NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Real-world Study in Acute Leukemia: Epidemiology, Treatment Patterns and Outcomes for B-cell ALL and AML in Adult Patients From Latin America – LOYAL Study
Protocol number	X9001302
Protocol version identifier	1.0
Date	20 April 2021
Research question and objectives	To describe the current epidemiology, treatment patterns, outcomes and healthcare resource use of adult patients diagnosed with B-cell ALL R/R and de novo AML in 4 Latin American countries.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
6MTP	mercaptopurine
AE	adverse event
AEM	adverse event monitoring
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
AraC	cytarabine
ATRA	all-trans retinoic acid
AYA	adolescents and young adults
BFM	German Berlin, Frankfurt, Muenster
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CR	complete remission; complete response
CRF	case report form
CRi	complete remission with incomplete hematological recovery or Complete response with incomplete blood count recovery
CRMRD-	complete remission without minimal residual disease
CSA	clinical study agreement
CVAD	cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone
DCT	Data collection tools
ECOG	Eastern Cooperative Oncologic Group
eCRF	electronic case report forms
EDC	electronic data capture
EFS	event-free survival
ELN	European LeukemiaNet
EMA	European Medicines Agency
EMD	extramedullary disease
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESMO	European Society for Medical Oncology
FAB	French-American-British
FDA	Food and Drug Administration
FLAG-IDA	fludarabine, cytarabine, G-CSF and idarubicin

Abbreviation	Definition
G-CSF	Granulocyte colony stimulating factor
GPP	Good Pharmacoepidemiology Practices
GvHD	graft-versus-host disease
HCT	hematopoietic cell transplantation
HSCT	hematopoietic stem cell transplantation
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committees
IQR	interquartile range
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IWG	International Working Group
KPS	Karnofsky performance status
LA	Latin America
LOYAL	Real-world Study in Acute Leukemia: Epidemiology, Treatment Patterns and Outcomes for B-cell ALL and AML in Adult Patients From Latin America
MDR-	complete remission without minimal residual disease
MFC or MPFC	multiparameter flow cytometry
MLFS	morphologic leukemia-free stat
MRD	minimal residual disease
MTX	methotrexate
NCCN	National Comprehensive Cancer Network
NIS	non-interventional study
OS	overall survival
PD	progressive disease
Ph-	Philadelphia chromosome - negative
Ph+	Philadelphia chromosome - positive
Ph1	Philadelphia chromosome
PPPY	per patient per year
PR	partial remission
R/R	relapsed/refractory
RFS	relapse-free survival
RT-qPCR	Real-time polymerase chain reaction
SAP	statistical analysis plan

Abbreviation	Definition
SD	standard deviation
TdT	nuclear terminal deoxynucleotide transferase
TKI	tyrosine kinase inhibitors
TLS	tumor sysis syndrome
TTNT	time to next treatment
WBC	white blood cell
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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PPD	Analyst	PPD	PPD
PPD	Sr. Consultant	PPD	PPD

The list of each Center Coordinating Investigators will be provided during the study and maintained separately. Available upon request.

4. ABSTRACT

Title	Real-world Study in Acute Leukemia: Epidemiology, Treatment Patterns and Outcomes for B-cell ALL and AML in Adult Patients From Latin America – LOYAL Study
Version	1.0
Date of the protocol	22 March 2021
Main author	PPD, PPD – Pfizer Oncology Emerging Markets
Co-author	PPD, H&V – PPD – Pfizer
Rationale and background	Acute myeloid leukemia (AML) is the most frequent leukemia among adults, while acute lymphoblastic leukemia (ALL) affects mainly children and young adults. To date there is scarce data on the epidemiology and treatment patterns of patients with acute leukemias in Latin America (LA).
Research question and objectives	What is the epidemiology, treatment patterns and outcomes and healthcare resource utilization of ALL and AML patients in LA? The aim of this study is to describe the current epidemiology, treatment patterns, outcomes and healthcare resource use of adult patients diagnosed with B-cell ALL relapsed/refractory (R/R) and de novo AML in four Latin American countries.
Study design	This is a retrospective multicenter non-interventional study using real-world data collected from medical records of newly diagnosed AML or with relapsed/refractory B-cell ALL diagnosed between 01 January 2015 and 31 December 2019 in 4 Latin American countries: Argentina, Brazil, Chile, and Colombia. In addition, as secondary objectives, the study will also describe molecular profile, cytogenetic risk, clinical outcomes, and healthcare resource utilization of treated B-cell ALL R/R and AML patients.
Population	Patients ≥18 years old at diagnosis, with confirmed diagnosis of relapsed/refractory B-cell ALL or newly diagnosis of AML between 01 January 2015 and 31 December 2019, as documented in the medical chart and according to the physician's notes, and with at least 1 line of treatment for B-cell ALL or AML within the study period will be eligible. Exclusion criteria includes patients with no medical chart available, with unreliable data as per investigator's opinion (eg, excessive missing data or inconsistence data) and that have participated in any interventional clinical trial for

	relapsed/refractory R/R B-cell ALL or denovo AML at any moment. Patients under any compassionate use is allowed. Patients with secondary AML or acute promyelocytic leukemia (APL) are also excluded.
Variables	Data on demographics, clinical characteristics, and treatment regimens, among others, will be collected. Healthcare resource utilization will be captured to understand the management pattern of both patient populations.
Data sources	All data will be extracted from patients' medical charts and entered into an electronic case report form (CRF) specifically designed to capture relevant information in accordance with the study outcomes
Study size	It is expected the study will enroll approximately 700 patients with B-cell ALL R/R and AML in a consecutive manner, in approximately 15 sites distributed across Argentina, Brazil, Chile, and Colombia
Data analysis	All relevant data reported in the medical chart since diagnosis date (index date) until the study enrollment, last visit, contact date or death, whichever comes earlier, will be assessed. Follow-up period, time to next treatment (TTNT), overall survival (OS), relapse-free survival (RFS), event-free survival (EFS) will be assessed.
Milestones	- CRF and electronic CRF (eCRF): June 2021 - Study documents (data management plan, data validation plan, statistical analysis plan): May 2021 - Start of data collection: July 2021 - End of data collection: August 2022 - Data analysis: August 2022 - Final study report: November 2022

