BD² Breakthrough Discoveries for thriving with Bipolar Disorder

Integrated Network Site Request for Applications (RFA)

October 20, 2022

KEY DATES	
RFA Released	October 20, 2022
Prescreening Application Due	November 18, 2022
Invitation to Submit Full Proposal	December 5, 2022
Submission Deadline	February 1, 2023
Review & Presentation/Site Visit*	Feb 20 – Mar 24, 2023
Projected Award Notification Date	May 5, 2023
Project Start	June 2023

*If deemed necessary, applicants may be requested to clarify and/or present their proposal orally. BD² will notify applicants in the event such a presentation is necessary.

About BD²

BD²: Breakthrough Discoveries for thriving with Bipolar Disorder is a collective force to transform what we know about and how we treat bipolar disorder. It's a commitment to the 40 million people living with bipolar disorder, those not yet diagnosed, and their loved ones.

The Baszucki, Brin, and Dauten families united with the Milken Institute to create BD² to advance discoveries for families like theirs. For too long, there have been limited advances in the study and treatment of bipolar disorder due to lack of collaboration and funding. It's time for a new approach.

BD² is establishing a network of interdisciplinary investigators to apply in-depth phenotyping, big data analytics, and an unprecedented data ecosystem to address bipolar disorder in an innovative, equitable, and rigorous way.

About Bipolar Disorder

Bipolar disorder is a highly complex and heterogeneous disorder that is often debilitating. Even though it is prevalent in approximately 3% of individuals worldwide, and is recognized as a leading cause of disability, little is known about its biology. Advancements in our understanding and treatment of bipolar disorder to date remain far from ensuring that everyone living with it can manage their condition and lead independent, fulfilling lives.

On average, people living with bipolar disorder have a lifespan that is decreased by 8-25 years (mostly attributed to cardiovascular disease). Outcomes have failed to significantly improve over the past 20 years, and death by suicide occurs all too often. Lithium remains a standard of care for bipolar disorder, yet decades after its introduction, we still have little understanding of its mechanism of action and many clinicians are reticent to use it. A contrasting dilemma is the extensive use of antidepressants in bipolar disorder with limited evidence of their effectiveness and concern for their contributing role in mood destabilization.

While the need to improve care and outcomes for those living with bipolar disorder is widely recognized, substantial challenges have impeded progress:

- the basic etiology and pathophysiology of bipolar disorder remain elusive
- the reasons for heterogeneity in trajectory and outcomes are not well understood
- biomarkers to personalize existing drug treatments (for e.g., when to use lithium or when to not use an antidepressant) are not known or available
- scientifically driven new drug targets and novel treatments are lacking

Mission

BD^2 was launched to realize the vision of a world where the etiology and biological mechanisms of bipolar disorder are known and well-understood, allowing the development of effective treatment interventions and optimized outcomes for all individuals with bipolar disorder.

Opportunity Snapshot

Applicants are invited to join the BD^2 Integrated Network. The Integrated Network is part of a multidisciplinary initiative to increase our understanding of the heterogeneity, progression, and underlying biology of bipolar disorder and, ultimately, to identify novel strategies for improved care and intervention. In partnership with people living with bipolar disorder, clinicians, and researchers, the BD^2 Integrated Network will bring together a community committed to dramatically improving systems of care and accelerating research.

The Integrated Network will generate in-depth clinical and biological data from a total of 4,000 longitudinal study participants. It will develop and subsequently launch a learning health network (LHN) with the goal of rapid integration of clinical care data analytics from research to inform clinical care. Applications demonstrating interest and an ability to capture in-depth, longitudinal, clinical, and biological data in a bipolar disorder LHN, will be considered.

Purpose

The purpose of the Integrated Network is to improve the health and well-being of people living with bipolar disorder by engaging a network of collaborating investigators and clinicians to:

i) implement and inform data-driven improvements in care

ii) build an unprecedented data ecosystem for bipolar disorder comprised of longitudinal clinical and biological data

iii) generate novel insights for interventional approaches

We are seeking the participation of investigators committed to realizing the vision of the initiative to build adaptive, networked approaches to mental health care and research. It is expected that investigators, and their associated health systems, will bring their leadership, capabilities, and resources to the effort. They will demonstrate a long-term commitment to building and participating in a community ready to meet the challenges of providing better care for those living with bipolar disorder.

As outlined in Figure 1, participant data will be aggregated from several sources to build in-depth clinical and biological profiles of bipolar disorder. The overarching goal of the Integrated Network is to use these data to identify key outcome measures for bipolar disorder, as well as interventions and strategies to improve clinical care and practice. A team of centralized raters will play a key role in standardizing assessments, harmonizing data across participating sites, and providing feedback to clinical care teams so that as our understanding of bipolar disorder grows, improved care measures can be rapidly identified, implemented, and evaluated.

Over a five-year period, BD² will enroll a cohort of 4,000 patients with a diagnosis of bipolar disorder type I (Figure 2). Each participant will be followed for a minimum of 5 years; in-person visits will occur at baseline and every 12 months for five years (constituting a total of 24,000 study visits), supplemented by more frequent remote tracking of mood and other related outcomes. The program will launch with six sites across the USA and expand globally to 15 sites over three years. Achieving a global presence will enhance both the diversity of participants and the overall impact of the Integrated Network.

