Schizophrenia

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Digital health technologies in the accelerating medicines Partnership® Schizophrenia Program

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Although meta-analytic studies have shown that 25-33% of those at Clinical High Risk (CHR) for psychosis transition to a first episode of psychosis within three years, less is known about estimating the risk of transition at an individual level. Digital phenotyping offers a novel approach to explore the nature of CHR and may help to improve personalized risk prediction. Specifically, digital data enable detailed mapping of experiences, moods and behaviors during longer periods of time (e.g., weeks, months) and offer more insight into patterns over time at the individual level across their routine daily life. However, while novel digital health technologies open up many new avenues of research, they also come with specific challenges, including replicability of results and the adherence of participants. This paper outlines the design of the digital component of the Accelerating Medicines Partnership® Schizophrenia Program (AMP SCZ) project, a large international collaborative project that follows individuals at CHR for psychosis over a period of two years. The digital component comprises one-year smartphone-based digital phenotyping and actigraphy. Smartphone-based digital phenotyping includes 30-item short daily self-report surveys and voice diaries as well as passive data capture (geolocation, on/off screen state, and accelerometer). Actigraphy data are collected via an Axivity wristwatch. The aim of this paper is to describe the design and the three goals of the digital measures used in AMP SCZ to: (i) better understand the symptoms, real-life experiences, and behaviors of those at CHR for psychosis, (ii) improve the prediction of transition to psychosis and other health outcomes in this population based on digital phenotyping and, (iii) serve as an example for replicable and ethical research across geographically diverse regions and cultures. Accordingly, we describe the rationale, protocol and implementation of these digital components of the AMP SCZ project. **Link to video interview: https://vimeo.com/1060935583**

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INTRODUCTION

The clinical high-risk syndrome for psychosis (CHR) provides a well-established paradigm for the early detection and intervention of psychosis[1,2]. Extensive research has characterized the CHR phase and identified predictors of the onset of a psychotic episode within this population[3]. In addition, meta-analytic studies show that the transition rate to a first episode of psychosis within three years ranges from 25%[4] to 33% (Fusar-Poli et al. 2019)[5,6] among those at CHR (see also Addginton et al. in this Special Issue [journal to add citation please]). However, the existing research paradigm is dominated by approaches that characterize groups of individuals at measurement time points separated by weeks or months rather than the known trajectories of early illness within individuals that can rapidly evolve over hours and days (Hedges et al. 2021[7];). Capturing these dynamic changes within individuals using modern deep phenotyping approaches is thus urgently required to enhance understanding of risk stages, empower clients with their own personal information, and ultimately create accurate medical devices to improve the prediction for prognoses, selection of the proper care at the right time[8], and to develop the next generation of preventative treatments[9].

Digital phenotyping offers the best opportunity to fill the gaps between traditional assessments by deeply assessing and quantifying the behavior of CHR individuals[6,10,11]. The approach involves the real-time quantification of an individual's phenotype in their natural environment utilizing data from personal devices, such as smartphones, to gain deeper, potentially more ecologically valid insights into mental health, especially with passive data streams[12]. Digital phenotyping encompasses both "active data" and "passive data," with active data requiring direct input from

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users, such as completing short self-report surveys or diaries (ambulatory assessment), while passive data are collected without active user participation, such as sensor data and phone usage patterns. Various temporal resolutions are possible with active data often collected daily and sensors continuously. This approach enables researchers to adjust the analysis to a spectrum of temporal granularities that best match the clinical question and specific data modality (surveys or sensors) in consideration. The combination of these data types, collectively referred to as "digital health technologies" or "DHT-derived data," facilitates multimodal data capture and comprehensive day-to-day mapping of experiences (e.g., through diaries), moods (e.g., via ecological momentary assessments [EMA]), and behaviors (e.g., via GPS or actigraphy) over more extended periods, thereby providing valuable insights into individual-level patterns and their change over time. By leveraging these rich datasets, researchers can potentially unravel subtle changes and individual-level temporal trends, contributing to a more detailed and rich understanding of behavior in CHR individuals beyond what clinical ratings can capture and moving towards personalized interventions and improved mental health care. Integrating digital phenotyping into the broader framework of CHR research may also offer new avenues for deciphering the complexities and heterogeneity of this syndrome, ultimately leading to enhanced diagnostic precision, prognostic predictions, targeted interventions, and treatment targeting that improve outcomes.