5. AMENDMENTS AND UPDATES

6. MILESTONES

The timeline starts after the protocol approval and consider the approval and consider the milestones below. It is important to highlight that the dates may change during the study conduction

Milestone	Planned date
Case report form (CRF) and electronic CRF (eCRF)	June 2021
Study documents: data management plan, data validation plan, statistical analysis plan	May 2021
Start of data collection	July 2021
End of data collection	August 2022
Data analysis	August 2022
Final study report	November 2022

7. RATIONALE AND BACKGROUND

7.1. Acute Myeloid Leukemia

Although acute leukemias are rare diseases, accounting for less than 3% of all cancers, they are the leading cause of death among children and young adults with cancer.[1] Acute myeloid leukemia (AML) is the most frequent leukemia among adults, accounting for 90% of all cases of acute leukemia in adults and representing 23.1% of all leukemia cases.[2,3] It is a disease with high mortality rate among patients over 65 years old, which is of special concern since its incidence has a J-shaped age-pattern.[1,4] Globally, the age-standardized incidence rate of AML increased from 1.35/100,000 in 1990 to 1.54/100,000 in 2017, being more commonly diagnosed in high-income countries located in Europe and North America.[5] In Latin America the epidemiology data on AML patients are scarce.

Acute myeloid leukemia is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. In most cases, it is a de novo malignancy in previously healthy individuals, however, it can also arise in patients with an underlying hematological disorder, or due to a prior alkylating therapy or radiotherapy.[4]

Regardless of its etiology, several chromosomal rearrangements and gene mutations were closely associated to the AML pathogenesis and prognosis. Indeed, the presentation of AML depends heavily on the interactions between different somatic alterations and chromosomal rearrangements. A meta-analysis of the AML genomic patterns identified 5234 driver mutations involving 76 genes or regions.[6] Among AML patients, around 20% were defined

according to fusion genes, 31% by chromosomal aneuploidies (including at least 1 aneuploidy), 46% by gene mutations only (in the absence of gene fusions and chromosomal aneuploidies), and 3% with no events.[7] With the advance of molecular and sequencing technologies the identification of key cytogenetic abnormalities and the molecular profiling have become a standard for an accurate diagnose of AML patients.[7] The pattern of co-existing mutations and cytogenetic abnormalities at diagnosis can determine therapeutic approaches to induce remission and is associated with the risk of presenting worse response.[8]

Besides older age, poor-risk prognostic parameters for AML include secondary disease, and adverse cytogenetics.[8] Although age, performance status at diagnosis, and other clinical factors have been used as important parameters for management decision, cytogenetics abnormalities are the strongest prognostic factors for complete remission (CR) and OS in AML.[4] Several classification systems are available for AML, including French-American-British (FAB) system; the World Health Organization (WHO) and the European LeukemiaNet. The FAB system was the first attempt to classify the AML according to the morphological and cytochemical characteristics of the leukemic cells.[4] Comprising genetic, morphology, immunophenotyping, and clinical presentation information, the WHO classification is already stabilized in the clinical practice of high-income countries, where the molecular and cytogenetic screening are part of the routine.[9] As for European LeukemiaNet system, later adopted in the clinical practice, AML patients can be stratified into favorable, intermediate or adverse prognostic risk groups based on the cytogenetic and gene abnormalities.[10,11] However, low-income countries have limited access to these costly and complex test which hampered a more complete diagnosis classification of AML patients. A national survey conducted in Brazil, showed that among private and public institutions, the karyotype analysis and the screening of gene mutations were available in 88% and 71% of institutions, respectively. Next generation sequencing analysis was used in only 7% of institutions.[12] Therefore, in many regions, the FAB classification is still under use.[13-15]

In this scenario, cytogenetics has been widely used to provide the framework for risk-adapted treatment approaches. In certain situations, cytogenetics is also a predictor of treatment effectiveness: in patients with the t(15;17)(q22;q21) /PML-RARA, for instance, the combination of all-trans retinoic acid (ATRA) and anthracycline-based protocols has resulted in a markedly improved outcome. In contrast patients with complex karyotype (≥3 or ≥5 abnormalities depending on the classification system), monosomal karyotype (such as monosomy 5/del(5q) or monosomy 7/del(7q)), or abnormalities of 3q have been shown to have inferior complete remission rates and overall survival and are currently considered for allogeneic stem cell transplant in first remission.[8] Despite the genetic abnormalities at diagnosis, the continued presence of particular gene mutations during or after treatment carries prognostic information for certain genetically defined AML subtypes. Therefore, minimal residual disease (MRD) detection, either by genetics or by multiparameter flow cytometry (MPFC), is also an important risk factor for relapse.[16]