Figure 1. Overview of the BD² Integrated Network

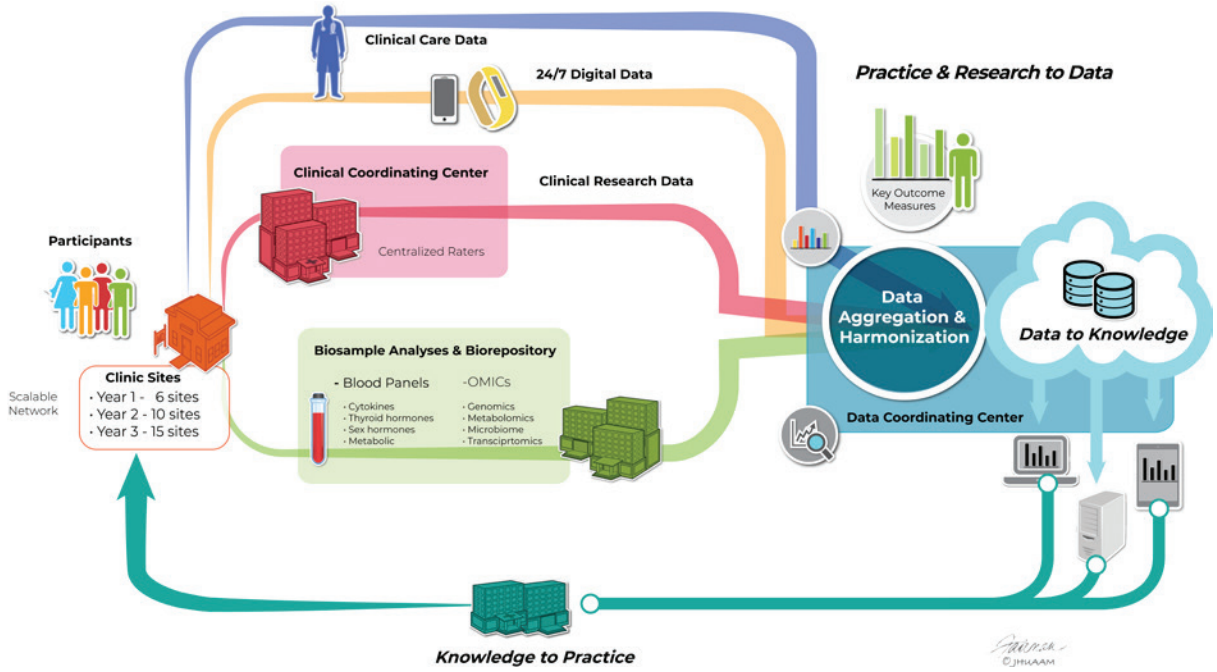
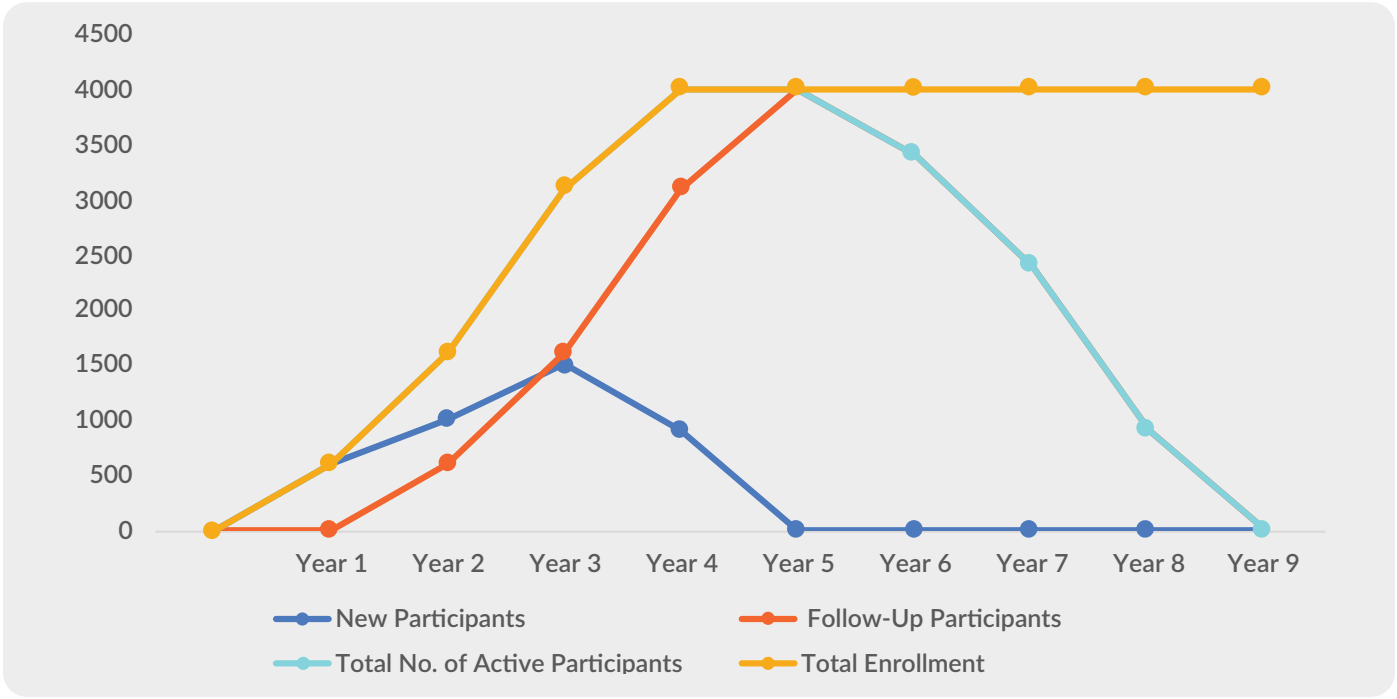


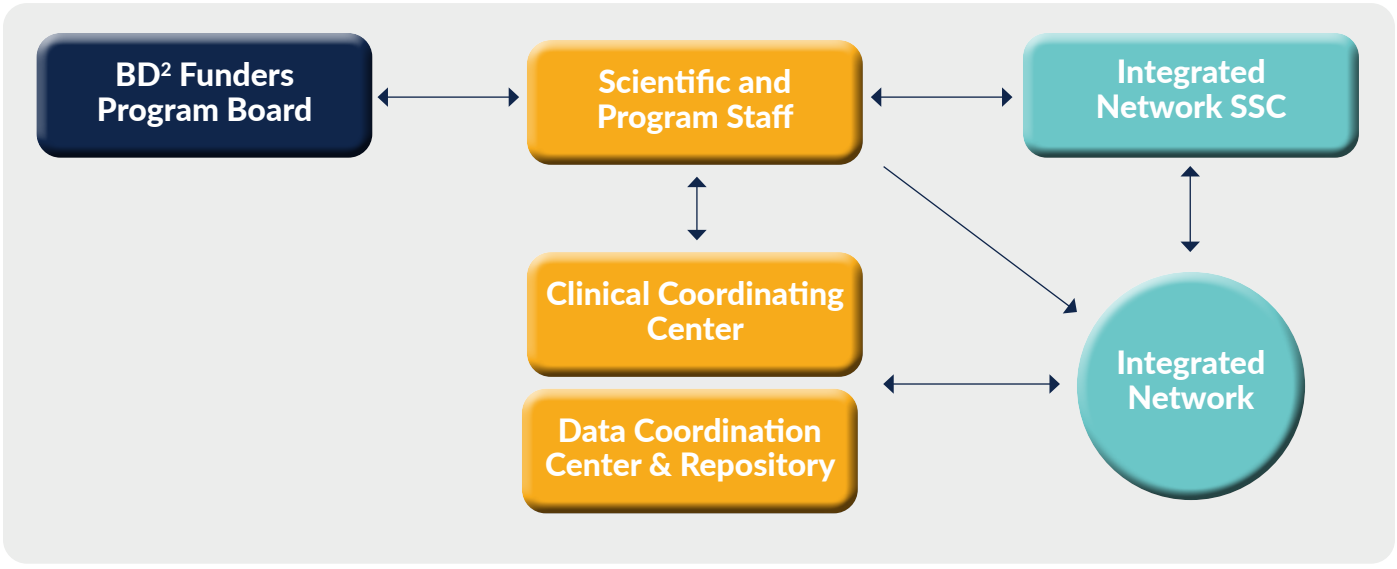
Figure 2. Enrollment Projections for the BD² Integrated Network



Governance

BD² is managed by a Program Staff in consultation with a funder's Program Board (PB) (Figure 3). The PB receives input and strategic advice from its scientific steering committee (SSC) who in turn guide and direct the operations of the Integrated Network and its centralized services, including a Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC).

Figure 3. BD² Integrated Network Governance Structure



The SSC is comprised of leading experts in the fields of psychiatry, clinical psychology, neuropsychology, neuroimaging, genomics, translational neuroscience, community outreach, and mental health informatics. The SSC will meet regularly with each of the awardee sites to discuss program design, implementation, and results.

A key goal of the program is to aggregate consistent and complete data from sites and core facilitates. To this end, the Integrated Network SSC will oversee data standardization and interoperability between sites and cores. The CCC and team of centralized raters will work in concert with the DCC and sites to support and enable the collection of standardized data.