Digital phenotyping enhances clinical characterization and personalization by creating new types of metrics known from other studies to be related to psychosis risk[13,14]. For example, frequently administered brief surveys can assess self-reported emotions, thoughts, and symptoms as they are experienced in the course of daily life, accelerometer data can be used to map patterns of activity or sleep duration and geolocation data can be used to understand patterns of mobility assessing social withdrawal or environmental risk (e.g., urbanization). Several studies in CHR have already shown that such approaches are feasible in this population[15–21] and digital tools have been used to screen community members for elevated psychosis risk[22] (McDonald et al. 2019[23]). Given that smartphone ownership is now nearly universal among youth in countries like the US (Pew 2017)[24,25] and among young people with psychosis (Abdel-Baki et al. 2017), and today more common than computer ownership among people with psychosis spectrum illnesses[26], these devices offer an essential means to increase access to diagnostic resources, especially in rural or underserved areas where access to traditional diagnostic assessments and procedures offered at medical centers is not available. In addition, a recent review found a large number of studies utilizing a new generation of smartphone-based interventions for CHR[27], further highlighting the potential interconnection of DHT measurements combined with responsive interventions at critical time-points during the development of illness.

Nonetheless, despite the potential and advantages of a digital approach, there are also challenges. Related research in depression and schizophrenia assessing the correlations or effect sizes of digital phenotyping metrics report that the signals are likely small. While small pilot studies have reported digital phenotyping correlations as high as $d = 0.6$ with symptoms related to both EMA self-report and clinical assessments of mood and anxiety (Guidi et al.[28]; Osmani et al.[29]; Alvarez-Lozano et al.[30], more recent and larger studies suggest more modest correlations[31,32]. Although these results are not from a CHR population, they suggest the need for large-scale studies to assess the robustness of digital phenotyping models for accurately capturing symptoms. Another challenge of digital phenotyping studies is that they are often difficult to replicate. This is because the digital phenotyping app used in a study is often not accessible to other teams or no longer functional, and the analytic pipelines used to transform the data into features is not shared in a manner that facilitates use. Examples of existing replication studies suggest results are not convergent[33] even in larger studies with sample sizes of $n = 415$[34]. Reviews of results in depression (De Angel et al.[35]), bipolar disorder[36], and schizophrenia[37] highlight the lack of replication of signals reported between studies and the need for greater transparency and standardization in the research methods employed. Given that interest in digital phenotyping is spurred by the scalable nature of this smartphone-based method, there is a need for research assessing the global potential of this approach in a generalizable manner. For this, similar research protocols should be followed at multiple sites, and methods and procedures should be openly shared.

A ubiquitous challenge across the entire digital assessment space is low user engagement. Numerous studies report poor participant engagement, especially with ambulatory assessment methods using repeated surveys where active engagement is required, which is especially problematic in longitudinal studies[38] as engagement often flags after several weeks. However, there are also examples of studies designed and conducted with high participant engagement, suggesting that it is possible to keep participants engaged in ambulatory assessments for longer periods of time (e.g., three[39] or six[40] months). However, other DHTs (e.g., GPS and accelerometer data from smartphones) can be assessed over longer periods (12 months or longer). Low engagement in completing the surveys may increase the risk of low-quality sensor data, as the collection of passive data is likely in part dependent on the app remaining active and open in the background, which is triggered by active use of the app (i.e., answering the surveys or looking at feedback; Currey & Torous, 2023).

The Accelerating Medicines Partnership® Schizophrenia (AMP SCZ, www.ampscz.org) initiative is a large, international collaborative project in which individuals at CHR for psychosis are followed over a period of two years. In addition to DHT-derived data, these individuals are assessed across a wide array of domains, including clinical [journal to cite the Addington et al. paper please] and cognitive [journal to cite the Allott et al. paper please] assessments, electroencephalography (EEG)[journal to cite the Mathalon et al. paper please], brain imaging [journal to cite the Harms et al. paper please] and speech sampling [journal to cite the Bilgrami et al. paper please] measures, as well as blood and fluid biomarker [journal to cite the Perkins et al. paper please] assessments. The goals of AMP SCZ include the development of tools to predict individual outcomes and accelerate medicine development by setting the stage for new preventative treatments. The collection of modern DHT-derived data in AMP SCZ will lead to global advances through the development of novel tools and methods. These measurements will allow AMP SCZ to improve current approaches to define CHR syndrome subtypes by obtaining detailed, real-life mapping of the experiences of the largest sample to date of CHR individuals over 12 months. It will also facilitate the investigation of the feasibility and replicability of digital assessments across many different countries and research settings. Indeed, it will be the largest and most deeply phenotyped multimodal DHT study in psychosis to date.

