STUDY TITLE:

Evaluating Patient-Reported Outcomes Monitoring in Routine Care of Patients with Chronic Myeloid Leukemia for Increasing Adherence and Clinical Response to THerapY: The EMPATHY Pilot Study

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Check any **applicable** boxes in the table below – you will be asked for further detail on these topics later in the protocol form:

Indicate Vulnerable Population(s) to be Enrolled	☐ Children ☐ Cognitively Impaired Adults ☐ Pregnant Women (IF the research activities will affect the pregnancy or the fetus) ☐ Prisoners (or other detained/paroled individuals)
International Research (check this box if you will collect data from individuals located outside the United States)	☒
Research involving external collaborators (some research activities will be carried out by individuals not employed by Northwestern or NU affiliates)	☒
Research has U.S. Federal government funding (e.g., NIH, NSF, other federal agencies/departments)	☒

1.0 Purpose of the study:

In less than two decades, clinical outcomes of patients with chronic myeloid leukemia (CML) treated with oral tyrosine kinase inhibitors (TKIs) have dramatically improved compared to previous standard chemotherapies. Life expectancy of these patients now approaches that of the general population. However, therapy is now lifelong and patients are required to take medication daily and typically experience multiple and diverse adverse effects (AEs) which persist over time and negatively affect adherence to therapy, healthcare utilization, cost, and health related quality of life (HRQoL).
Several studies have documented the problem of non-adherence to oral TKI therapies in CML, clearly documenting that symptomatic AEs are the most frequent cause of treatment non-adherence. This has major clinical implications, as empirical evidence demonstrates that full exposure to TKI treatment schedule, is necessary to maximize response to therapy. Systematic collection of Patient-Reported Outcomes (PRO) in routine practice in other cancer conditions has shown several advantages, including the enhancing of treatment tolerability and resulting adherence. A key question that remains unanswered is whether systematic collection of relevant PRO information in routine CML care will result in improved adherence to TKI therapy and associated treatment effectiveness, including improved HRQoL.

We propose to assemble a network of treatment sites across the US (Northwestern University and Augusta University) and Italy (Italian Group for Adult Hematologic Disease, "GIMEMA"), with the goal of developing and piloting a tailored monitoring intervention targeting symptomatic, patient-reported AEs in CML patients undergoing first-line TKI therapy. The tailored monitoring intervention will draw primarily from the PRO-CTCAE Item Library, with additional items drawn from the FACIT and EORTC Item libraries as necessary. In all cases, items will be selected based on two criteria: 1) a side effect observed (any grade) in >10% of patients based on clinical trial reports of monotherapy administration; and 2) available in approved and certified English and Italian versions. After identifying the full set of AEs to be monitored, we will load the patient assessment and report program into tablets for electronic administration in the busy clinic setting. We will then pilot a six-month intervention aimed to monitor and manage emerging AEs, coupled with assessment of intervention feasibility, patient acceptability and satisfaction, provider acceptability and clinical management utility, adherence to TKI therapy, and HRQoL.

We expect that adherence to therapy, clinical response, and HRQoL will be enhanced by such an intervention. However, before testing this in a large international randomized controlled trial (RCT), we propose to demonstrate the intervention's feasibility and acceptability across three treatment organizations spanning the US and Italy. We anticipate that systematic monitoring of PRO in CML routine care is broadly acceptable to patients and physicians, practically feasible and capable to facilitate clinical management. Our proposed plan will investigate preliminary evidence of the efficacy of systematic monitoring of patient-reported symptomatic AEs in CML practice, in terms of self-reported adherence and pill count, HRQoL (including fatigue), and clinical response to therapy. Most importantly, this proposed study will demonstrate the ability of this

network to work together on a common project in order to best inform the development of a large international RCT.

Our specific aims for this intervention development and feasibility pilot study are:

1) To develop an online platform for systematic monitoring of patient-reported AE assessment that is tailored to the unique demands of TKI therapy for CML.

2) To assess patient and physician acceptability and satisfaction with use of this platform in CML routine practice and evaluate its value in improving symptom management, HRQoL, adherence to therapy as well as preliminary efficacy.

We hypothesize that systematic collection of PROs in routine practice of CML patients will enhance patient-physician communication, enabling physicians to more promptly adopt strategies to reduce dose, address side effects, or switch to another TKI, before treatment becomes 'too burdensome'. Ultimately, we expect this approach will positively influence treatment outcomes. In this pilot study, we will also explore clinical responses as secondary outcomes according to predefined international criteria.

2.0 Background / Literature Review / Rationale for the study:

CML is a hematopoietic disorder characterized by the malignant expansion of bone marrow stem cells, with the presence of a reciprocal translocation between chromosomes 9 and 22 resulting in the fusion gene, BCR-ABL a constitutively activated tyrosine kinase, which is present in virtually all patients with CML[1]. This knowledge led the development of a number of orally active small molecule TKIs that inhibits BCR-ABL kinase activity[2-4]. Since the introduction of TKIs, clinical outcomes of patients with CML have dramatically improved compared to previous interferon (IFN)-based standard chemotherapies[2]. Indeed, life expectancy of these patients now approaches that of the general population[5].

Although TKIs have revolutionized CML therapy, patients are required to take medication daily since therapy is lifelong, and TKIs produce unpleasant, often chronic side effects that must be managed in routine care. Considering the chronic nature of TKI administration and the fact that patients are to be on treatment indefinitely and assume the drug on a daily basis, even low grade AEs have been found to significantly interfere with daily functioning and negatively affect HRQoL[6-8].