7.2. Acute Lymphoblastic Leukemia

Unlike AML, acute lymphoblastic leukemia (ALL) affect mainly children and young adults. It is a disease with higher incidence in developing countries, with Honduras presenting the highest incidence rate in 2017 (3.83/100,000), followed by Mexico.[5] The pathogenesis of ALL involves the abnormal proliferation and differentiation of a clonal population of lymphoid cells. In the majority of cases, it appears as a de novo malignancy in previously healthy individuals. Chromosomal aberrations are the hallmark of ALL, but are not sufficient to generate leukemia. Characteristic translocations include t(12;21)[ETV6-RUNX1], t(1;19) [TCF3-PBX1], t(9;22) [BCR-ABL1], rearrangement of MLL and a variant with a similar gene expression profile to (Philadelphia) Ph-positive ALL but without the BCR-ABL1 rearrangement.[17]

Most of the clinical manifestations of ALL reflect the accumulation of malignant, poorly differentiated lymphoid cells within the bone marrow, peripheral blood, and, extramedullary sites. In general, it is observed signs of bone marrow failure (anemia, thrombocytopenia, leukopenia) associated with general symptoms such as fever, weight loss, bleeding, fatigue, dyspnea and infection. Similarly, to the AML, the ALL can be also classified according to the WHO and FAB criteria.

The ALL can be originated from a progenitor cell of the B- or T-cell.[18] The malignant cell expresses surface antigens according to their respective lineage developments and may influence the choice of the treatment. Therefore, precursor B-cell ALL cells (B-cell ALL) typically express on their surface membrane peptidase CD10, CD19, CD34, and nuclear terminal deoxynucleotide transferase (TdT), while precursor T-cell ALL cells are mainly CD2, CD3, CD7, CD34, and TdT.[19]

The genetic information of the leukemia cell can provide prognostic expectations and treatment directions.[20] About 20% of adults and a small percentage of children with ALL present *BCR-ABL* fusion gene, which characterizes the Philadelphia chromosome (Ph1).[21] In contrast, the Ph1 occurs in only 1% to 2% of patients with AML. The identification of Ph1 by molecular analysis, such as reverse-transcriptase polymerase chain reaction (RT-PCR), is mostly important for B-cell disease.[22] Besides Ph1, other chromosomal abnormalities are associated with poor prognosis and may also be investigated, such as *myc* gene rearrangements (in Burkitt leukemia), and *MLL* gene rearrangements.[23-26]

Additionally, other factors affect prognosis and survival such as age, central nervous system impairment, and cellular morphology.[27] Studies show that younger patients, less than 35 years old, have better prognosis when compare to other ages.[28,29] Moreover, the involvement of central nervous system influence both treatment and prognosis for leukemia, with the needed for a more aggressive therapy strategy.[30] That aggressiveness in chemotherapy regimens can also be applied for patients that are identified with L3 cell morphology.[31,32]

7.3. Treatment for AML and ALL

Among the therapeutic approaches, patients can be selected for an intensive treatment, which consists of either systemic or local (including intrathecal) chemotherapy.[33] Besides chemotherapy, other types of treatment can be recommended according to patient status, including hematopoietic stem cell transplantation (HSCT); investigational products offered in clinical trials and targeted therapy. According to the patient´s characteristics, patients should first undergo an induction therapy to achieve complete remission, with a subsequent consolidation therapy in order to achieve a negative minimal residual disease (MRD).

Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, prognosis in the elderly who account for the majority of new cases remains poor. Even with current treatments, as much as 70% of patients 65 years or older will die of their disease within 1 year of diagnosis.[4] Except for those with acute promyelocytic leukemia, approximately 50% of patients under 60 years and 90% of patients over 60 years will.[3]

The main induction therapy for AML changed minimally over the past 40 years and consist of the 7+3 regimen, which combines 7 days of continuous infusion cytarabine with 3 days of anthracycline.[34,35] The combination of fludarabine, cytarabine, Granulocyte colony stimulating factor (G-CSF) and idarubicin (FLAG-IDA), which was traditionally used for the treatment of relapse, has also been shown to be a reasonable alternative to standard induction regimens and results in similar CR rates and overall survival (OS) with higher rates of CR after a single course.[4] Nevertheless, the treatment approach for elderly patients with AML are not a consensus. These patients usually have a poor response to the conventional regimens, and in some cases are indicated for supportive care and palliative chemotherapy.

Recently, new therapies approved or in clinical trials are being combined with the standard care, including intensive (gemtuzumab, ozogamicin, midostaurin) and non-intensive regimens such as improved chemotherapies (glasdegib), mutationally targeted inhibitors (sorafenib, midostaurin, lestaurtinib, quizartinib, crenolanib, and gilteritinib), pro-apoptotic agents (venetoclax), microenvironment targeting molecules (uproleselan), cell cycle checkpoint inhibitors (alisertib, barasertib, palbociclib, dinaciclib), and epigenetic regulators (bromodomain and clinical studies with extraterminal protein family inhibitors).[35-40]

As for ALL, treatment usually differs for Ph+ and Ph- patients and according to age.[41-43] For induction therapy in adolescents and young adults (AYA) – defined by the National Cancer Institute as cancer care or research focused on those diagnosed with cancer between the ages of 15 to 39 years old – with Ph+, the treatment are frequently tyrosine kinase inhibitors (TKI) associated with chemotherapy, considering hematopoietic cell transplantation (HCT) as consolidation therapy whenever possible.[44] For Ph+ adults, the treatment could be similar, with the increase of corticosteroids for adults with comorbidities.[41-43,45] For adults Ph- patients with less than 60 or even 65 years old without comorbidities, induction usually includes 4 to 6 drugs: vincristine, anthracycline, corticosteroids, asparaginase, cyclophosphamide, cytarabine (AraC) and mercaptopurine (6MTP); consolidation may include methotrexate (MTX) at high doses or divided doses, and long-term maintenance