Funding

BD² intends to fund six sites during the first year of the program. This will expand to a network of up to 15 sites over three years. The anticipated award date for the initial six sites is approximately May 5, 2023.

Each applicant site may request $2,250,000 (USD) for use over five years to administer the longitudinal study cohort protocol and LHN as outlined in this RFA. This includes costs to recruit a goal of **100 bipolar I disorder participants within the first year, collecting longitudinal data for an additional four years, and the necessary clinical and administrative process changes to support a learning health network within their institution**. All grant totals are inclusive of indirect costs up to a maximum of 15% of the site budget.

In years 2 and 3, additional milestone-based funding will become available as follows:

Once the initial 100 participants are recruited, each individual site will be eligible to apply for an additional $1,300,000 to recruit a new cohort of 100 participants. A third milestone-based grant valued at $1,300,000 to recruit another 100 participants is also available once the site has recruited a total of 200 participants. Thus, each site will be eligible for funding to support the recruitment of a total of 300 participants – each of whom will be followed for five years.

Organizational Eligibility

Proposals will be accepted from any US-based public or private-sector organization, including non-profit and for-profit organizations that provide clinical care for people with bipolar disorder.

Qualified applicants must demonstrate the capacity to:

- Recruit and provide care for 100 individuals with a diagnosis of bipolar I disorder into the initiative per year for three years, for a total of 300 participants
- Provide clinical care and treatment to a diverse population of people diagnosed with bipolar disorder
- Implement, manage, and oversee the data collection protocol of the longitudinal study protocol
- Participate in the planning and community building of the LHN

Organizations with prior experience in longitudinal studies (particularly in the field of psychiatry), clinical coordination, outcomes research, and the development of large, multi-center programs relevant to bipolar disorder are encouraged to apply.

Sites outside of the US will be recruited in years 2 and 3 under a separate RFA.

Project Goals

The ultimate goal of the Integrated Network is to facilitate the development of precision-based care for bipolar disorder. Knowledge and insight generated by the program will be used to optimize the treatment approach, based upon each individual's specific characteristics. Towards that goal, the Integrated Network will:

I. Establish a longitudinal cohort. The Integrated Network will support deep phenotyping of a diverse group of people with bipolar I disorder to accurately capture the trajectory of disease and to clarify its underlying biology. This will enable the identification of key clinical (e.g., recurrence rate, comorbid diagnoses, early life adversity, sleep disruption, cardiovascular risk), neural (e.g., structural changes in gray matter, white matter disease, cognitive deficits), and biological (e.g., inflammation, elevated stress hormones, genomics) processes that drive outcomes in bipolar disorder.

II. Establish a learning health network across sites. The Integrated Network will engage care teams (e.g., physician leader, RN, coordinator or staff, patient/family member) and organizational leaders to drive transformational efforts based on point of care clinical data, and the new insights generated by the cohort study.

A full overview of the longitudinal protocol and plan for the LHN can be found in appendices A and B, respectively.

Scope of Work

To help achieve our goals, we are seeking up to six institutional partners who are dedicated, not only to improving the standards of care for people with bipolar disorder, but also to challenging the status quo to advance our scientific understanding. Investigators at these institutions will lead the longitudinal study protocol and guide the design and buildout of the LHN. Our overall goal is to recruit and retain 4,000 participants with bipolar disorder within the Integrated Network within four years of its launch.

The Longitudinal Cohort Study

Each participating site will recruit 100 individuals living with bipolar I disorder into the longitudinal cohort study according to the protocol found in Appendix A. The goal is to enroll 100 individuals per year and monitor outcomes for five years. Each site will be supported by a CCC that will perform standardized assessments via telehealth and a DCC as describe below (Centralized Services). The opportunity to enroll additional participants (up to 200 additional participants) will be milestone driven and based upon review of the efficiency and retention rates at each site.

Data generated by the longitudinal study will be deposited within a Centralized Data Repository (CDR), which will aggregate, harmonize, and share data across sites. A research team at the site will be responsible for these data collection efforts and ensuring that the site carries out the longitudinal protocol with rigor. The range and cadence of data captured through the longitudinal study will reflect the complexity of the illness and its dynamic nature. This will provide researchers with an opportunity to integrate clinical, behavioral, and biological data from participants to gain new insights into pathophysiology, illness trajectory, and treatment response. This will allow for a more complete understanding of the disease and charter a path toward precision care optimized at the level of each individual.

The Learning Health Network

The Learning Health Network (LHN) will be designed and implemented in conjunction with the six inaugural sites. Investigators will be expected to engage care teams (e.g., physician leader, RN, coordinator or staff, patient/family member) and organizational leaders to drive accelerated efforts to improve care. A more complete overview of the rationale and approach to building an LHN can be found in Appendix B. Investigators will collaborate with other sites in establishing measurement systems to learn from variations in care, and they will test and deploy best practices and innovations aimed at improving care.

Centralized Support

A foundational characteristic of this initiative is the use of centralized cores. This includes a Clinical Coordinating Center (CCC), a Data Coordination Center (DCC), and a centralized biosample processing and storage facility. These cores will standardize clinical and data processes, including administration of psychological assessments, data capture, governance, and distribution. Additionally, centralizing these services should reduce administrative and cost burden from sites to focus on recruitment and engagement in the LHN. Cores will work closely with the participating investigators to assist with any issues, provide clinical and data support, and ensure that sites are standardized across the network. Investigators can also access data from the CDR to directly improve care and learn from efforts within the network, as well as analyze data for research.

The Clinical Coordinating Center

The CCC will be managed by a team of bipolar disorder clinicians and care providers. Once the site recruits a participant, members of the CCC team will perform a variety of clinical assessments including structured interview-based validation of the bipolar I diagnosis and comorbid psychiatric diagnoses, mood symptom ratings, sleep surveys, and more. Centralizing these services will allow for improved standardization of the assessments. The data will be summarized and sent back to the sites so that the clinicians can use the data in treatment planning and to track their patients more rigorously over time to inform care. The CCC team will also work with each site's research members to ensure that the clinical assessments performed on site, including cognitive and functioning assessments, are standardized and rigorous. Note that the CCC will provide services distinct from clinical management/treatment of bipolar disorder which will remain the responsibility of the participating site clinical team.

Data Coordination Center and Centralized Data Repository

The DCC and CDR will be managed by a central team of data scientists. This repository will house clinical (including data derived from electronic health records), biospecimen, imaging, and mobile health data collected from study participants. Sites will send clinical and imaging data directly to the data repository. Data scientists within the repository will work with data teams on site to ensure that incoming data are correctly standardized, rigorous, and meet the initiative's criteria. The DCC team will also help troubleshoot and provide any support required by the site on data-related matters.

Biosample Processing and Biorepository

Biospecimens collected on site will be processed, stored, and then shipped to selected third party vendors for processing. The vendors will send the resulting data to the DCC.

Data Sharing and Analyses

Central to the success of the initiative, is the formation of a bipolar disorder data ecosystem. In-depth clinical and biological data contributed by the participating sites, will form the foundation of this system. The ecosystem will support open sharing of the data alongside cutting-edge analysis and visualization tools to facilitate engagement with the global research community. Clinicians will be able to access data from their patients, as well as aggregate data that could inform care from other sites within the network. Clinicians and researchers at the site will be able to access the various data domains to analyze trends, generate hypotheses, and produce new insights into bipolar disorder to develop novel and improved interventions. Participants in the study will also be able to access much of their own data to track changes in relevant metrics.