Remarkably, empirical data in CML research indicates that AEs are the most frequent cause for non-adherence to TKI therapy[9]. There is convincing evidence that full adherence to TKIs therapy is a critical factor to obtain and maintain an optimal response to therapy[10,11]. Importantly, it has also been found that early response to therapy (i.e., at 3-month assessment from start of therapy) is the most important factor in predicting long-term outcomes[10]. Therefore, there is urgent need to develop effective strategies that may

facilitate medication-taking behaviors (possibly from the very beginning of therapy), to boost drug effectiveness and maximize chance to obtain optimal long-term outcomes. Despite compelling evidence of the need to improve adherence to TKI therapy in order to improve clinical outcomes in CML[10-12], intervention studies aimed at this goal are lacking[13]. Our proposed study is innovative in the following ways: 1) it will assemble a comprehensive list of symptomatic AEs relevant for the CML population under TKI therapy; 2) it will develop an online platform specifically devised to monitor patient-reported AEs in CML; 3) it may establish a new model for routine CML care that could increase treatment-free remissions (TFRs). Finally, a major innovation of this proposal is its international element, across Italy and the Unites States, allowing us a window to explore cultural variation in response to the intervention.

In this regard, another major point of innovation of our proposed research is the potential to establish a new model of routine CML care that could maximize clinical response (by increasing adherence to therapy) and eventually offer the possibility to stop lifelong TKI treatment to a greater proportion of CML patients. Also, considering, the high costs of TKI therapies, which currently impose a substantial financial burden to many CML patients and healthcare systems[14], any research effort aimed at maximizing chances to TFR, such as the one proposed in this application, may have major implications in reducing healthcare costs.

Ultimately, according to previous findings showing that an 'integrated' patient-centered approach of PRO evaluation in clinical practice is feasible and associated with a number of benefits[15-17], we plan to conduct a large international RCT to investigate whether prospective and systematic electronic PROs collection in newly diagnosed CML patients improves clinical response to therapy and long-term patient outcomes.
The intervention that will be piloted is the real-time collection of patient-reported AEs during clinical visits, with real-time feedback to treating physicians who will then have this data available, already at the time of consultation.

3.0 Inclusion and Exclusion Criteria:

Patient inclusion criteria will include:

1) Diagnosis of Philadelphia chromosome positive and/or BCR-ABL positive CML confirmed by cytogenetic and/or molecular analysis;
2) Newly diagnosed chronic phase (CP)-CML patients planned to receive one of the three TKI approved as first line treatment (i.e., imatinib, dasatinib or nilotinib);
3) Adult patients (≥18 years) at the time of study entry; Children under the age of 18 will be excluded from the study. The exclusion of children is justified by the following circumstances: a) The condition is relatively rare in children, as compared to adults; b) Issues of study preclude direct applicability of hypotheses and/or interventions to both adults and children.
4) Written informed consent.
5) Written informed consent from patient's physician as a participant.

5) Newly diagnosed chronic phase (CP)-CML patients who are within 4 weeks of first line TKI therapy (any of the three TKI approved in the USA and Europe, that is: imatinib, dasatinib or nilotinib).
6) Ability to read/converse in English (Northwestern University and Augusta University sites). Ability to read/converse in Italian (GIMEMA site).

Patient exclusion criteria will include:
1) Major cognitive deficits or psychiatric problems hampering a self-reported evaluation;
2) Having received any CML treatment prior to therapy with imatinib, dasatinib or nilotinib for more than three months.

This project will focus on CML, which affect both men and women. Therefore, there are no exclusion/inclusion criteria based on sex/gender. In addition, there are no exclusion/inclusion criteria based on race and ethnicity.

Physician inclusion criteria will include:
1) Provider of clinical care for patient who meets inclusion criteria for the study

Please note that physician consent is requisite for the patient to be enrolled as a participant in the study.

4.0 Sample Size:

Sample size is based on the available resources for conducting this study. We define the adherence rate (AR) as the overall proportion of pills taken out of those prescribed, from baseline to six months, averaged over the number of pill-count assessments. Based on adherence rates reported by previous works[10,18], we defined 72% as a minimum threshold of AR (H0). In order to detect at least 85% of AR (H1), with power of 80% and 2.5% type I error probability (one sided exact test for binomial proportions), we will need 84 patients. However, considering overall 11% of attrition rate, 94 patients are actually required.

5.0 Recruitment and Screening Methods:

Each study site will follow the same recruitment and screening methods.

Study staff at each site will have IRB/HIPAA compliant approval to access electronic medical records (EMR) systems and will be able to pre-screen patient medical records prior to the patient visits. Once a patient is identified as potentially eligible based on the EMR pre-screen, research staff will discuss the case with the attending physician and medical staff and obtain approval prior to making contact with the patient. Data extracted from the medical records during the pre-screen will be destroyed at the earliest opportunity for patients that do not consent to participate in the research study. To ensure HIPAA compliancy, each potential participant will first be approached or contacted by his or her physician or a member of the treatment team who will explain the study.

Potentially eligible newly diagnosed patients will be consecutively invited to in the designed research location at the earliest convenience. Once the patient provides written informed consent, they will be asked in the waiting room (just before each scheduled clinical visit), to complete the newly developed touch-screen PRO-CML Survey. At the time of enrollment, the local clinical research staff member will register the participant in the CHES platform, which will generate a login ID and password enabling the participant to log in to CHES. The clinical research staff member will instruct each patient to complete self- reported questions via tablet computers. The appointed clinical research staff member will provide technical assistance to patients, if necessary, but will not be allowed to provide assistance in symptom rating. At each clinical visit, a tablet computer will be brought to participants, possibly in a private area of clinic waiting rooms to complete the survey. The clinical research staff member will bring the participant's CHES log-in information up on the tablet, enabling the participant to log in and complete the survey.