(6MTP continuous and MTX weekly).[41-43,45] For AYA Ph- patients, pediatric protocols are generally used, such as German Berlin, Frankfurt, Muenster (BFM) or cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone (HyperCVAD), which includes the drugs cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone. Depending on the physical evaluation, adult Ph- patients could receive asparaginase, MTX and Ara-C in consolidation therapy.[45,46]

Induction therapy aims to achieve complete remission, after which patients may undergo allogeneic (HSCT) – usually the best option for long-term survival – or progress to the consolidation and maintenance phases.[47] In order to start the HSCT, a complete response to therapy is typically required. Unfortunately, only approximately 40% of patients after the first salvage therapy achieve a complete response.[17,48-50]

Currently, immunotherapies have emerged as a novel treatment option for ALL and AML patients, including monoclonal antibodies, conjugated monoclonal antibodies, bispecific T cell engagers, and chimeric antigen receptor T cell therapies.[38,39,46,48] Among immunotherapies, inotuzumab ozogamicin (Pfizer, Philadelphia, PA, USA) and blinatumomab (Amgen, Thousand Oaks, CA, USA) are both approved by Food and Drug Administration (FDA), and demonstrated efficacy in their respective phase III studies.[51-53]

The are several treatment guidelines for AML and ALL, including those developed by each country; however, some of the most cited guidelines in literature include National Comprehensive Cancer Network (NCCN) guidelines for AML[54,55] and ALL;[41-43] European LeukemiaNet (ELN) recommendations and revised versions[10,11] and Clinical Practice Guidelines developed in accordance with the European Society for Medical Oncology (ESMO) for AML;[56,57] Guías de Diagnóstico y Tratamiento developed by Sociedad Argentina de Hematología for both AML and ALL.[45]

7.4. Rationale

To date there is scarce data on the epidemiology and treatment patterns of patients with acute leukemias in Latin America. Despite the various guidelines and recommendations for diagnosis, risk assessment, and therapy strategies most of them are not feasible in the clinical practice of a low/middle-income region. The lack of access to technologies for cytogenetic analysis and molecular profiling, besides the limit access to target therapies are important hurdles in the care of patients with AML and ALL.

There are guidelines developed by the Ministries of Health and the local hematology/oncology medical societies for ALL and AML in Brazil,[3,58-60] Argentina,[45] Colombia [61] e Chile.[62-64] However, the understanding of ALL and AML in the real-world context of developing countries is very limited. Progress in being made in the real-world setting, leading to improvements in the way the diseases are managed.[65] Therefore, this non-interventional study aims to describe the current epidemiology, treatment patterns and health care resource use of adult patients diagnosed with B-cell ALL relapsed/refractory (R/R) and de novo AML in four Latin American countries.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to describe the current epidemiology, treatment patterns, outcomes and healthcare resource use of adult patients diagnosed with B-cell ALL R/R and de novo AML in four Latin American countries.

8.1. Primary Objective(s)

- To describe the clinical and demographics characteristics of newly diagnosed AML (and follow up treatment for R/R disease when available) and relapsed/refractory B-cell ALL patients.
- To assess treatment patterns in current practice of newly diagnosed AML and relapsed/refractory B-cell ALL patients.

8.2. Secondary Objective(s)

- To describe the cytogenetic and molecular profile of newly diagnosed AML and relapsed/refractory B-cell ALL patients, when available.
- To evaluate the risk stratification of newly diagnosed AML and relapsed/refractory B-cell ALL patients.
- To describe the clinically relevant events of newly diagnosed AML and relapsed/refractory B-cell ALL patients.
- To estimate event-free survival (EFS) of newly diagnosed AML and relapsed/refractory B-cell ALL patients.
- To assess patient response rate to treatment for newly diagnosed AML and relapsed/refractory B-cell ALL patients.
- To describe, for relapsed/refractory B-cell ALL patients, treatment received when newly diagnosed for ALL (frontline B-cell ALL treatment).
- To estimate the overall survival (OS) and the 1, 3- and 5-year overall survival (OS) of newly diagnosed AML and relapsed/refractory B-cell ALL patients.
- To estimate relapse-free survival (RFS) for newly diagnosed AML patients.
- To describe healthcare resource utilization of newly diagnosed AML and relapsed/refractory B-cell ALL patients.

9. RESEARCH METHODS

9.1. Study Design

The current study is a retrospective multicenter non-interventional study using real-world data collected from medical records to describe the epidemiology of acute leukemias and treatment patterns among patients diagnosed with B-cell ALL R/R or AML in 4 Latin American countries: Argentina, Brazil, Chile, and Colombia. In addition, as secondary objectives, the study will also describe molecular profile, cytogenetic risk, clinical outcomes, and healthcare resource utilization of treated B-cell ALL R/R and AML patients.

All patients with newly diagnosed AML or with relapsed/refractory B-cell ALL diagnosed between 01 January 2015 and 31 December 2019 will be included in the study for medical chart abstraction. Data on demographics, clinical characteristics, treatment regimens, among others will be collected. Healthcare resource utilization will be captured to understand the management pattern of both patient's population. All relevant data reported in the medical chart since diagnosis date (index date) until the study enrollment or death, whichever comes earlier, will be assessed.

9.2. Setting

For this study, data from patients treated at public or private healthcare facilities in Argentina, Brazil, Chile, Colombia, diagnosed with R/R B- cell ALL or AML between 01 January 2015 and 31 December 2019 will be considered for the analysis.