Proposal Requirements

There are three stages for the funding opportunity: i) prescreening application ii) written proposal and ii) finalist site interview (and site visit, if deemed necessary).

Prescreening Application
Interested applicants should complete the prescreening application through the online grant portal, Submittable. The prescreening will assess the applicant's suitability to join the Integrated Network and is comprised of a series of short answer questions.

Following review, successful candidates will be invited to submit a full proposal using the guidelines outlined below.

Proposal
Applicants should submit a twelve (12) page proposal, with at least 11-point font and 1-inch margins on all sides of the document, which explicitly address the questions listed below. You may include a combination of text, images, or diagrams.

Organization and clinic profile (1 page)

- Please include organization name and mission statement.
- What diversity, equity, and inclusion strategies are in practice within the organization?
- How many patients are currently followed by the clinical practice?
- How many of those patients have a confirmed bipolar I disorder diagnosis?
- What percentage of these patients receive care from a specialty clinic? What percentage receive care from a primary care provider?
- How many new bipolar I disorder patients were added to your clinical practice in the past year?
- How many providers are in the clinical practice?
- Does your clinical practice use measurement-based care (e.g., patient reported outcomes)? If so, is it embedded in the EHR system?

Leadership (3 pages)

1. How do you envision the future of bipolar disorder clinical care and research? What is your site's role in this future? How does this align with the BD^2 Integrated Network?
2. Describe your proposed leadership structure and management strategy. Please identify site PI, clinical lead, and research lead, and relevant structures and organizations.
3. What is the collaboration history of each investigator? Please include reference to past multi-team experience where relevant.
4. Discuss institutional buy-in and relationships between bipolar disorder clinical and research programs with relevant institutional bureaucracies that will ensure efficient implementation and management of the program.
5. Does the PI have a track record of data sharing and open science?

Bipolar Disorder Expertise (4 pages)

1. Describe your clinical infrastructure that serves the bipolar disorder community. This includes the demographic information of clinicians providing care for bipolar disorder, including percent breakdown of gender, race, ethnicity, and relevant specialties.
2. Provide general demographic descriptions of the bipolar disorder population you serve. This should include percent breakdown of gender, race and ethnicity, diagnoses of bipolar I disorder and bipolar II disorder.
3. Describe your participant recruitment strategy, including ways to enhance recruitment (e.g., from patient registries, or inviting patients who have already given permission to be contacted for research studies). What explicit policies and strategies will you implement to ensure that you recruit a diverse population with regards to race, gender, age, and socioeconomic status of participants?
4. Describe your experience in implementing longitudinal bipolar disorder studies. What types of data are/were collected?
5. What equipment will be used to support the collection of longitudinal data? Specifically outline how imaging will be performed and the capacity of current equipment.
6. Does your site have an existing biobank? What types of biospecimens have been and are currently being collected?

Data (4 pages)

1. Describe your data infrastructure. This includes electronic health record (EHR) system (e.g., vendor, your EHR's existing relational database or data warehouse), hardware, software, and network setup.
2. Is your site currently set-up, with appropriate personnel (e.g., clinical informatics) and technology, to interact with a DCC and facilitate data capture into a CDR?
3. What types of data are currently being collected?
4. Does your site routinely collect patient reported outcomes? If so, which ones and for what clinical purposes (e.g., screening, monitoring, or measurement-based care)?

5. What are your data sharing policies internally and externally? If relevant, provide examples of successful collaborations involving shared data.

6. What is your capacity to perform onsite data management and analysis (data clean-up and standardization, interface with DCC to facilitate EHR data capture, and initial insight generation)? For example, could your site conduct natural-language processing (NLP) of clinicians' notes, securely transfer EHR data or connect to external APIs?

Budget & Supplemental Information (not included in 12-page limit)
Sites can apply for up to $2,250,000 of funding to cover the recruitment and care of 100 participants in the Integrated Network. **Funding to support the recruitment of additional cohorts will be awarded on a milestone-basis and should not be reflected in the current application or budget.**

In this section, please answer the following:

1. Describe how the funding will be used to ensure that there is expeditious and efficient use of funds to carry out the LHN as well as the longitudinal cohort components of the initiative.

2. Justify any proposed use of funds that were not outlined in the proposed budget framework, or any major discrepancies or differences from the framework.

Funding must cover:

- Staff time to administer the following:
  - Clinical screening
  - Cognitive and functional assessments
  - Biosample collection, pre-processing, storage, and shipment
  - fMRI neuroimaging and pre-processing
  - Data clean-up, entry, and local management
- Protected time for the PI to participate in LHN activities, which include engagement in learning and teaching activities with clinicians, researchers, participants with lived experience, and hospital administrators (recommend 0.1 FTE for approximately three providers)
- Study participant reimbursement
- Neuroimaging equipment costs (hourly rate)
- Equipment costs to cover biosample collection
- Licensing costs for clinical assessments
- IRB and other required regulatory committee review costs

Please also include:
- A biosketch of the lead investigator and co-investigators utilizing the NIH template, is required and shall not exceed five (5) pages per investigator. If a proposed team member does not have a biosketch in an NIH template, a CV is acceptable with a similar 5-page limit.
- A letter of commitment signed by each investigator, as well as a letter of support from institutional leadership (department chair and/or other relevant leadership; letters are not included in 4-page limit)

Review Process

Written proposals will be reviewed by the Integrated Network Scientific Steering Committee (SSC), including experts from the bipolar disorder field, and BD² Program Staff. Proposals will be evaluated based on the responses to all requirements in this RFA. The evaluation of an organization's ability to provide the required services will be based on the written material submitted, interviews, and, if requested, presentations. If deemed necessary, site visits may also be requested.

Final Selection

Following proposal review, the BD² Integrated Network Program Director (PD), Program Staff and SSC will convene and select the successful applicants. Final decisions will be confirmed by the Program Board. Once notified, the organization will work with the PD and Program Staff to begin work.

Evaluation and Monitoring

Once investigators are funded and the initiative is implemented, progress reporting and assessments will be required. Site leadership teams will meet regularly with other site teams, the Program Staff, as well as the SSC. Regular monitoring by centralized cores will ensure continuous rigor of data collection. A formal review will be performed by members of the Program Staff every six months.

Funding Awarded in BD²'s Discretion

Responding to this RFA and/or submitting an application does not entitle any individual or organization to receive funding from BD². Funding, if any, would be provided in BD²'s sole discretion pursuant to the terms of a written agreement executed by BD² and the selected organization, the terms of which BD² may require to be acknowledged by the awardee.

Contact Information

An automated email confirmation is generated upon application submission. If you do not receive confirmation within 24 hours of submitting your application, please check spam filters then contact integratednetwork@bipolardiscoveries.org.

For inquiries about scientific priorities, eligibility requirements, and application submission please contact integratednetwork@bipolardiscoveries.org. For all other questions, including general and media inquiries related to BD², please contact: info@bipolardiscoveries.org.