For physician participants, once a patient is identified as potentially eligible based on the EMR pre-screen, research staff will discuss the case with the attending physician and medical staff and obtain approval prior to making contact with the patient. Each potential physician participant will be approached by a member of the research team who will explain the study and obtain written informed consent. Potentially eligible newly physician participants will be consecutively invited to participate at the earliest convenience.

Inclusion of women

This project will focus on Chronic Myeloid Leukemia, which affects both men and women. There are no exclusion/inclusion criteria based on sex/gender. Therefore, 50% of the sample will be women and 50% of the sample will be men approximately. In the event that we have over-representation of either men or women, we will over-recruit to have a roughly equal distribution of men and women.

Inclusion of minorities

Subject recruitment will be performed by the Northwestern Medical Group, the GIMEMA Research Network and Augusta University. There are no exclusion/inclusion criteria based on race and ethnicity. Patient population will reflect the diversity of the general population of the recruiting centers. Concerning the U.S. population, we will enroll a sample that is representative of the U.S. population. Approximately 17% of the US population identifies as Hispanic/Latino, 13% identifies as Black or African American, and 5% identifies as Asian. Therefore, we will enroll a minimum of 15% of participants who identify as Hispanic/Latina (8% women, 7% men) and another 15% (8% women, 7% men) who identify as Black/African American and another 4% will identify as Asian. We will monitor recruitment on a weekly basis to ensure that our sample is representative of the US population. In the event that our sample is not representative, we will work with the Northwestern Medicine enterprise data

warehouse to identify racial/ethnic minority patients and over-recruit minorities to ensure their representation in our sample.

6.0 Research Locations:

1. Northwestern University

Robert H. Lurie Comprehensive Cancer Center Comprehensive Cancer Center (RHLCCC)
The Robert H. Lurie Comprehensive Cancer Center of Northwestern University provides state-of-the art therapies and comprehensive cancer care to patients in two modern outpatient clinical cancer center locations. The outpatient Clinical Cancer Center in Northwestern's Galter Pavilion offers leading-edge medical, surgical and radiation oncology treatment options, as well as access to specialized research, clinical trials and diagnostic services. Both locations are supported by on-site pharmacy and lab services, as well as a comprehensive nutrition and Supportive Oncology Program. All Lurie Cancer Center physicians are full-time faculty of Northwestern University's Feinberg School of Medicine, applying the knowledge and experience gained from clinical research and education to their practices at Northwestern Memorial Hospital. 9 We also have several connections with clinical, research, and administrative staff at the Robert H. Lurie Comprehensive Cancer Center. All these medical facilities have well integrated electronic medical record systems that will facilitate identification and recruitment of potential participants consistent with IRB and HIPAA guidelines. Drs. Cella, Yanez and Penedo will work close with the oncology clinics following similar procedures for current studies to facilitate access and recruitment of participants meeting study criteria.

Clinical Research Resources Available to the Study Team: Access to study population. We have several connections with clinical, research, and administrative staff at the Robert H. Lurie Comprehensive Cancer Center. All these medical facilities have well integrated electronic medical record systems that will facilitate identification and recruitment of potential participants consistent with IRB and HIPAA guidelines.

2. The GIMEMA Foundation (Italian Group for Adult Hematologic Diseases)
The GIMEMA (Italian Group for Adult Hematologic Diseases) is a non-profit research Cooperative Group, with a long-standing history of clinical research in haematology. It consists of a well established network of about 150 haematology centers throughout Italy (including both Community and University-based Hospitals) plus a Data Centre (located in Rome). The GIMEMA Data Center is in charge of centralizing data collection of any GIMEMA sponsored study and is also responsible, for quality assurance, management and statistical analysis in accordance with the highest methodological and regulatory standards. The GIMEMA Data Center operates according to the highest quality and transparent international standards of clinical research, so as certified by quality procedures of the European Clinical Research Infrastructure Network (ECRIN) (http://www.ecrin.org/en/). The scientific leadership of the GIMEMA is composed by

nine GIMEMA Research Working Parties (WPs), each of which is focused on a specific hematologic disease area. In addition there is also the GIMEMA Quality of Life (QoL) Working Party whose mission is to foster Patient-Reported Outcomes (PRO) studies in hematologic disease and provide assistance in the design and the conduct of any GIMEMA trial including a PRO component. The large and well established research network of centers affiliated to the GIMEMA is an asset for the successful conduct clinical research in patients with hematologic disease by ensuring rapid enrolment of patients into clinical trials. GIMEMA has been conducting clinical trials at an international level in collaboration with major clinical trial Groups including a long-standing collaboration with the European Organization for Research and Treatment on Cancer (EORTC).

GIMEMA Quality of Life (QoL) Working Party
The GIMEMA Working Party Quality of Life (WPQoL) was set up in 2010. The mission of the WPQoL is to coordinate all GIMEMA studies including a PRO component. The GIMEMA WPQoL consists of the Advisory Board composed by five international QoL specialists, plus a number of persons with various professional backgrounds, including physicians, statisticians and administrative staff members. The GIMEMA WPQoL data centre has specific expertise in the design, collection and analysis of patient-reported outcomes (PROs) and QoL data.

GIMEMA Research Network. The GIMEMA Medical Group is currently involved in about 30 clinical trials, and include about 150 hematology centers throughout Italy. Hospital staff is composed by highly professional medical doctors and healthcare providers, who guarantee a collaborative network operating across the country to assist the patient during the disease path.

3. Augusta University
The Division of Hematology/Medical Oncology at the Medical College of Georgia at Augusta University strives to excel in the care of patients with cancer and blood disorders with a focus on treatment, education, and research advancement. The division has witnessed continued growth, both in the inpatient and outpatient settings. The Hematology/Medical Oncology division provides services to the CSRA community through several comprehensive programs.