The eligibility period of 5 years was determined to increase the overall patient representativeness, and to allow ample follow-up to assess survival outcomes.

The study will be conducted in approximately 15 sites distributed across Argentina, Brazil, Chile, and Colombia, and is expected to enroll approximately 700 patients with R/R B-cell ALL and AML in a consecutive matter. To assure the representativeness of each country, the number of sites and the total expected enrolled patients will be limited according to the country, considering the prevalence/incidence of the diseases. These will be estimated after a country level feasibility assessment.

Data collection will occur in a period of up to 12 months following the independent ethics committee (IEC)/ institutional review board (IRB) approval and study set up. Patients will be consecutively enrolled, considering both target population, with no set proportion of AML and R/R B-cell ALL patients to be included in the study. However, it is expected a higher proportion of AML patients in the cohort. The study period will comprise since diagnosis date (index date) until the study enrollment or death, whichever comes earlier.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Patients with ≥18 years old at diagnosis;

2. Confirmed diagnosis of relapsed/refractory B-cell ALL or newly diagnosed of AML between 01 January 2015 and 31 December 2019, as documented in the medical chart and according to the physician's notes;

3. Patients that received at least one line of treatment for R/R B-cell ALL or denovo AML within the study period; for R/R B-cell ALL patients, data on previous therapy will also be collected if available.

9.2.2. Exclusion Citeria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with no medical chart available.

2. Patients with unreliable data as per investigator's opinion (eg, excessive missing data or inconsistence data).

3. Patients that have participated in any interventional clinical trial for relapsed/refractory B-cell ALL or AML at any moment. Patients under any compassionate use is allowed.

4. Patients with secondary AML.

5. Patients with any concomitant primary malignancy.

6. Patients with acute promyelocytic leukemia (APL).

9.2.3. Study Definitions

- Patients with AML: patients with diagnosis of AML according to the physician´s note in the medical chart participants.
- Patients with B-cell ALL R/R: B-cell ALL R/R is defined as ALL patients with type B - cell that are classified as relapsed and/or refractory according to medical chart.
- Concomitant medications: drug treatment for comorbidities, supportive and prophylaxis therapies, or to treat adverse events.
- Consolidation therapy: according to the medical chart. A shorter and more intense treatment phase to further reduce the number of cancer cells. Also called intensification therapy and postremission therapy.[66]

- Death in aplasia: according to the medical chart. Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia.[10]
- Death from indeterminate cause: according to the medical chart. Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available.[10]
- Genetic classification and response to therapy for patients with AML and relapsed/refractory treatments for patients with B cell ALL: according to the medical chart and exemplifications are described in ANNEX 3. ADDITIONAL INFORMATION: Appendix 3 and Appendix 4.[10]
- Induction therapy: according to the medical chart. The first treatment that is given to greatly reduce the extent of cancer.[66]
- Intrathecal therapy: according to the medical chart. A treatment with cell-killing drugs that are injected into the brain and spinal fluid.[66]
- Maintenance therapy: according to the medical chart. A treatment phase that is given to prolong good treatment results.[66]
- Palliative therapy. according to the medical chart. Health care that includes symptom relief but not cancer treatment. Also sometimes called supportive care.[66]
- Primary chemotherapy: one or more cell-killing drugs that are used to rid the body of cancer.[66]
- Relapsed disease: according to the medical chart. The return or worsening of cancer after a period of improvement.
    - Hematologic relapse (after CRMRD, CR, CRi) Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease.
    - Molecular relapse (after CRMRD) If studied pretreatment, reoccurrence of MRD as assessed by Real-time polymerase chain reaction (RT-qPCR) or by MFC.
- Re-admission: according to the medical chart, generally defined as a hospital admission, occurring ≤30-days after the index admission.
- Re-induction therapy: according to the medical chart. After the first induction therapy fails.[67]
- Refractory disease: a cancer that does not improve with treatment.[66]
- Regimen: a plan for the dose, schedule, and length of treatment. A regimen can be a treatment that consists of one or combined (two or more) drugs.[66]

- Remission: the absence of cancer signs and symptoms after treatment.[66]
- Recurrence therapy: according to the medical chart. Treatment for cancer that has returned after a cancer-free period.[66]
- Treatment failure: according to the medical chart. Refractory disease or Death in aplasia or Death from indeterminate cause.[10]
- Treatment lines: lines will be defined as distinct combinations. The initial treatment or regimen administered will be first line. Do not include a stem cell transplant, induction, consolidation or maintenance therapies in your counting of lines. A line of therapy ends and a new line of therapy begins when the patient discontinued treatment with a regimen; if a regimen was added to the ongoing treatment this should be considered a new line of therapy. If a drug within a combination is held or discontinued this should not be considered a new line of therapy.
- Treatment response
    - Complete remission or complete response (CR): a patient's response to treatment according to the medical chart. Usually, AML complete remission defined as no physical signs of leukemia, bone marrow with active hematopoiesis, <5% bone marrow blasts and more than 1×10^9/l granulocytes and more than 100×10^9/l platelets in the blood and no circulating leukemic blasts or evidence of extramedullary leukemia.[10]
    - Complete response with incomplete blood count recovery (CRi): also known as CR with incomplete hematologic recovery, also a patient's response to treatment according to the medical chart. Definition includes all CR criteria except for residual neutropenia ($<1.0 \times 10^9$/L [1000/μL]) or thrombocytopenia ($<100 \times 10^9$/L [100 000/μL]).[10]
    - Partial remission: a patients response to treatment according to the medical chart. All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%.[10]
    - Progressive disease (PD): according to the medical chart. Progressive disease is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms. Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood is defined by European LeukemiaNet (ELN).[10] as:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level (>0.5 × 10^9/L [500/µL], and/or platelet count to >50 × 10^9/L [50 000/µL] nontransfused). According to ELN recommendations, the date of progression should then be defined as of the first observation date; or
- >50% increase in peripheral blasts (white blood cell (WBC) × % blasts) to >25 × 10^9/L (>25 000/µL) (in the absence of differentiation syndrome); or
- New extramedullary disease.