Appendix A

Longitudinal Cohort Protocol for Deep Phenotyping

I. Background and Significance

Bipolar disorder is a recurrent mood disorder with a cumulative lifetime prevalence of 2-4% worldwide and ranks seventh among diseases causing disability. Bipolar disorder is characterized by significant mood swings consisting of episodes of mania and depression with intervening periods of euthymia (normal mood). It is recognized to be a chronic and relapsing disorder, with over 50% of the time experienced in a subsyndromal yet symptomatic state. Depression is among the greatest therapeutic challenges. Many challenges remain in the understanding of the fundamental biology of the illness as well as the basis for therapeutic interventions. The systematic care and management of bipolar disorder is outlined in several available treatment guidelines that have been proposed based on review of the extant literature. There is general agreement for first line treatment options. However among the second- and third-line options, there is considerable debate on subsequent prioritization of medical trials and non-pharmacological treatment guidelines are remarkably limited.

Bipolar disorder is a complex and heterogeneous disorder. Although bipolar disorder is characterized as an episodic illness with inter-episode recovery, neither complete symptomatic remission nor functional recovery are the norm. While it is true that some bipolar disorder patients function very well throughout their lives, others struggle with significant disability. The vast range in functioning is paralleled by heterogeneous clinical course (e.g., differential recurrence rates, non-uniform treatment response), variability in treatment response, and substantial cognitive heterogeneity. There are recognized clinical subtypes (bipolar I disorder vs. bipolar II disorder, psychotic vs. non-psychotic), which reflect historical attempts to address diagnostic heterogeneity. However, these subtypes are neither based on neurobiological evidence nor do they provide a roadmap for treatment decisions or predicting outcomes. Even within these clinical subtypes, there is substantial heterogeneity and evidence-based treatment guidelines are limited. New methods and comprehensive approaches are needed to identify *the modifiable clinical and biological predictors of poor outcome in bipolar disorder to provide the field with potential therapeutic mechanistic targets for future intervention and prevention efforts*.

To date, no study has been able to work at sufficient scale and duration to understand the underlying biology of bipolar disorder. This document describes the protocol for the largest and most comprehensive prospective longitudinal study ever conducted in bipolar disorder, with the potential to change the face of treatment and optimize outcomes for all people with bipolar disorder.

II. Specific Aims and Objectives

Data acquired from the Integrated Network will revolutionize the understanding of the key unanswered questions about all aspects of bipolar disorder, many of which revolve around clinical and functional heterogeneity, complexities introduced by common comorbid conditions, and temporal dynamics of the disorder.

The Integrated Network protocol is designed to address several unanswered questions and to fill gaps in our understanding of bipolar disorder. This will be achieved by incorporating core measures of clinical, cognitive, circuit-based, and biological processes that are believed to be relevant to bipolar disorder pathophysiology. These comprehensive assessments will be done annually, with the option of introducing an off-schedule assessment visit, if indicated. The study is also designed to provide a solid foundation upon which additional studies can be built.

The Integrated Network study will provide deep phenotyping of a diverse group of people with bipolar disorder over time, to accurately capture the trajectory of the disease and to clarify its underlying biology. This will allow for the development of a precision-based treatment approach, where treatment strategies can be optimized for each individual patient based upon their specific characteristics. While there are many questions that can be addressed using this study design, an overarching goal of this study is:

The identification of key clinical (e.g., recurrence rate, comorbid diagnoses, early life adversity, sleep quality, cardiovascular risk); neural (e.g., structural changes in gray matter, white matter disease, cognitive deficits); and biological (e.g., peripheral inflammation, elevated stress hormones) factors that drive poor outcomes in bipolar disorder.

III. General Description of Study Design

The Integrated Network study is a multisite, prospective longitudinal cohort design that will enroll an initial cohort of 4,000 patients with a diagnosis of bipolar I disorder. In-person visits will be every 12 months, supplemented by more frequent remote tracking of mood and other related outcomes.

Each of the Integrated Network sites will enroll approximately an equal number of participants, to be followed over at least a five-year study period. Integrated Network sites will also be part of an associated learning health network (LHN), providing comprehensive clinical care for participating bipolar disorder patients.

IV. Subject Selection

Inclusion Criteria:

1. Age 18-75;
2. Diagnosis of bipolar I disorder as per the Structured Clinical Interview for DSM-5 (SCID-5-RV);
3. Ability to consent to the study based upon clinician's judgment;
4. Mood and related symptoms that are stable enough to participate in the protocol based upon clinician's judgement; and
5. Montreal Cognitive Assessment (MoCA) score ≥ 19.

Exclusion Criteria: Any unstable medical disorder that, at the discretion of the site PI, would substantially interfere with participation. This includes progressive neurodegenerative disorders and dementing conditions, general medical disorders known to affect mood disorders (e.g., Cushing's disease, metastatic cancers, or cardiovascular disorders that are affecting the central nervous system).

Demographic Considerations:

- ***Age*:** As the modal age of onset of bipolar disorder is 25 years old, 30% of the cohort will be 30 years or younger at the time of study entry to allow for a sufficient investigation into the early stages of the disease.
- ***Sex*:** Most studies report an equal sex ratio in bipolar I disorder prevalence (~1%); therefore, this study will enroll approximately an equal number of male and female participants.
- ***Race/Ethnicity*:** Bipolar I disorder prevalence does not differ significantly by race or ethnicity, so this study will enroll a racially and ethnically diverse cohort.

Recruitment Procedures:
Each site will establish a recruitment strategy that is appropriate to their environment and based upon prior experience. This may include recruitment through electronic health records and outpatient/inpatient clinical care settings, advertising, or community-based programs aimed towards recruitment of participants. This protocol will be embedded within an LHN across all participating sites. Referral into the study may occur in several possible ways; however, enrollment into the Integrated Network will encourage the participant to agree to receive their care via the LHN and vice versa.

The identification of potential participants at each site will be followed by a standardized pre-screening process prior to the informed consent, where no data will be recorded but general eligibility criteria will be reviewed.

V. Subject Enrollment

Information on the study will be provided to potential participants through their clinical psychiatry care setting/LHN participation or the site's research study staff to include web-based information that describes the initiative and outlines the process and expectations of the study.

Integrated Network study staff will share recruitment/onboarding materials with the participant and any family members/caregivers who are involved in the care of the patient. A member of the study team will be available to answer questions about the Integrated Network study prior to initiating the informed consent process.

If a potential participant chooses to join the study, informed consent will be obtained by a trained study staff. Consent may be in person and paper-based or electronic-based, utilizing REDCap (by phone or video call). The REDCap eConsent Framework provides standardized tools to obtain consent and store consent documentation with a certification screen and a storage function which automatically generates a "hard copy" PDF of the signed form.

In recognition that there is a specific focus on ascertainment of a diverse cohort, the sites will be encouraged to provide a diversity plan that takes into account the local population characteristics. For example, in communities with a large Spanish-speaking population, a written translation of the entire English version of the consent form into Spanish will be included. Sites will also be required to arrange for a medical interpreter fluent in both English and Spanish to be present, or available by phone or videoconference, during the consent process.