All required permissions and/or approvals are already obtained or will be obtained at each research location prior to project implementation.

Procedures for coordination of study activities
Both PIs will provide scientific and administrative oversight for all proposed activities and scientific aims in this application including program development, procedures for participant recruitment and assessment, data coordination and data flow to NU. They will also oversee and direct integrated scientific activities across the three performance sites (e.g., standardization of study protocol, coordination of multi-site staff training and

research meetings). They will also be responsible for ensuring that systems are in place to guarantee institutional compliance with US laws, EU laws, DHHS and NIH policies and regulations including protection of human subjects, data concerns and facilities.

Dr. Cella will serve as contact PI and in that role, serve as the primary contact person in correspondence with NCI. He will assume responsibility for maintaining communication with the NIH and submission of annual reports, after obtaining input of Dr. Efficace. Dr. Efficace will serve as scientific project director surrounding the development of the intervention and its associated clinical report. He will also be responsible for training implementation and supervision of psychosocial assessment and intervention procedures, assuring standardization across sites and coordination of data transfer to NU. Cella and Efficace together will be responsible for recruitment and will finalize outcome measures and ensure quality data collection, as complete as possible. Both PIs will collaboratively share responsibility for local standardization of intervention procedures (Cella in US and Efficace in Italy), and coordination/standardization of all other scientific activities across sites. PIs Cella and Efficace will work together to discuss any changes in the direction of the proposed research and the redirection of funds, if necessary. A publication policy will be established based on the relative scientific contributions of the PIs and other key personnel.

Procedures for data collection and safeguard

The sources of research material obtained from participants will be the participants themselves in the form of medical history and patient-reported data. Participants will furnish demographic and psychosocial information and patient-reported outcomes. We will also collect medical treatment and disease characteristics (e.g., type of treatment, time since diagnosis, etc.). Medical treatment and disease characteristic information will be collected via chart review by our research team under procedures established in prior work. All material will be obtained exclusively for research purposes and in full IRB and HIPAA compliance. All sources of information will be coded using a special participant number, which precludes it being matched with identifying information. Because all our participants will be individuals treated for CML, the issues surrounding confidentiality are of supreme importance. The participants will sign a statement attesting to their understanding that the information they provide will be held as personal and confidential to the extent permitted by law. Access to the computer data files will be by password codes. The list matching participant number to identifying information will be maintained in a locked drawer in the office of the PI. Additionally, in order to be able to track participants across the longitudinal period of the project, we will keep a separate record of each participant's address, telephone number and contact person information. This record will indicate whether or not a participant has completed an assessment but will not include information concerning their assessment or intervention performance. Participants will be made explicitly aware at the time of the informed consent of the nature of the two separate records that will be kept.

Patient assessment and report program will be loaded into tablets for electronic administration in the clinic setting. The **CHES** platform enables this administration with an already existing web-based software. Therefore, the **CHES** web-based platform, will

be used by all participating sites in order to ensure standardization of PRO assessment and outcomes interpretation. At each site, a clinical research staff (CRS) member will be appointed to undergo a standardized 20/30 minute, web-enabled teleconference before initiation of enrollment to learn how to use the secure online platform system. Treating physicians also will be trained to use the web-based platform and interpret graphical display of outcomes. Participating sites will be assessed for wireless internet connectivity in clinic waiting areas and also wireless tablet computers will be provided to sites if needed.

Northwestern Memorial Hospital has an electronic medical records (EMR) management system that will be accessed by our staff consistent with IRB/HIPAA guidelines as we have in our prior studies. Procedures across all recruitment sites follow similar approaches and our approach encompasses a highly integrated recruitment relationship between the medical professionals at each location and our research staff. All medical facilities have well integrated electronic medical record systems that will facilitate identification and recruitment of potential participants consistent with IRB and HIPAA guidelines. All psychosocial data, participant tracking and flow, and intervention data will be collected via **CHES** (for further details: Provisions to Protect the Privacy and Confidentiality of Participants and the Research Data).

GIMEMA Data Center has well integrated electronic medical record systems that will facilitate identification and recruitment of potential participants consistent with IRB and HIPAA guidelines. In addition, the GIMEMA WPQoL has a specific server (QoL server), located at the WPQoL's office. The server provide web services, database services, file storage, and print services. Server management is allowed only to specific IT personnel, while network access is limited to the GIMEMA WPQoL data center staff, and each authorized person has his unique ID and password. GIMEMA WPQoL has its own internal Information Technology group that manages all hardware, software, and support needs also for the GIMEMA WPQoL. Computers use either Windows or MacOS operating system and run individual firewalls and antivirus.
All sites involved in this study by GIMEMA have well integrated electronic medical record systems that will facilitate identification and recruitment of potential participants consistent with IRB and HIPAA guidelines.

Drs. Efficace, Cella, Yanez, Penedo and Kota will work close with the oncology clinics following similar procedures for current studies to facilitate access and recruitment of patients meeting study criteria.

We confirm that all non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

7.0 Multi-site Research (research that involves external collaborating institutions and individuals):

Drs. Cella and Efficace are the two Study PIs. In addition to their role as Study PIs, they each serve as the Site PI at Northwetsern University and GIMEMA, respectively. Dr. Kota is not a Study PI, but serves as the Site PI at Augusta University. He will not be involved in overall study oversight beyond recruitment and data collection at Augusta University.