- Refractory disease: according to the medical chart. No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause.[10]
- Relapse from CR or CRi: according to the medical chart.[40,53]
  - Appearance of leukemic blasts in the peripheral blood.
  - Appearance of extramedullary disease.
  - ≥5% blasts in the bone marrow not attributable to another cause (eg, recovery of normal cells following chemotherapy-induced aplasia).
  - If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is ≥5%

- Tumor Lysis Syndrome (TLS): according to the medical chart. Descriptive TLS criteria are described in ANNEX 3. ADDITIONAL INFORMATION: Appendix 2[68]

9.3. Variables

This is an observational study to access the real-world treatment practices and clinical outcomes in a Latin American population of adults' patients with acute leukemias. All treatment, procedures and overall management information of the target population will be collected according to the availability on the medical chart.

9.3.1. Outcomes

9.3.1.1. Primary Outcomes

- Description of demographic and clinical presentation characteristics at the moment of relapsed/refractory B-cell ALL or AML diagnosis.
- Treatment description considering the front-line therapy and subsequent regimen(s) required for patients with relapsed/refractory B-cell ALL and AML, including any systemic chemotherapy, target therapy, hematopoietic stem cell transplantation (autologous/allogenic), intrathecal chemotherapy and palliative management.

9.3.1.2. Secondary Outcomes

- Description of subtypes of AML and B-cell ALL based on the cytogenetic and molecular abnormalities, according to the WHO classification.
- Proportion of patients of each prognostic-risk group (favorable, intermediate, adverse) among newly diagnosed AML patients, based on cytogenetic profile
- Description of the treatment standard from diagnosis to inclusion of R/R ALL patients.
- Description of clinically relevant events presented by AML and relapsed/refractory B-cell ALL patients since treatment initiation until loss of follow-up or death from any cause.
- The EFS will be the measure of time since treatment initiation until failure to achieve complete remission (CR), or disease progression after CR, or death from any cause for both AML and relapsed/refractory B-cell ALL patients.
- The OS will be the measure of median time since treatment initiation until death from any cause for both AML and relapsed/refractory B-cell ALL patients.
- The OS will also assess the proportion of AML and relapsed/refractory B-cell ALL patients alive after 1, 3 and 5 years since treatment initiation.
- For AML patients who achieved CR, the RFS will be the measure of time since the CR attainment until relapse or death from any cause.
- For AML patients the response to induction and consolidation therapy will assess the proportion of patients who achieve complete remission (CR), complete remission with incomplete hematological recovery (CRi), complete remission without minimal residual disease (MDR-), partial remission (PR), and progressive disease.
- For relapsed/refractory B-cell ALL patients the response to the rescue treatment will access the proportion of patients with complete remission (CR), complete remission without minimal residual disease (MRD-), partial remission (PR), and progressive disease.

- Heath care resource utilization description, considering the outpatient utilization, inpatient admissions, hospitalization length of stay, and concomitant medication prescription since diagnosis until the loss of follow-up or death from any cause.

9.3.2. Variables and Epidemiological Measurements

The information will be extracted only if available in the medical chart. No assumptions or interpretation should be done in order to describe the parameter of interest. The following variables will be collected:

- **Patient demographics**: age at diagnosis, gender at birth, country of residence.
- **Medical history:** comorbidities, family history, prior exposure to toxic agents, prior malignancy, therapy for prior malignancy, information on smoking, history of bleeding episodes.
- **Clinical information at diagnosis**: age at diagnosis, performance status (Karnofsky performance status [KPS] or Eastern Cooperative Oncologic Group [ECOG]).
- **Diagnosis information**: hematological parameters (total blood count, differential count, hemoglobin level), bone marrow aspirate/biopsy, cytogenetics, screening for gene mutations and rearrangements, immunophenotyping assessment.
- **Treatment information:** all treatment regimens used since diagnosis until loss of follow-up or death. It will include front-line induction therapies, consolidation therapies, rescue therapies, conditioning therapy, hematological stem cell transplantation (autologous/allogenic), intrathecal chemotherapy, palliative care.
- **Clinically relevant events:**
  - Hematological toxicities described as: febrile neutropenia, anemia/thrombocytopenia that requires blood transfusion, bleeding events.
  - Hematological stem cell transplantation (autologous/allogenic) and transplant complications such as graft-versus-host disease (GvHD), stem cell (graft) failure.
  - Gastrointestinal toxicities: oral mucositis, nausea, vomiting, diarrhea.
  - Hepatotoxicity: hepatic enzymes elevation, jaundice, ascites, abdominal pain.
  - Other events: tumor lysis syndrome, fatigue, dysgeusia, alopecia, muscle spasm, Infections and sepsis.
  - Secondary malignancy or central nervous system (CNS) involvement.
  - Any serious adverse even.t
- **Patient response at the end of treatment**:
  - Patient response according to International Working Group (IWG) criteria.[69]
  - Methodology for the assessment of minimal residual disease.

