING AND INSURANCE

15.1 Sources of monetary support

The study was support by PHRC
This study was financed in the frame of the call for projects: “Programme Hospitalier de Recherche Clinique en Cancérologie 2015” by the French Ministry of Health.

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor’s own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participants and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. Compensation cannot be refused on the grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any agent (doctor or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique - CSP (French Public Health Code).

16 PUBLICATION RULES

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is not important
- Each of these affiliations must be identified by an address and separated by a semicolon
- The AP-HP institution must feature under the acronym "AP-HP" first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Clinical Research and Innovation Department)"

16.3 Mention of the funder in the acknowledgements of the text

- The research was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2015 (Ministère de la Santé)

This research program will be registered on the website http://clinicaltrials.gov/ (include the registration number once registered).

17 REFERENCES

1. Boissel, N. *et al.* Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **21,** 774–780 (2003).
2. Dombret, H., Cluzeau, T., Huguet, F. & Boissel, N. Pediatric-Like Therapy for Adults with ALL. *Curr. Hematol. Malig. Rep.* (2014). doi:10.1007/s11899-014-0210-9
3. Huguet, F. *et al.* Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **27,** 911–918 (2009).
4. Dhedin, N. *et al.* Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) In Adults With Philadelphia Chromosome (Ph)-Negative Acute Lymphoblastic Leukemia (ALL): Results From The Group For Research On Adult ALL (GRAALL). *Blood* **122,** 552–552 (2013).
5. Pui, C.-H., Mullighan, C. G., Evans, W. E. & Relling, M. V. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? *Blood* **120,** 1165–1174 (2012).
6. Mody, R. *et al.* Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood* **111,** 5515–5523 (2008).
7. Oudin, C. *et al.* Prevalence and risk factors of the metabolic syndrome in adult survivors of childhood leukemia. *Blood* **117,** 4442–4448 (2011).
8. Sanders, J. E. *et al.* Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* **87,** 3045–3052 (1996).
9. Hill, J. M. *et al.* A comparative study of the long term psychosocial functioning of childhood acute lymphoblastic leukemia survivors treated by intrathecal methotrexate with or without cranial radiation. *Cancer* **82,** 208–218 (1998).
10. Benadiba, J. *et al.* Health status and quality of life of long-term survivors of childhood acute leukemia: the impact of central nervous system irradiation. *J. Pediatr. Hematol. Oncol.* **37,** 109–116 (2015).
11. Löning, L. *et al.* Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood* **95,** 2770–2775 (2000).
12. Langer, T. *et al.* CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. *Med. Pediatr. Oncol.* **38,** 320–328 (2002).
13. Berbis, J. *et al.* A French cohort of childhood leukemia survivors: impact of hematopoietic stem cell transplantation on health status and quality of life. *Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant.* **19,** 1065–1072 (2013).
14. Tichelli, A. *et al.* Late complications after hematopoietic stem cell transplantation. *Expert Rev. Hematol.* **2,** 583–601 (2009).

15. Mohty, M. & Apperley, J. F. Long-term physiological side effects after allogeneic bone marrow transplantation. *Hematol. Educ. Program Am. Soc. Hematol. Am. Soc. Hematol. Educ. Program* **2010,** 229–236 (2010).
16. Bhatia, S. *et al.* Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. *Blood* **110,** 3784–3792 (2007).
17. Solh, M., Arat, M., Cao, Q., Majhail, N. S. & Weisdorf, D. Late-onset noninfectious pulmonary complications in adult allogeneic hematopoietic cell transplant recipients. *Transplantation* **91,** 798–803 (2011).
18. Friedman, D. L. *et al.* Increased risk of breast cancer among survivors of allogeneic hematopoietic cell transplantation: a report from the FHCRC and the EBMT-Late Effect Working Party. *Blood* **111,** 939–944 (2008).
19. Campbell, S. *et al.* Predictors of avascular necrosis of bone in long-term survivors of hematopoietic cell transplantation. *Cancer* **115,** 4127–4135 (2009).
20. Syrjala, K. L., Martin, P. J. & Lee, S. J. Delivering care to long-term adult survivors of hematopoietic cell transplantation. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **30,** 3746–3751 (2012).
21. Rizzo, J. D. *et al.* Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. *Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant.* **12,** 138–151 (2006).
22. Majhail, N. S. *et al.* Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Bone Marrow Transplant.* **47,** 337–341 (2012).
23. Grulke, N., Albani, C. & Bailer, H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. *Bone Marrow Transplant.* **47,** 473–482 (2012).
24. Sundberg, K. K., Wettergren, L., Frisk, P. & Arvidson, J. Self-reported quality of life in long-term survivors of childhood lymphoblastic malignancy treated with hematopoietic stem cell transplantation versus conventional therapy. *Pediatr. Blood Cancer* **60,** 1382–1387 (2013).
25. Watson, M. *et al.* Adverse impact of bone marrow transplantation on quality of life in acute myeloid leukaemia patients; analysis of the UK Medical Research Council AML 10 Trial. *Eur. J. Cancer Oxf. Engl. 1990* **40,** 971–978 (2004).

18 LIST OF ADDENDA

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