1) Northwestern University (Site PI: Cella)
   Role: recruitment, consent, study-related procedures (described in greater detail in section 9.0), patient-reported outcome data collection via CHES, medical record (identifiable) data collection, de-identified data analysis and interpretation

2) GIMEMA foundation research network (Site PI: Efficace)
   Role: recruitment, consent, study-related procedures (described in greater detail in section 9.0), patient-reported outcome data collection via CHES, medical record data (identifiable) collection, de-identified data analysis and interpretation

3) Augusta University (Site PI: Kota)
   Role: recruitment, consent, study-related procedures (described in greater detail in section 9.0), patient-reported outcome data collection via CHES, medical record data (identifiable) collection

Reliance Agreement: We propose that Northwestern University will serve as the IRB of record for the Augusta University site. An IRB Authorization Agreement will be completed and uploaded to the application prior to the implementation of any study activities at Augusta University. The fully completed and signed IAA will be uploaded as a modification to this submission upon its arrival and following the initial approval of the submission.

A reliance agreement is not needed for the GIMEMA site because they will be obtaining IRB approval externally at their site. Upon approval from GIMEMA's IRB, the approval letter will be uploaded to this submission as a separate modification.

8.0 International Research (where data collection will occur outside the United States and U.S. territories)

The study includes one international site, GIMEMA Foundation, located in Italy. Although Dr. Efficace has an adjunct appointment at Northwestern University, for the purpose of this study, he will be serving as the site PI at GIMEMA (his primary affiliation), not in his capacity as adjunct faculty at NU.

The GIMEMA site will be obtaining IRB approval externally at their site. Upon approval from GIMEMA's IRB, the approval letter will be uploaded to this submission as a separate modification.

Dr. Efficace has a strong track record in conducting patient-reported outcome data in Italy. We do not anticipate any cultural or literacy barriers to eligible participants at the GIMEMA site.

All study procedures will comply with the European Union General Data Protection Regulations.

9.0 Procedures Involved:

Aim 1. To develop an online platform for systematic monitoring of patient-reported AE assessment that is tailored to the unique demands of TKI therapy for CML.

We propose to assemble a network of treatment sites across the US (Northwestern University and Augusta University) and Italy (Italian Group for Adult Hematologic Disease, "GIMEMA"), with the goal of developing and piloting a tailored monitoring intervention targeting side effects (i.e., patient-reported AEs) in CML patients undergoing first-line TKI therapy. The tailored monitoring intervention will draw primarily from the well-established PRO-CTCAE Item Library[19], with additional CML-specific items drawn from the FACIT[20] and EORTC item[21] libraries as necessary. While we expect that the majority of selected symptoms will be drawn from the PRO-CTCAE Item Library, we anticipate this might not include specific TKI side-effects. Therefore, a comprehensive list of items for CML patients has to be also drawn from other available sources (FACIT and EORTC). Items to be implemented will be selected based on two criteria: 1) a side effect observed (any grade) in >10% of patients based on clinical trial reports of monotherapy administration; and 2) available in approved and certified English, and Italian versions. At this stage, the main goal will be that of identifying a parsimonious set of items so as to reduce patient burden as much as possible. We will aim for a list not including more than 20 items so as to make this assessment feasible in a busy clinical practice. After having identified this set of relevant AEs items to be monitored (i.e., PRO-CML Survey), we will load the patient assessment and report program into tablets for electronic administration in the clinic setting. CHES enables this administration with an already existing web-based software. Therefore, a common web-based platform, housed at NU, will be used by all participating sites in order to ensure standardization of PRO assessment and outcomes interpretation. At each site, a clinical research staff (CRS) member will be appointed to undergo a standardized 20/30 minute, web-enabled teleconference before initiation of enrollment to learn how to use the secure online platform system. Treating physicians also will be trained to use the web-based platform and interpret graphical display of outcomes. Participating sites will be assessed for wireless internet connectivity in clinic waiting areas and also wireless tablet computers will be provided to sites if needed. Aim 1 does not involve any participant procedures.

Aim 2. To assess patient and physician acceptability and satisfaction with use of this platform in CML routine practice and evaluate its value in improving symptom management, HRQoL, adherence to therapy as well as preliminary efficacy.

If a patient is eligible and would like to participate, the consent procedures will be conducted and patients will be asked in the waiting room (just before the scheduled clinical visit), to complete the newly developed touch-screen PRO-CML Survey. Reasons for refusal to participate will be systematically tracked. At the time of enrollment, the local clinical research staff member will register the participant in CHES platform, which will generate a login ID and password enabling the participant to log in to CHES. The clinical research staff member will instruct each patient to complete self- reported questions via tablet computers. The appointed clinical research staff member will provide technical assistance to patients, if necessary, but will not be allowed to provide assistance in symptom rating. At each clinical visit, a tablet computer will be brought to participants, possibly in a private area of clinic waiting rooms to complete the survey. The clinical research staff member will bring the participant's CHES log-in information up on the tablet, enabling the participant to log in and complete the survey. PRO—CML Survey results will be feed-backed in real time to physicians who will have this data available (in a graphical format to ease interpretation) at the time of consultation on their computers. (No results related to adherence will be communicated to physicians). Similarly, to previous studies[22], symptoms will be graded on a five-point scale from 0 (not present) to 4 (severe). At subsequent clinic visits, patients will be reminded by a staff member of the opportunity to log in the system, but such logins will not be mandatory. Similarly, to previous studies[22] whether to and how to incorporate a discussion of PRO-CML Survey results into routine visits will be left to patient and their treating physician discretion. In addition, patients will be given a remote access option, enabling completion of the Survey at their convenience, between scheduled clinic visits at home. A clinical research staff member will provide participants with an envelope containing a piece of paper that includes the link to the study on CHES, as well as their log-in information. For home log-in session between visits, there will be no automatic reminders to patients. However, the web-system will be programmed to trigger e-mail alerts to a designated member of the clinical staff, whenever a patient-reported symptom will worsen by >1 point; or will reach an absolute grade of 3. A report tracking participants' PRO-CML Survey symptoms will be printed at each clinic visit for the treating physician. No specific guidance will be provided to physicians about what actions to take in response to alerts or printed symptom profiles[22]. We intend to provide this intervention for the first six months of treatment, typically covering 8-10 clinical encounters. We anticipate that participants will complete 8-10 surveys, which will take approximately 5-10 minutes to complete. The time to complete the surveys may vary since certain surveys will only be administered at certain time points. These surveys will be administered via tablet devices using CHES web-based platform.