- **Cytogenetic risk**:
  - Favorable, intermediate, adverse for AML.
  - Good, intermediate, poor, undetermined for B-cell ALL.
- **Healthcare resource utilization:** outpatient encounters (office visits, ancillary procedures, and ER visits), day-patient admission, inpatient admissions, hospitalization length of stay, concomitant medication (prophylactic therapy for infections, and other conditions related to the AML/ALL treatment or disease).

9.4. Data Sources

Given the noninterventional, observational nature of this study, its protocol does not recommend the use of any specific treatments, and no specific treatment is required for entry into the registry. Screening of data in medical records will be conducted retrospectively to identify study candidates, followed by data collection from registrants in a manner consistent with each investigator's practice (with recording of data using electronic case report forms).

All information will be capture from patient´s medical chart, since diagnosis until the most recent data available at study enrollment.

9.5. Study Size

As a descriptive study, sample size calculations are not applicable. The expected number of patients eligible for the study is approximately 700. An initial estimation of 15 sites across Argentina, Brazil, Chile and Colombia. The number for each disease will be estimated based on the feasibility assessment. Study size was estimated according to incidence of the diseases in Latin America and population size of each country.[5] In Latin America, the incidence varied from 0.51/100,000 to 2.0/100,000 for AML and from 0.81/100,000 to over 1.0/100,000 for ALL from 1990 until 2017.[5] Considering all leukemia cases in 2017, global incidence trends corresponds to 23.1% and 12.4% for AML and ALL, respectively. Higher trends were found in Southern Latin America, with 27.7% and 14.9% for AML and ALL, respectively.

9.6. Data Management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic case report forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the electronic data capture (EDC) system and followed up for resolution.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to an electronic data record.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless IQVIA and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Analyses will be descriptive in nature, as no hypothesis is being tested. Disease staging, comorbidities, demographic, clinical characteristics will be described at the date of diagnosis and/or treatment initiation for patients diagnosed with B-cell ALL R/R or AML. Treatment and clinical information will be assessed up to the most recent data available at the study enrollment. The treatments will be described in sequence according to the chronological order of administration. The duration through the number of cycles will be evaluated. Dose reduction information will also be collected.

Continuous variables will be described as mean and standard deviation (SD), and/or as median, minimum, maximum, interquartile range (IQR, 25^{th} and 75^{th} percentiles). Categorical variables will be described by simple and cross contingency tabulation, with absolute frequencies and percentages. Missing values will be included in the denominators for the calculation of percentages and missing categories will be presented.

All time-to-event analysis will be described using a Kaplan Meier plot, if appropriate. The following definition and parameter analysis will be considered:

- Follow-up period – considered the time elapsed since B-cell ALL R/R or AML diagnosis until the study enrollment. It will be presented in years.
- Time to next treatment (TTNT) – considered as the time from the start date of the front-line therapy to the start date of a subsequent line of therapy. It will be presented in months.
- Overall survival (OS) – considered as death from any cause from the time of initiation of diagnosis or treatment.[70,71] The median overall survival (OS) and the % of alive patients in 1, 3- and 5-years follow up of newly diagnosed AML and relapsed/refractory B-cell ALL patients will be assessed.
- Relapse-free survival (RFS) for newly diagnosed AML patients – considered as measured from the date of achievement of a remission until the date of relapse or death from any cause; patients not known to have relapsed or died at last follow-up are censored on the date they were last examined. Defined only for patients achieving CR, or CRi.

- Event-free survival (EFS) of newly diagnosed AML and relapsed/refractory B-cell ALL patients – considered as the measured from the date of initiation of treatment to the date of primary refractory disease, or relapse from CR, or CRi, or death from any cause; patients not known to have any of these events are censored on the date they were last examined

All computations and generation of tables, listings, graphics, and data for figures will be performed using R® version 3.5.3 or newer version (R Core Team), or a comparable statistical software package.

Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 2.1 (V2.1) or newer version will be used as a standardised medical terminology. Medicinal product names will be codified using World Health Organisation Drug Dictionary (WHODrug), a dictionary maintained and updated by Uppsala Monitoring Centre (UMC).

The resource utilization (eg, number of hospital admissions, hospitalization period, procedures during hospital admissions) will be presented as mean number per patient per year (PPPY). According to the sample distribution, the data will be presented with a standard deviation (SD) or a 95% confidence interval (95% CI), which will be estimated either by Poisson regression or Gama distribution. The PPPY will be calculated as the sum of all event observed in the cohort divided by the total follow-up period (in years) of all patient in the cohort (including those who did not present the event).

9.8. Quality Control

In general, missing data will not be imputed and the data will be analyzed as they are recorded in the study CRFs. However, if more than 10% of data is missing for 1 or more key variables, the impact of missing data on the analysis will be discussed, and the pattern of missing data may be explored. If there is evidence of bias in the missing data, and variables that are considered good predictors of the missing data are available, the multiple imputation method at the study level may be used to replace missing values as secondary exploratory analyses. If the multiple imputation method is used, a sensitivity analysis will be carried out comparing results from the complete case analysis (where records with missing data will be dropped) and the full set analysis (with imputed data). Another potential strategy is a mixed-effects model repeated-measures analysis. This approach helps to conserve patient data in the event of missing observations. It is also potentially advantageous in registry studies with often irregularly spaced clinic visits and observations.

9.9. Limitations of the Research Methods

The limitation of retrospective study is that the data are often incomplete. Individual or entire series of records can be missing, either because the data were misplaced or because data were not recorded. Quality and completeness of data collected in this study will depend on the level of detail and accuracy with which patients' medical charts are kept in participating sites. However, taking into consideration that patients are generally referred to and treated in specialized sites, these sites are likely to have the resources and systems working to keep patients' records appropriately.