VI. Study Procedures

Study Visit Summary
After a potential participant is identified, they will undergo the following procedures:

Screening Visit: An initial visit will be conducted via phone or video call to introduce the participant to the Integrated Network study and answer any questions he/she/they may have about the protocol. Initial eligibility will be assessed via a short pre-screening checklist and, if deemed broadly eligible, based on the answers to a series of screening questions that address the inclusion and exclusion criteria, informed consent will be documented. Once consented, the baseline visits will be scheduled.

Baseline Assessments: There will be two forms of baseline assessments – a visit based on a virtual (remotely administered) clinical diagnostic assessment of the participant and an in-person assessment that addresses those features that are best accomplished in person.

Remote Baseline Visit: The clinical diagnostic baseline assessment will be conducted remotely and includes a clinical diagnostic interview based on the SCID-5 instrument, cross-referencing medical records, wherever available, and a series of clinical symptom severity assessments by a highly trained centralized rater, alongside a detailed medical and family history questionnaire.

Following the baseline assessment, a summary of diagnostic and clinical features will be written and reviewed prior to being shared with the LHN clinical team.

In-Person Baseline Visit: The second of two baseline visits will be conducted in-person at the Integrated Network study site and will comprise the assessments that require in-person evaluation. This meeting will occur within one week of the Remote Baseline visit. These include cognitive testing, structural and functional brain magnetic resonance imaging (MRI) protocols, and a blood draw.

Annual Follow-Up Visits: Follow-up visits will be scheduled at 12-month intervals based on the date of completion of the Baseline visit. These visits will include a subset of the baseline assessments and will be done in a hybrid (remote and in-person) format using the same structure as noted for the Baseline visit assessments.

Unscheduled Visits: These visits are included in the protocol to allow for the flexible assessment of a participant during a period that is not defined by the above visit schedule. The schedule for these visits will mimic that described for Annual Follow-up visits and can be implemented as indicated.

Interim Assessments: These assessments will serve to track mood and related symptoms during the time between the annual in-person visits. Assessments conducted during this interim period will include data collected via both passive/continuous measures (e.g., activity and sleep data captured using a wearable device such as the Fitbit) and active assessments that will be triggered bi-weekly (e.g., app-based questionnaires sent via email or smartphone for completion by the participant).

Participants will be incentivized to engage in three forms of assessments over the course of the year: 1) Fitbit or other personal wearable monitoring; 2) clinically-oriented assessments (patient-reported outcomes at point of care) integrated with the LHN; and 3) self-report assessments that are part of an app-based system.

Assessments (see Appendix for a detailed description of all measures)
All clinician-based diagnostic and clinical symptom ratings will be done via a centralized clinical core (an academically based CRO and/or academic institution serving as a core resource) to ensure efficiency, uniform training, and high inter-rater reliability.

Diagnostic Assessment: Following consent, each participant will be administered the Structured Clinical Interview-DSM-5 (SCID-5-RV) to confirm and document primary and comorbid Axis I diagnoses. A brief version of the SCID will be conducted during each annual visit to document any changes to diagnoses and capture detailed information on illness-associated events (e.g., new episodes, hospitalizations) that have occurred over the past 12-month interval.

Clinical Assessment:

Current symptom severity will be assessed annually utilizing the Young Mania Rating Scale (manic symptoms; YMRS), the Montgomery Asberg Depression Rating Scale (depressive symptoms; MADRS), and the Brief Psychotic Rating Scale (psychotic symptoms; BPRS). Centralized raters will also be trained on protocols to evaluate and appropriately address suicidality.

Premorbid/Early life history will be assessed using an intake questionnaire at baseline, which will be updated annually to include demographics, family history, and medical history. The Premorbid Adjustment Scale (PAS) will evaluate childhood academic and social experiences and the Adverse Childhood Experience Questionnaire (ACEs) will measure childhood trauma history — both scales will only be completed once (at baseline).

Sleep quality will be assessed at each annual visit using the Pittsburgh Sleep Quality Index (PSQI). Circadian preference (chronotype) will be assessed one time (at baseline) using the Morningness-Eveningness Questionnaire (MEQr).

Treatment history will be detailed using the Massachusetts General Hospital Bipolar Disorder Treatment Response Questionnaire (MGH BTRQ), a retrospective interview conducted at baseline, cross-referencing medical records wherever available. Ongoing treatment will be captured via the regular clinician visits (as part of the LHN) using the Medication Recommendation Tracking Form (MRTF) and standard medical record notation.

Physical health metrics will be captured at each annual visit and include vital signs (body temperature, pulse rate, respiration rate, blood pressure) and metabolic readout inclusive of height, weight, waist-hip ratio, and body mass index (BMI).

Interim/remote tracking of mood symptom severity will be implemented using a set of app-based brief questionnaires including the Patient Health Questionnaire (depression; PHQ-9), the Patient Mania Questionnaire (mania; PMQ), and the combined digital survey of mood in bipolar disorder (depression and mania; digiBP). These mood ratings will be pushed to the participant via text or email biweekly throughout the study. In addition, related factors will be assessed in between the annual visits that include life stress [Everyday Discrimination Scale (EDS) and the Perceived Stress Scale (PSS)] and general wellness [WHO Five Wellbeing Index (WHO-5)].

Digital (passively-collected) activity and sleep assessments will be implemented continuously. A wearable device will be provided at the baseline in-person visit to all participants. Study staff will help participants set up their device such that it is connected to the relevant data-management platform to facilitate collection and analysis of participant data. If a participant is currently using a wearable (e.g., Oura ring, Fitbit, Apple watch), we will request that they share their raw or minimally processed data with us via an application programming interface (API). For active remote data collection, study staff will download a custom app which will be used for the collection of remote clinical assessments.

One-time remote assessments (at participant's convenience) will be collected using an online survey method (REDCap) and will include measurement of personality traits including the "Big 5" personality descriptors measured with the NEO Five-Factor Inventory-3 (NEO-FFI-3), affective temperament using the Temperament Evaluation of Memphis, Pisa, and San Diego Auto questionnaire (TEMPS-A short version), and resilience assessed by the Connor-Davidson Resilience Scale 10-item (CD-RISC).

Note: All diagnostic and clinical assessments can be administered remotely or in-person, with exception of vitals and metabolic readout. Place of administration will be flexible to accommodate participant engagement.

Cognitive Assessment:

The selection of tasks to be included in this protocol was guided by the recommendations made by the International Society for Bipolar Disorder (ISBD) Cognition Task Force and includes many tests from the ISBD-BANC, with the addition of several other tasks that are believed to be pathophysiologically-relevant in bipolar disorder. All tests will be administered in-person at baseline and a subset of the tests will be repeated

at each annual visit. Testers at each site will be trained to administer all tests per standardized instruction and evaluated for reliability. The baseline battery will take approximately two hours to complete, and follow-up visits will include a shorter battery to be completed in approximately one hour.

In addition to objective measurement of cognition, one scale that assesses perceived cognitive impairment will be administered at baseline and at each annual follow-up visit: the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA).

Everyday functioning in the community will be assessed at baseline and at each follow-up visit with the Functioning Assessment Short Test (FAST). Employment status will also be recorded.

Neuroimaging Assessment:

All imaging will be acquired using 3 Tesla MRI scanners. We will acquire structural (grey and white matter) and connectivity (resting state) data during a 60-minute scan. Structural and functional MRIs will be conducted at baseline and repeated at each annual follow-up visit.