Our proposed plan will investigate preliminary evidence of the efficacy of systematic monitoring of patient-reported symptomatic AEs in CML practice, in terms of self-reported adherence and pill count, HRQoL (including fatigue), and clinical response to therapy. Most importantly, this proposed study will demonstrate the ability of this

network to work together on a common project in order to best inform the development of a large international RCT.

Primary Outcome Measures

Adherence to therapy will be evaluated in two ways. These two measures are based on previously published recommendations[23], and on empirical evidence in CML indicating that pill count is associated with clinical response to TKI therapy[11].

Pill Count Adherence to therapy (PCA): Pill count will be based on data from the pharmacy database and computed, for each patient and scheduled treatment period, as the following proportion: (number of pills delivered at T_j – number of pills returned at T_{j+1})x100, divided by number of pills delivered at T_j [24]. We will assess pill count from baseline to six months, averaged for each patient over the number of pill-count assessments. This data will be obtained from specialty oncology pharmacies in the treating clinics of the participating sites. We do not anticipate the need to obtain pill count data from entities other than the participating sites; however, should this need arise, we will obtain HIPAA authorization from these entities prior to any data collection outside of the three participating sites.

Self-reported adherence to therapy: The Adherence to Refills and Medications Scale (ARMS) will be used to evaluate self-reported adherence[25]. ARMS will be assessed via CHES -10 at 3 and 6 months, with reassurance that treating physicians will not have access to results.

Secondary Outcome measures

Health Related Quality of life (HRQoL): The Functional Assessment of Cancer Therapy-General (FACT-G) (version 4)[26] will assess HRQoL. The FACT-G has four subscales: physical well-being, social / family well-being, emotional well-being, and functional well-being, with higher scores indicating better outcomes. Score range is 0-108). Selection of this questionnaire is based on its extensive use in clinical trials, and evidence indicating its sensitivity to improvement when using PRO in clinical practice[16]. This outcome will be evaluated at: baseline and at 3 and 6 months.

Fatigue: Fatigue, a component of HRQoL, has been chosen as one of the key patient outcome measure in this study, given previous data indicating this is a main concern for CML patients receiving TKIs[6,27]. Fatigue will be evaluated with the PROMIS Fatigue SF13a[28]. This outcome will be evaluated at: baseline and at 3 and 6 months.

Feasibility: Based on similar feasibility studies[29] feasibility is considered to be demonstrated if 80% of participants complete online questionnaires on more than 60% of follow-up visits (i.e., after initial visit up to six months) including the total number of visits across the six months of follow up (typically 8-10 visits). Reasons for missing PRO collection at follow-up visits will be recorded. This outcome will be evaluated at: 3 and 6 months.

Patient acceptability and satisfaction: An intervention-tailored questionnaire will be developed and administered using items adapted from available sources, with guidance provided by those that have been used successfully in similar research to assess patient acceptability and satisfaction[29]. This outcome will be evaluated at: 3 and 6 months.

Physician acceptability and clinical management: After seeing each patient, physicians will be asked to take note (by completing a brief paper checklist) the clinical usefulness of the collected PRO information for the individual encounter. They will then be asked to summarize this information in a more structured ad hoc paper questionnaire reporting whether they found the PRO data valuable towards accuracy of AEs documentation, clinical decisions, or discussions with patients. This outcome will be evaluated at: 3 and 6 months.

Clinical response to therapy: During the first year, both European[30] and US NCCN Guidelines[31], recommend evaluation-time benchmarks (i.e., at baseline, and at 3, 6 and 12 months) for establishing treatment efficacy. On this basis, we plan to assess TKI responses at 3 and 6 months in accordance with follow-up planned for this study. Specifically, this will be examined in two ways: 1) by inspecting the proportion of patients achieving treatment milestones, as defined by international guidelines[30,31]; 2) by examining time to achieve treatment response.

Data analysis plan

Primary analysis

Based on H0 and H1, power and Type I error (α=0.025) as specified in the section "Sample size", we define the intervention achieving an *optimal adherence rate* if at least 82% of patients (n=69/84) will take at least 90% of prescribed drug (Marin D, Bazeos A, Mahon FX, et al. J Clin Oncol. May 10 2010). We define adherence as *acceptable* if at least 72% of patients (n=61/84) take at least 90% of prescribed drug. Thus, we will consider 82% and 72% as thresholds defining respectively *optimal* and *acceptable* adherence rates based on the actual number of enrolled patients. Proportions of TKI responses at three and at six months and time to achieve treatment milestones will be reported. We will estimate HRQoL and fatigue outcomes trajectories over time by a repeated measure linear mixed model, assessing possible changes from baseline by an overall F-test testing the null hypothesis of no difference. Reasons for missing PRO collection at follow-up visits will be collected as well. Based on similar studies (Basch E, Iasonos A, Barz A, et al. J Clin Oncol. Dec 01 2007; 25(34):5374-5380) the intervention will be considered feasible if at least 80% of participants complete online questionnaires at more than 60% of follow-up visits (i.e., after initial visit up to six months). We will describe all outcomes regarding feasibility, patient and physician acceptability by absolute frequencies and proportions. In addition, we will use the generalized linear mixed model (GLMM) to investigate about possible determinants of single relevant aspects (items) of acceptability, both for patients and physicians. Using the same GLMM approach, we will estimate the impact of the initial TKI on the adherence rate, accounting

