

Integrated Network Concept Brief

Overview	2
An Integrated Vision.....	2
Longitudinal Cohort Study	
Learning Health Network	
Centralized Coordinated Data	
Theory of Change	3
Deep Phenotyping	
Consensus Guideline Adherence and Development	
Tracking of Outcome Measures to Compare Practice Across Sites	
Integration of Research and Care Across Sites	
A Phased Build	5
Core Infrastructure	
Site Selection	
Site Onboarding	
Network Development	
Knowledge to Practice, and Back Again	

Overview

The BD² Integrated Network represents a truly innovative model where deep phenotyping, translation to care, and iterative improvement are all possible. It is our expectation that this will transform care for people living with bipolar disorder and set a new bar for clinical research across not only psychiatry but medicine.

The Integrated Network brings together two key models of advancing medicine. The first is the systematic collection of data from a defined set of participants over time, known as a longitudinal cohort study. The second is the development of a system to iteratively improve care for patients, known as a learning health network.

Scientists and clinicians recognize that longitudinal data collection in bipolar will revolutionize our understanding of trajectories and patient heterogeneity, paving the way for the identification of patient subtypes, optimized care, and development of new treatments. However, traditional models of scientific advancement have been slow to lead to changes in clinical practice across medicine. While developing the Integrated Network concept, the guiding scientific committee challenged themselves to envision a new model that would streamline the translation of findings to care settings borrowing from innovations in learning health systems. By aligning these two concepts, we envision an efficient pathway to translate new findings into improved care for people living with bipolar disorder.

An Integrated Vision

While it is easiest to understand the Integrated Network as a summation of its component parts, the real potential of the initiative will come from the synergy and interplay across the effort. Clinicians will have data available that has never been systematically available for their patients. Researchers will have data from the largest cohort of bipolar participants ever collected with diagnostic validity and evidenced-based care. Participants will have quality care that rapidly updates as the evidence-base grows. Each of these advances requires all components. However, to provide greater detail, we have provided a deeper explanation of each component below.

Longitudinal Cohort Study

Clinical sites will be supported to initially recruit 100 participants with bipolar I disorder and collect clinical, cognitive, and imaging and physiological markers according to a longitudinal research protocol. These data will be shared across sites through a centralized data repository, laying the groundwork for data harmonization complex analyses, and the generation of insights. 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 reflects 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 individual level.