This protocol will utilize the same neuroimaging approach described by the ABCD study, which entails an optimized MRI acquisition protocol to measure brain structure and function that is harmonized to be compatible across three tesla (T) scanner platforms: Siemens Prisma, General Electric 750, and Phillips at multiple sites. The protocol includes 3D T1- and 3D T2-weighted images, and diffusion weighted images for measures of brain structure; and resting state connectivity using functional MRI to measure brain function.

Biosample Collection:

Blood will be collected by a trained phlebotomist at baseline and again at each in-person annual visit. Stool collection kits will be provided at in-person annual visits and participants will complete kits from home and ship directly to the laboratory for processing.

Detailed methods for biosample collection, processing, and shipping will be shared with all sites, along with information on tissue type (blood, plasma, serum), assay planned, and cadence of collection. In brief, at each in-person visit, each participant will provide a sample of ~100 ml of venous blood collected by a research nurse skilled in venipuncture. Samples will be processed locally at each site following the same protocol. Plasma will be separated from cells within two hours of collection and will be frozen immediately to remain frozen until tests are conducted (critical frozen). In addition, two teaspoons of the blood sample will be isolated into DNA after which it will be banked until genetic analyses are conducted.

Schedule of Assessments	Screen	BL Day 1	BL Day 2	In	Y1	In	Y2	In	Y3	In	Y4	In	Y5
Informed Consent	X												
Intake Form (demographics, medical history, family history, comorbidities)		X			X		X		X		X		X
SCID-5-RV		X			X		X		X		X		X
SCID Update					X		X		X		X		X
MGH-BTRQ		X			X		X		X		X		X
ALDA Scale		X											
YMRS		X			X		X		X		X		X
MADRS		X			X		X		X		X		X
BPRS		X			X		X		X		X		X
BACS: Symbol Coding			X		X		X		X		X		X

Schedule of Assessments	Screen	BL Day 1	BL Day 2	In	Y1	In	Y2	In	Y3	In	Y4	In	Y5
Category Fluency: Animals			X		X		X		X		X		X
Trails A			X		X		X		X		X		X
CPT-I/P			X		X		X		X		X		X
WMS-3 Spatial Span			X		X		X		X		X		X
HVLT-R			X		X		X		X		X		X
Stroop			X		X		X		X		X		X
Trails B			X		X		X		X		X		X
WASI-II: Vocab & Reasoning			X		X		X		X		X		X
Penn ERT			X		X		X		X		X		X
BART			X		X		X		X		X		X
COBRA			X		X		X		X		X		X
FAST			X		X		X		X		X		X
PAS			X										
ACEs			X										
PSQI			X		X		X		X		X		X
MEQr			X										
PHQ-9				X*		X*		X*		X*		X*	
PMQ				X*		X*		X*		X*		X*	
digiBP				X*		X*		X*		X*		X*	
EDS				X**		X**		X**		X**		X**	
PSS				X**		X**		X**		X**		X**	
WHO-5				X**		X**		X**		X**		X**	
Wearable			Continuously from baseline to end of study										
NEO-FFI-3			X										
TEMPS-A Short			X										
CD-RISC			X										
Vital Signs			X		X		X		X		X		X
MRI			X		X		X		X		X		X
Metabolic Readout			X		X		X		X		X		X
Blood			X		X		X		X		X		X
Stool			X***		X***		X***		X***		X***		X***

*Completed bi-weekly; **Completed monthly; ***Kit sent home for in-home collection

Key: Structured Clinical Interview for DSM-5 (SCID); Mass General Hospital Bipolar Disorder Treatment Response Questionnaire (MGH BTRQ); Retrospective Assessment of the Lithium Response Phenotype Scale (ALDA); Young Mania Rating Scale (YMRS); Montgomery Asberg Depression Rating Scale (MADRS); Brief Psychotic Rating Scale (BPRS); Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding; Continuous Performance Test – Identical Pairs (CPT-I/P); Wechsler Memory Scale 3rd Edition (WMS-3); Hopkins Verbal Learning Test – Revised (HVLT-R); Wechsler Abbreviated Scale Intelligence 2nd Edition (WASI-II); Penn Emotion Recognition Test (ERT); Balloon Analog Risk Task (BART); Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA); Functioning Assessment Short Test (FAST); Premorbid Adjustment Scale (PAS); Adverse Childhood Experience Questionnaire (ACEs); Pittsburgh Sleep Quality Index (PSQI); Morningness-Eveningness Questionnaire – Revised (MEQr); Patient Health Questionnaire-9 (PHQ-9); Patient Mania Questionnaire (PMQ); Combined digital survey of mood in bipolar disorder (digiBP); Everyday Discrimination Scale (EDS); Perceived Stress Scale (PSS); WHO Five Wellbeing Index (WHO-5); NEO Five-Factor Inventory-3 (NEO-FFI-3); Temperament Evaluation of Memphis, Pisa, and San Diego Autoquestionnaire – Short (TEMPS-A); Connor-Davidson Resilience Scale 10-item (CD-RISC)

Specimen Banking

Samples will be collected, processed, and stored locally (at the participating site) until they are batched and shipped to the central repository. Any personally identifying information connected to these blood samples will be removed before the samples are sent off-site and identification will be maintained by the site using a linking code.

Study Endpoints

The study is designed to collect several potential endpoints for analyses, including clinical, cognitive, biological, neural, and functional outcomes. This is a data banking protocol; therefore, a number of analyses will be conducted that are not pre-defined.

There are a multitude of questions that this banking protocol can address. The protocol can be used for pilot or preliminary data to guide additional studies including clinical treatment trials and for the discovery of new insights into disease, which will result in the publication of manuscripts. There will be many kinds of analyses performed on the data, to address such questions as:

- Are there distinct subgroups of patients with bipolar disorder with differential illness trajectories?
- What are the clinical features and biomarkers that are associated with poor functional outcomes in bipolar disorder?
- Are there measurable changes in brain structure or functional connectivity over the short-term longitudinal course in bipolar disorder? If so, how do they associate with illness course and treatment?

These are just a few examples. There are many questions that can and will be addressed by this database that will add substantially to the understanding of the pathophysiology of bipolar disorder, its treatment, and how best to optimize outcomes in all bipolar disorder patients.

Statistical Plan

There are a wide range of possible analyses to be conducted, none are based on a priori hypotheses; therefore, a structured statistical plan is not provided here. A formal power analysis is also not possible; however, the collection of comprehensive longitudinal data from 4,000 bipolar I patients will represent the single largest study of this type in existence. We are certain that this will provide adequate power to address numerous possible questions and, by using this as a discovery cohort, it will generate new hypotheses and will guide more specific studies and analyses in the future.

Appendix B

Learning Health Networks

The purpose of the Integrated Network is to dramatically improve the health and well-being of people living with bipolar disorder by creating the infrastructure to rapidly create and translate new knowledge to improved care. Ultimately, we envision an ecosystem that includes patients, caregivers, clinicians, researchers, and health system leaders that work together to break down the barriers between research, clinical care, and quality improvement. Within this system, any member can develop innovations, share data, and conduct collaborative research to improve the health, well-being, and experience of patients.

I. Background and Significance

Despite the best efforts of all participants in the U.S. healthcare system, it consistently comes up short in supporting good health. In part, this is because the U.S. national research infrastructure is too slow, too costly, and often produces results that are not meaningful to people's lives and care and that do not inform the decisions they and their clinicians need to make.