for the different subject-specific number of pill count assessments over time and for the within-subject correlation of measurements. Successful management of emergent adverse events caused by the initial TKI does include the option of switching to a different TKI and we will not consider this as adherence failure. That is, we will measure adherence primarily as the composite use of all TKI agents. However, we will investigate the impact of these changes on the outcomes of interest via sensitivity analyses. We will assess the potential impact of initial TKI on different outcomes including this information as a covariate in all corresponding analyses. Unless not differently specified above, all the statistical tests will be two-sided with statistical significance set as $p<0.05$.

10.0 Research with Vulnerable Populations

Not applicable.

11.0 Incomplete Disclosure or Deception:

Not applicable.

12.0 Consent Process:

Potentially eligible newly diagnosed patients will be consecutively invited to participate in the study by a member of the medical team (e.g., physician, advanced providers, patient navigators) at the earliest convenience (in any case, after local ethics approval). The member of the medical team will inform patients about the study, handing or mailing a recruitment study brochure and query whether the patient would like to learn more about participating. When a patient expresses interest, before compilation of informed consent, all the information about the study will be explained in a non- technical fashion to patients, and they will have ample time to ask any questions to the investigator or to the study staff. Furthermore, patients will be asked if they have any specific questions or concerns about the study and they will be informed about every precaution that must to be taken in order to protect the privacy of patients and the confidentiality of their personal information. Patients younger than eighteen years old and/or having major cognitive deficits or psychiatric problems hampering a self-reported evaluation and the compilation of informed consent will be not enrolled in the study. At the time of recruitment, the study research assistant (RA) will obtain participants' informed consent and HIPAA authorization according to IRB approved procedures. Potential subjects wishing to participate will be asked to read the consent and HIPAA forms in their entirety and will be given time to discuss the study and ask questions prior to signing. Patients wanting additional time may take consents home to review.

Because all our participants will be individuals treated for CML, the issues surrounding confidentiality are of supreme importance. The participants will sign a statement attesting to their understanding that the information they provide will be held as personal and confidential to the extent permitted by law.

For patients recruited at the GIMEMA site, all consent procedures and forms will be in Italian.

Process to Document Consent:
The study RA will obtain participants' informed consent and HIPAA authorization in writing. The informed consent document will be stored by the study RC in locked enclosures. It is accessible only by staff on the study team.

13.0 Research with Children – Parental Permission, Child Assent, and Other Considerations:

Not applicable.

14.0 Waiver of Participant Signature on Consent Form:

Not applicable.

15.0 Waivers and Alterations of Consent Information:

Not applicable.

16.0 Financial Compensation:

This study involves minimal risk to study participants, thus financial compensation for research related injury is not applicable.

17.0 Audio/Video Recording/Photography

Not applicable.

18.0 Potential Benefits of this Research:

The specific objectives of the proposal aim to monitor intentional and non-intentional reasons for not be adherent to therapy in CML patients during standard care, in order to more promptly adopt strategies aiming to enhance patient-medication-taking behavior and so improving response to therapy. This study will contribute to establishing the feasibility of an intervention program to improve the management of adverse events (AEs) among individuals diagnosed with CML. Constant physician monitoring of AEs, should enhance communication with patients and induce a more promptly adopt strategies to lessen side effects, or to switch to another tyrosine kinase inhibitors (TKIs),

before treatment becomes 'too burdensome'. Therefore, participants could have direct benefits from the study intervention. Once clinical efficacy is established in a future RCT, findings will increase the likelihood that web-based interventions can be used to improve the clinical management of CML patients taking TKIs. As risks are relatively low and easily managed, and because benefits for participants are potentially substantial, the balance of risks-to-benefits are reasonable.

19.0 Risks to Participants:

Participants will incur no appreciable physical risks through participation in this study, though they may undergo psychological discomfort at some time points. During participation in our study, participants will be given CML-related information, as well as be asked to complete assessments of sensitive topics that may lead some to experience transient and mild anxiety. In addition, some participants are likely to manifest signs of severe symptom burden and in some rare cases, disease progression, throughout the follow-up component of the study. These participants are likely to experience affective distress. There is a slight risk of loss of confidentiality. While communications being sent to and from the Website are protected, there is some possibility that others may see the participant's open the website. The main intervention risk is that patients occasionally try to access the website or participate in assessments while walking or driving using a tablet or Smartphone.

Participants will be informed during the consenting process and throughout the study that they can stop at any time, that they do not have to answer any questions that may make them uncomfortable, and that they can withdraw their participation at any time if they so choose. They will be instructed to promptly contact David Cella (at Northwestern University), Vamsi Kota (at Augusta University), Fabio Efficace (for GIMEMA foundation research network) and study staff of each site (staff will be determined later) with their questions and concerns. Every measure will be taken to ensure the safety of research participants throughout the duration of their study participation.

Participants will be informed during the consenting process and throughout the study that they can abstain from any question that is too uncomfortable or too difficult for them, and that they can withdraw their participation at any time if they so choose. Participants will be informed during the consenting process of what they can do if they should have questions or concerns during study participation. They will be instructed to promptly contact David Cella (at Northwestern University), Vamsi Kota (at Augusta University), Fabio Efficace (for GIMEMA foundation research network) and study staff of each site (staff will be determined later) with their questions and concerns, or if they have any illness or injury during their time on this study. Since some of the questions in the assessment packet deal with anxiety, depression, and well being, and could be answered in ways that signal distress, the research team will promptly report signs of distress to the study investigators.