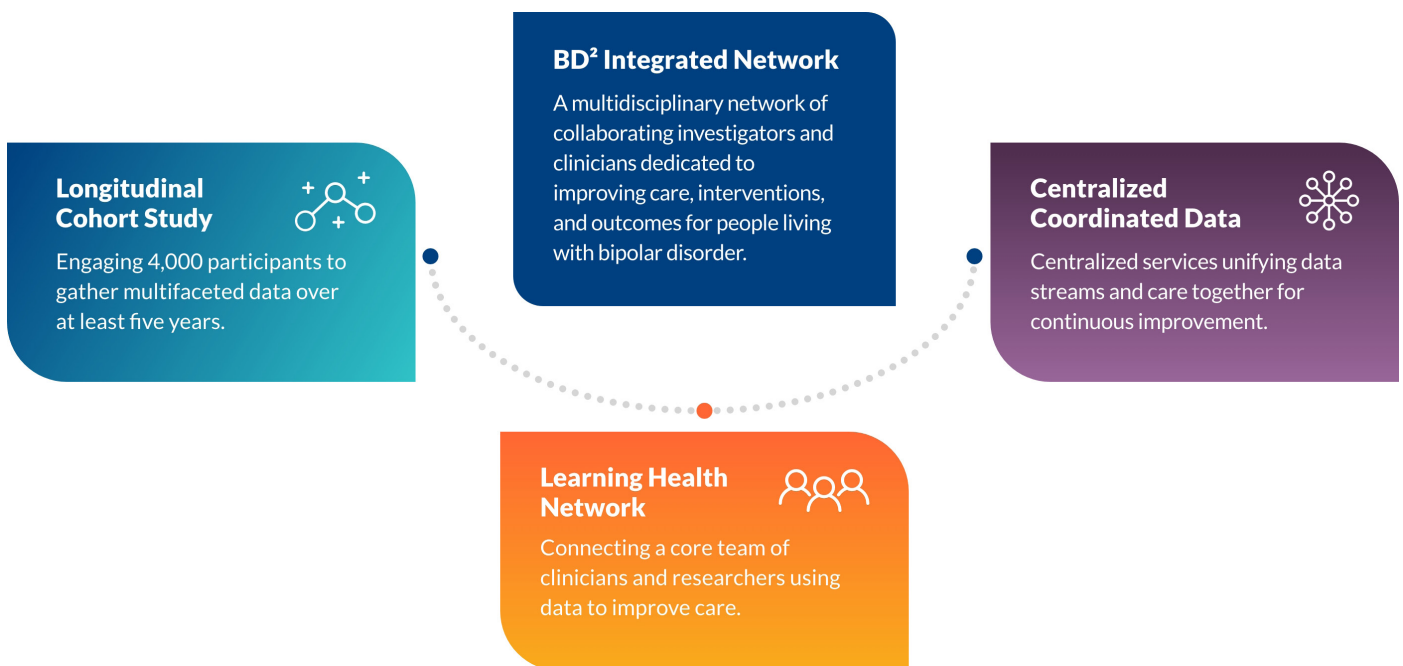
Learning Health Network

Sites participating in the longitudinal cohort study will also play a critical role in the design and implementation of a Learning Health Network (LHN) for bipolar disorder. A core team of clinicians will carry out best clinical practices with their patients and learn from other teams within the network to augment their care through evidence-based approaches. These clinicians will be champions of the LHN within their

institution, and provide on-the-ground, near-real-time changes in clinical care based on outcomes seen within the network. Clinicians will engage care teams (e.g., physician leader, RN, coordinator or staff, patient/family member) and organizational leaders to further drive transformation efforts. Further, sites will collaborate with one another 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 Coordinated Data

A foundational characteristic of this initiative is the use of several centralized cores to create shared resources and standardize processes across sites. This service unburdens clinical sites from performing lengthy assessments, and also will provide standardized information back to clinicians that will be more in-depth than traditional clinical assessments of diagnosis and medical history. These centralized services include a Clinical Coordinating Center (CCC), centralized biosample processing and storage, Data Coordination Center (DCC), and a Centralized Data Repository (CDR). 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.



Theory of Change

The Integrated Network will drive clinical improvement using several levers: 1. Deep phenotyping of participants, 2. Consensus guideline adherence and development, 3. Tracking of outcome measures to compare care practice across sites, 4. The integration of research and care across sites. Each of these drivers are discussed below.

1. Deep Phenotyping

The bipolar research and clinical communities lack rich longitudinal data. The Integrated Network aims to bring scale, time, and depth to phenotyping a cohort of people living with bipolar disorder. Researchers and clinicians see this data as the key to understanding patient subtypes, trajectories, and developing targeted interventions that will transform patient experience.

This initial focus on bipolar I disorder allows the initiative to identify relevant patterns faster because diagnostic validity is stronger leading to less variation in the participants.

2. Consensus Guideline Adherence and Development

The bipolar clinical community has guidelines developed for clinical care; however, repeated epidemiological assessment of health records shows that an alarming number of patients diagnosed with bipolar disorder are treated with therapeutics that are counter-indicated. Further, bipolar disorder is consistently misdiagnosed and incorrectly diagnosed, leading to inappropriate interventions and years-long delays in gaining access to appropriate treatments. While clinical practice cannot be mandated, the Integrated Network leadership identified initial consensus guidelines (ISBD/CANMAT, 2018) that will guide care across the network and act as a foundation from which new guidelines can be developed. Regular learning modules will support network clinicians in implementing these care guidelines within their practices. Further, collaboration and feedback from the Clinical Coordinating Center (CCC) team will provide critical feedback on team's diagnostic accuracy. In combination, these supports will lead to network clinics providing better care and diagnoses across their BD population.

Over time, this network will develop improved practices that will be translated into new guidelines for dissemination to the broader bipolar community.

3. Tracking of Outcome Measures to Compare Practice Across Sites

While initial improvement and insights will come from improving adherence to consensus care guidelines, improved diagnosis, and longitudinal data collection, the systematic analysis of outcomes will drive a third mechanism for improving outcomes. Through analysis of outcomes across sites and clinicians, the network will be able to identify and highlight positive deviants, or those who perform consistently better than average. As sites and/or individual clinicians show improved outcomes compared to other sites, the network will work to understand how their practice is different and elevate their differences for other clinicians within the network. This process of improvement is expected to generate further improvement that can quickly propagate through the network. Where applicable, these improvements can be extended into the guideline development process referenced above.

4. Integration of Research and Care Across Sites

The Integrated Network brings together research and care in a unique way. The ultimate model of change will come from combining these data streams and processes in unique ways. We envision and will facilitate the application of findings from the longitudinal data to care settings intentionally. For example, researchers and clinicians expect that we will identify biologically and behaviorally defined subtypes of people living with bipolar. Based on the profile of the individuals identified, clinicians could partner with researchers to identify and test alternative treatment approaches that are aligned with their biological profile. While these sub-studies are several years away, our infrastructure and network of providers make this vision uniquely possible and rapidly scalable.

A Phased Build

The development of the Integrated Network is already underway as dozens of potential partners are excited about its launch and considering potential avenues to participate. However, the first 12 months will represent a rapid build followed by refinement of the network as new knowledge and best practice develop. The phases below highlight the progressive nature of the model starting from points of strength allowed by our extensive planning and then evolving to be a more flexible structure that will be shaped in partnership with the clinical sites.