Learning Health Networks are an innovative and energized approach that addresses the gaps in health care and research in health care by accelerating the translation of data to knowledge in the benefit of those receiving care. The networks form at the intersection between health care and research with the goals of implementing findings efficiently and evaluating subsequent outcomes.

Networks large and small that have organized as Learning Health Networks (LHN) integrate research, quality improvement, healthcare services, and care, and build the capacity of everyone who participates in these systems (from community members to researchers to clinicians) to work together to accelerate research and improve health (outcomes, experience, and value).

Foley et al. Realising the Potential of Learning Health Systems, May 2021

Learning Health Networks are emerging in psychiatry. For example, FondaMental Advanced Center of Expertise for Bipolar Disorders (FACE-BD), a consortium in France, has achieved a 50% reduction in hospitalizations through the implementation of a system of external diagnostic evaluation combined with consultation and evidenced-based care in a network of bipolar centers of excellence.

The Integrated Network will accelerate the ability to generate new knowledge in bipolar disorder, efficiently implement these findings in the clinic, and progressively and substantially improve outcomes.

Achieving a Learning Health Network means:

1. Aligning all stakeholders around a shared commitment to better health for communities of people with bipolar disorder.
2. Deep engagement of all participants so that patients, caregivers, clinicians, researchers, and health system leaders work together to improve healthcare services and research.
3. A system that allows transparency, sharing, collaboration, and synergy across institutions, organizations, and communities to accelerate sharing of ideas, identifying best practices, and conducting research — dramatically reducing the time from research to implementation.
4. Effective use of technology to capture and re-use data from point-of-care clinical visits and data contributed by people with bipolar disorder and their clinicians.
5. A network business model designed to bring value to all stakeholders and users — patients, families, clinicians, researchers, health systems, payers, and sponsors.
6. Core resources to train, mentor, and support centers in local quality improvement efforts.

Establishing an LHN for bipolar disorder will allow clinicians to utilize and develop the most effective practices for care and motivate participants to engage with their healthcare team. Further, the network will quickly adapt to new evidence resulting directly from the embedded longitudinal study that prospectively captures and analyzes cutting-edge research data across neuroimaging, cognitive, clinical, and biological domains.

The longitudinal protocol serves as the foundation to better understand the trajectories and heterogeneity of bipolar disorder, and findings from the data will be implemented immediately in the LHN to be systematically evaluated for beneficial effects on key health outcomes.

The Integrated Network will:

Identify the determinants of heterogeneity, temporal, and system dynamics of bipolar disorder.
The Integrated Network will launch an innovative longitudinal protocol for deep phenotyping. Data acquired from this study have the capacity to revolutionize our understanding of the key unanswered questions about all aspects of bipolar disorder, many of which focus on heterogeneity in key outcomes of importance to people living with bipolar disorder, complex dysregulated systems, and the temporal dynamics of the disorder. The longitudinal study will allow for deep phenotyping of a diverse group of people with bipolar disorder, to better understand trajectory and biology, with the ability to validate new insights in real-time in a clinical care setting, via the LHN.

Accelerate improvement in health outcomes for people with bipolar disorder through open, active collaboration.
People living with bipolar disorder, clinicians, and researchers in the network will work together to measure performance and identify and learn from variations at the site and network levels about what is working best (and what is not working). Training and mentoring support to participating sites will enable them to integrate new learnings reliably into care plans while reducing fragmentation of care across participants, their primary caregivers, and clinicians. This will set the stage for the accelerated updating of the existing, though still suboptimal, evidence-base for treatment of bipolar disorder. While the participating Integrated Network sites will have first access to training and protocols for improved care, the network will work to share results and resources rapidly with the field, so that all patients living with bipolar disorder can benefit.

How will we work together and what's involved?
The overarching strategy is to collaborate by collecting, sharing, and using outcomes data for clinical care, outcomes improvement, and research. With this in mind, the clinical improvement arm of the Integrated Network will be developed and evolve with selected sites. To join, all must agree to collect standard data (initial required data is outlined in the longitudinal protocol) and share data on outcomes while agreeing not to use these data for competitive purposes. All involved will participate in design sessions with a philosophy that everyone has something to teach, and everyone has something to learn. We will collectively identify best practices and use the data we generate to identify the outcomes that are of greatest value to measure and target for improvement. Collectively, we will agree to learn from all information gathered to identify approaches that optimize these key outcomes, change practice, and systematically assess the impact of those changes on health outcomes in real time.

Another important aspect is to agree to adapt and teach clinicians and patients about evidence-based guidelines so that they can readily deploy guideline-informed care to reduce unnecessary variability in care while still allowing clinicians and their patients to customize care to the unique needs of individual patients. Standardization is the foundation for faster progress towards identifying effective combinations of treatments not yet studied. With this in mind, we plan to use the International Society for Bipolar Disorders (ISBD)/ Canadian Network for Mood and Anxiety Treatments (CANMAT) (2018) guidelines as a starting point to guide care and trainings but will grow and evolve recommendations with the Integrated Network over time.

II. Participating Site Requirements and Expectations

We are seeking health systems committed to creating communities with the primary goal of improving outcomes for all people with bipolar disorder. Participating health systems must demonstrate a commitment to: (1) evolve their system to create a networked community of patients, caregivers, researchers, and clinicians working together to accelerate research, provide more reliable care, and improve outcomes; (2) rapidly engage in funded research; (3) openly share what they are learning with other sites; and (4) align and integrate with institutions across the network.

An unwavering focus on better health. We are seeking sites willing to commit to fundamental transformation in the health and well-being of people with bipolar disorder. Sites should be eager to design and build better systems of care through the development of a culture of transparency and openness focused on improved outcomes for people with bipolar disorder.

Health system leadership commitment to excellent, equitable results and generous sharing of ideas. The challenges of improving bipolar disorder care, will not be possible without alignment of the capabilities of health systems with the needs of patients. Sites will be asked to identify a team including site champion, a clinical coordinator, and a Quality Improvement (QI) lead with dedicated time to consistently advance the goals of the local clinical team and contribute to the broader Integrated Network.

Scale up. Following design and testing of new approaches amongst a small group of clinician champions of the LHN, we will develop a plan and approach to scale up methods of better care to include the other clinic staff, and then across the entire health system. Additional scaling beyond the local context is planned for years two and three.

Data sharing. Organizations will participate in data collection and sharing of participant health data that will be accessible in a centralized data repository. Clinic level outcomes data will be assessed and shared back with all participating sites in a noncompetitive manner for the purpose of identifying opportunities for care improvement.

Expected Results:

By the end of year one, successful clinical sites are expected to have:

- A community of motivated and involved stakeholders including patients, clinicians, researchers, and health system leaders.
- Measurable progress towards improved processes for care and research.
- Protocols in place for successful EHR and longitudinal data collection.
- A culture of contribution and peer-to-peer sharing achieved through a shared commitment to transparency.
- A strategic plan for each site's continued evolution towards a Learning Healthcare System, as well as plans for sustainability.
- A research agenda and projects focused on closing the most important gaps in outcomes.
- Improvement and systems change capability.
- A growing pool of sharable network resources.