Participants may be withdrawn from the study without their consent under the following circumstances: (1) no longer meet inclusion and exclusion criteria (e.g., become

bedridden, or physical debilitation, such that study participation would not be feasible or would create undue hardship; leaves active surveillance protocol to receive definitive therapy); (2) unsuitable as group participant (e.g., verbal or physical aggression toward study team or other research participants); early termination of study by study P.I. Participants who complete the study will be sent a Thank You and Debriefing message via email or postal mail, explaining the details of the study and thanking them for their participation in the research study. They will be also given the option of receiving information on study results and publications that result from the study upon study termination.

Participants may choose to withdraw from the study at any time. The withdrawal reasons data that participants provide will be collected for study purposes.

20.0 Provisions to Protect Participant Privacy and Data Confidentiality:

All psychosocial data, participant tracking and flow, and intervention data will be collected via CHES. Medical record data will also be entered in the AC platform. AC is securely stored at the Northwestern University (NU) Research Data Center and available via the web. The data management environment meets the security requirements identified in the Agency Automated Information Systems Security Program (AISSP) Handbook. AC requires use of current passwords and log-on codes to protect sensitive AIS (Automated Information System) data from unauthorized access: All system access requires a user name and password. All users who require anything more than "internet user" security to the NU campus network must have a unique ID assigned. The NU ID is used to control access to data files and applications that reside on the network. Every NU ID is required to have a complex password assigned. Access to AC is restricted to participants by means of a username and password incorporated within the participant registration process. Restriction to AC involves maintaining an encrypted list of current users and authorizations based on permissions and roles assigned to each user. NU provides AC administrators with secure Virtual Private Network (VPN) access. Operating system and database based permissions are set by the AC administrators. User accounts have limited system resource access. The availability and flow of data is limited to the security access identified and signed off by management, and is controlled by the database administrator who pre-defines security access levels. This ensures that only data necessary for that individual's work function are viewable. All requests are validated before attempting to submit data to the database. Any internal or stored reference to a participant is accomplished through a unique identifier key. Data is stored and accessed in full compliance with institutional IRB and governmental regulations regarding privacy and security. NU has a secure data center that houses all servers. This center is limited to authorized employees via the use of a card swiping system and biometric reader on the entrance doors.

21.0 Data Monitoring Plan to Ensure the Safety of Participants:

This study involves minimal risk to study participants. Risks associated with website use and walking or driving will be managed by informing the participants that they are not permitted to use the phones while driving and very minimal use while walking or driving. The data safety and monitoring board (DSMB) will be chaired by Dr. Laurie Wakschlag (who is otherwise not associated with the project), and will include Drs. Sofia Garcia. Judith Moskowitz, and Susan Yount (also not associated with the project). The DSMB will meet annually. Occurrence of serious adverse events (e.g., hospitalization, injury, or death of a study participant) will be discussed at weekly project meetings at each site. Adverse events will be documented, logged and submitted to the NU-IRB in writing within 10 working days as mandated. The PI will review data safety quarterly, and a cumulative report will be submitted to the IRB on an annual basis as required for continuing review and/or final report. Interim study analyses for the purpose of discontinuing the study will only be conducted if during a review of adverse events it seems that risks or complications appear to be greater than those originally stated. If the PI suspects that an unusual number of adverse events is occurring, our Statistician in collaboration with Ms. Beaumont, Manager of the Quantitative Methods Core, Department of Medical Social Sciences at NU (not associated with the study), will break the condition assignment and participant identifier code and determine if the adverse events occur significantly more frequently in any one condition. The DSMB will be convened at this point (in addition to biannual meetings) to address unexpected complications. As the potential source of adverse events is likely to come from psychosocial assessment, our statistician will attempt to assess any relationship between these factors and adverse events. In the unlikely event of such analyses, the IRB will be kept informed of the results in a timely manner. Moreover, all the IRB will be notified within one working day of any temporary or permanent suspension of the study protocol.

22.0 Long-term Data and Specimen Storage and Sharing:

All data is kept in encrypted and password protected files on a locked Northwestern University network. Participant names and all other identifying information are kept in a separate, locked and protected location Data will be stored for a period of five years after the study results have been published. At this point any paper-based data will be shredded and electronic data will be deleted. Data may be released to a third party if required by law (e.g., court order). All data will be kept in encrypted and password protected files on a locked Northwestern University network. Participant names and all other identifying information are kept in separate, locked and protected locations to ensure participant identity cannot be linked to their study data.

The subcontract Institutions agree to transfer to NU Research Data Center the study database in the existing format (SAS, ASCII) and according to the applicable national law and regulations.

23.0 Qualifications of Research Team to Conduct the Research:

Key investigators on this project are Prof. David Cella (mPI) and Prof. Fabio Efficace (mPI), who have been collaborating on common projects[32,33]. Also, Prof. Efficace has a primary appointment in a National Cooperative Group in Italy (GIMEMA) which has a long-standing experience of clinical research in CML and will actively be involved in this study. Prof. Efficace also holds an appointment as, Adjunct Professor, in the Department of Medical Social Sciences (MSS) at Northwestern University (NU) lead by Prof. Cella. Other investigators from the Department of MSS with expertise in health outcomes research, include Prof. Betina Yanez and Prof. Frank J. Penedo. Other key clinical (hematologists) investigators include: Prof. Vamsi Kota, from Augusta University (USA) and Prof. Michele Baccarani, an internationally renowned CML expert (Chair of the GIMEMA CML Working Party, Italy), whom will provide invaluable clinical expertise for the successful conduct of the project.

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