9.10. Other Aspects

All efforts are made in this protocol to reduce inclusion bias. Potential sources of bias in this study, and the approach(es) for addressing and minimizing these biases are discussed below.

Selection bias: may arise if the study sample differs substantively from the underlying target population of patients with B-cell ALL R/R or AML. To minimize selection bias, the study protocol has selected eligibility criteria that are as liberal as possible: age ≥18, newly diagnosed B-cell ALL R/R or AML, and willing to consent, in case ICF waiver is not approved by the ethics committee. Patients will also be recruited from a heterogeneous reservoir of study sites. Finally, where applicable, minimal de-identified information, including the reason for nonparticipation, will be collected for patients who are not enrolled in the study to assess whether there may be any systematic differences between participants and non-participants.

Measurement bias: inaccurate assessment of study variables can occur in observational research. The present study will seek to limit measurement bias by instructing investigators to conduct their patient care in the customary fashion and that observations will be made in a nonintrusive manner that will focus on medical records and not infringe on Latin American healthcare provider's and patient interactions.

Bias due to Missing Data or Study Variables: reference is made to Section 9.9 regarding strategies for handling missing data. Briefly, the impact of missing data on the analysis will be evaluated, and appropriate measures will be taken to address the missing information if any bias is likely.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code.

The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

This research presents no more than minimal risk of harm to patients and involves no physical procedures with patients, therefore, a waiver of informed consent will be requested as only retrospective collection of anonymized, non-personally identifiable data will be performed. Alternatively, patients will be informed accordingly, and will be asked to give their consent on data handling procedures in accordance with national regulations in place in each of the countries included in the study.

All data will be extracted from patient´s medical chart and entered into an electronic CRF specifically designed to capture relevant information in accordance with the study outcomes. Prior to the enrollment of any patient, the study must be evaluated by the local independent ethics committees (IEC) and/or institutional review board (IRB) and a formal approval must be provided.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. opies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2016; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891.

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp.

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/.

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/.

- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml.

- The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies http://www.encepp.eu/code_of_conduct/.

- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf.

- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf.

- FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

To ensure the quality and integrity of research, this study will be conducted under the guidelines good pharmacoepidemiology practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the Case report form (CRF) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness”, “Study Drug”, and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

This study aims to achieve quality results to be published in abstracts/posters at national and international scientific congresses and/or peer reviewed journals. The authors of all publications resulting from this study will be determined in accordance with the requirements of the International Committee of Medical Journal Editors (ICMJE), which states:

- Authorship should be based on: (1) substantial contributions to the design and design of the study, data collection, or analysis and interpretation of data, (2) critical writing or review of its content, (3) final approval of the version to be (4) agree to be responsible for all aspects of the work to ensure that issues related to the accuracy or completeness of any part of the work are properly investigated and resolved. Authors must comply with conditions 1, 2, 3 and 4. All authors should be identified in accordance with ICMJE criterion 1 with the expectation that they will provide input on the publication to meet criteria 2-4. Criteria 1 stipulates that a substantial contribution prior to the publication is required."

- When the research is conducted in multiple centers, the group should identify individuals who accept direct responsibility for the manuscript. These individuals must fully comply with the authorship criteria defined above. A limit of seven authors from the seven centers with the largest number of participants will be invited as authors.

- Obtaining funding, data collection or general supervision of the research group does not justify the authorship;

- All persons designated as authors must be qualified for authorship, and all qualified persons should be listed;

- Each author must have reasonably participated in the research in order to assume public responsibility for appropriate parts of the content.

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14. LIST OF TABLES

None.

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

None.

ANNEX 3. ADDITIONAL INFORMATION

Appendix 1. WHO Classification of Myeloid Neoplasms and Acute Leukemia[72]

WHO myeloid neoplasm and acute leukemia classification
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with t(15;17)(q22;q21)/ *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS

WHO myeloid neoplasm and acute leukemia classification
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21

Appendix 2. 2017 ELN Risk Stratification by Genetics in AML[10]

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated *RUNX1*¶
	Mutated *ASXL1*¶
	Mutated *TP53*#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.
*Prognostic impact of a marker is treatment-dependent and may change with new therapies.
†Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT.
‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).
¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
#*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Appendix 3. Genetic Classification by Prognosis of B-cell Acute Lymphoblastic Leukemia[73]

Good Prognosis	Intermediate Prognosis	Poor Prognosis	Undetermined Prognosis
Hyperdiploid karyotypes	t(1;19); TCF3-PBX1	Hypodiploid karyotypes	t(5;14); IL3-IGH*
t(12;21);ETV6-RUNX1 (TEL-AML1)		t(9;22); BCR-ABL	
		Philadelphia-like ALL	
		11q23 MLL rearrangements	

* t(5;14);IL3-IGH is a World Health Organization classified acute leukemia and prognosis data has not been determined.

Appendix 4. Response to Therapy will be Classified According to the International Working Group (IWG) Criteria 2003[69]

Response Criterion	Neutrophils (microL)	Platelets (microL)	Bone Marrow Blasts (%)	Other
Early treatment	NA	NA	<5	
Morphologic leukemia-free state	NA	NA	<5	Flow cytometry EMD
Morphologic CR	>1,000	>100,000	<5	Transfusion EMD
Cytogenetic CR	>1,000	>100,000	<5	Cytogenics - normal, EMD
Molecular CR	>1,000	>100,000	<5	Molecular - negative, EMD
Partial remission	>1,000	>100,000	>50 or decrease to 5-25	Blasts <5% if Auer rod positive

Abbreviations: CR, complete remission; EMD, extramedullary disease.