Core Infrastructure

A unique and critical component of the Integrated Network system is the networking of information and people across partner sites. This will occur through shared data, resources, and knowledge. A first step in the development of the Integrated Network is the identification of partners that will provide and coordinate the site services. This will include the identification of the Clinical Coordinating Center, Data Coordinating Center, and ultimately greater support for facilitation of learning across sites. These partners will be solicited via a Request for Application (RFA) process and vetted by the Steering Committee prior to selection. Contracts for these partners will be milestone-oriented to ensure that we can pace our expenses with the network needs.

Site Selection

Partner sites will be responsible for the recruitment, care, and research coordination of Integrated Network participants. Sites must be 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 clinicians engaged in the care network will guide the design and buildout of the LHN. With this in mind, site selection criteria will focus on ensuring that the sites are able to implement the longitudinal protocol as well as display enthusiasm about participating in the learning health network. Sites will be recruited via an open RFA and vetted on their track record of recruiting participants into studies, the assembled teams, and commitment to work in collaboration with other sites to improve care.

While each site will be required to identify key research and clinical personnel, the makeup of those teams is intentionally flexible to allow variability and local level optimization. We intend to prioritize diversity of site “types” to enhance the network of learning within the Integrated Network. Specifically, we envision that the network will include bipolar disorder centers for excellence, as well as Institutional Affiliate clinics. Additionally, we hope to see site PIs who are practicing clinicians with a strong network of collaborators as well as PIs who are renowned researchers with long-standing partnerships with clinical teams.

Site Onboarding

Once sites are selected, we will immediately begin the work of establishing a functional network. Sites will be required to navigate institutional review of the established protocol. While this will be streamlined through a centralized IRB, many sites will require an additional review. Sites will also begin to recruit participants into the study which requires site level workflow development within the designated clinics.

Simultaneously, we will begin to work with the clinical care teams to align practice across sites. In the RFA for site recruitment, we noted an initial grounding in the ISBD/CANMAT 2018 Guidelines for Bipolar Treatment. These guidelines provide direction for first, second-, and third-line treatment for bipolar disorder based

on available evidence and minimization of problematic side-effects. The guidelines go further providing considerations for older adults, individuals with co-morbid conditions, and include a specific section on managing co-morbid metabolic disorders. All sites must agree to implement these care guidelines as part of their practice, but with an acknowledgement that clinicians will use the guidelines as a starting point and specific care plans for each patient will be individualized and optimized with the patient's input.

Finally, sites will develop workflows to capture EHR data, biosamples, and coordinate evaluation with the Clinical Coordinating Center team. In this initial step, we will focus on capturing all relevant data at sites in an accurate and timely manner.

Network Development

Once sites can perform the basic functions: recruit patients, provide evidence-based care (defined by ISBD/CANMAT 2018 guidelines), collect longitudinal protocol data and share these data with the Data Coordinating Center, we will focus on building a functional network across sites. This will be facilitated using several tools.

- **Outcome measures:** Sites will collectively determine specific outcome measures that provide meaningful insight into participant wellness. These outcome measures will be assessed at all sites to track improvement. While specific measures will be determined with site and participant input, several SSC members have suggested that scales such as the PHQ-9, GAD7, and PMQ could be a helpful starting point.
- **Clinician network:** Clinicians within the network will be asked to participate in recurring virtual discussions. Early discussions will focus on optimizing care using current evidence-base guidelines, but over time, these discussions will provide a forum to elevate sites and individual practitioners who show quantitative improvement in outcome measures within their patient population.
- Data collected within the centralized data repository will facilitate identifying points for improvement. The CDR vendor will work with clinicians to develop clinical dashboards that site clinicians can use to more quickly identify points for intervention and mechanistic insights.
- Site personnel and dedicated staff in the Data Coordinating Center will be actively working with the growing dataset to identify phenotypic clusters that represent unique subtypes and trajectories of illness as well as correlations suggesting unexpected clinical improvement. These findings will be drawn out of the data and follow up with research and clinical teams during recurring network meetings.

Knowledge to Practice, and Back Again

While initial setup and first revolution of the network implies directionality of knowledge development originating from the longitudinal cohort and subsequent data analysis informing clinic practice, we are aiming for the development of a more fluid model of knowledge sharing and exploration once the network is established. Clinical findings could lead to updates to the cohort study design over time. Early signals in the data can be further explored in the clinic or used to justify grants for further study from other funders. Clinicians will have a ready-made platform to support small-scale clinical trials and novel mechanistic investigations. The accumulated knowledge will lead to the development of improved clinical practice guidelines. This unique platform of deep phenotyping, translation to care, and iterative improvement will accelerate the field's ability to develop and improve the guidelines and teachings for all bipolar disorder clinicians both within and beyond the network.