This paper outlines how the digital component of the AMP SCZ project was designed, harmonized, and implemented. The aims of the digital component are threefold: (i) to delineate the symptoms, real-life experiences, and behaviors of those at CHR, (ii) to improve the prediction of transition to psychosis and other health outcomes in this population and (iii) to serve as an example for harmonized research across geographically diverse regions and cultures.

METHODS

AMP SCZ

The AMP SCZ project consists of a data processing, analysis and coordination center (PREDICT-DPACC) and two research networks (ProNET and PRESCIENT) that together encompass 43 study sites across the globe. CHR and community control participants take part in this observational study for up to two years. The AMP SCZ project involves a range of assessment activities leading to multiple data types, including clinical interviews, cognitive testing, EEG, brain imaging, blood samples, saliva samples, speech samples, and an optional digital component, covering daily surveys and smartphone sensing to gather DHT-derived data for one year.

The digital components of AMP SCZ are identical for CHR and community controls participants and comprise two main approaches: smartphone-based digital phenotyping and actigraphy utilized across all sites. In this study, smartphone-based digital phenotyping encompasses active data collection (short daily self-report surveys and voice diaries) and passive data capture (geolocation, on/off screen state, and accelerometer). All smartphone data are continually transmitted from the participant's device to a server at one of the two research networks. Each server is maintained at the network hub sites (Yale for ProNET, Melbourne for PRESCIENT) and not accessible to anyone outside the respective network. Within this system, each hub then shares the data with the National Institute of Mental Health (NIMH) Data Archive (NDA) which shares it with the PREDICT-DPACC. Actigraphy data are collected using an Axivity wristwatch. All actigraphy data are manually uploaded from each site by a local research assistant to the network hub sites, using Box at ProNET and Mediaflux at PRESCIENT. These data are then also shared with the PREDICT-DPACC and the NDA. This process is described in further detail in the Data Flow paper in this issue. The different types of DHT-derived data are described below in more detail. In particular, we describe the process of our decision-making in setting up the protocol.

Platform selection. The mindLAMP app has been built iteratively over the last five years with continual feedback from patients, clinicians, family members, and researchers (ref. [11]; Rodriguez-Villa et al. 2021[41]). The LAMP in mindLAMP stands for 'L'earn, 'A'sses, 'M'anage, and 'P'ortal which represent the four main participant/patient-facing features offered by the platform. While this study only utilizes the Assess features to capture data (outlined below) and the Portal feature to share that data back to participants, the mindLAMP platform can support psychoeducation/learning as well as brief interventions/management skills in other deployments, studies, and clinics (Macrynikola et al. 2023[42]) representing the ability to extend and expand off the digital component of this present study. Before this study and beyond prior research with people with schizophrenia spectrum disorders, the platform had been used in research with children (Gansner et al. 2023[43]), people with medical and neurological conditions (Beight et al. 2022[44]; Weizenbaun et al. 2022[45]), and in international contexts (Li et al. 2021[46])—reflecting its versatile nature.

However, in this study, the use of mindLAMP is focused on the assessment of diverse data streams that are divided into active (surveys and voice diaries) and passive (sensors) which are discussed extensively below. Given the nature of data collected, mindLAMP has been co-designed and created to meet the needs of end users and patients. Based on considerations and review for the ethical use of mobile health technology in psychiatry[47], the initial design of the app occurred over a one-and-a-half-year period and was guided by feedback from numerous focus groups resulting in a framework combining the intersection of patients' need for trust in the platform, control of data, and community use with researchers' need for transparent, data driven, and translational features[11]. The initial app underwent continual improvements based on real-time feedback from patients, family members, researchers, and clinicians, leading to a completely new version being released on the iTunes and Apple Store in 2020. It has continued to adapt based on feedback. There is also a formal patient advisory panel that meets quarterly to offer additional feedback and review updates to the app.

Given the nature of data collected, mindLAMP features numerous layers of data security including technical protections such as passwords, data encrypted in flight using the TLS v1.3 protocol atop the HTTP/2.0 transmission format, and stored at rest using AES-256 encryption through a secret key unique to each site hosting the app. mindLAMP also supports OAuth2.0, an industry-standard protocol for authorization, meaning that it is possible to delegate and verify access through third party services as Google. The ability for individual local or hub sites to deploy the app and store data at one site or across a network enabled international research to be conducted in compliance with local laws in India and across Europe even before this study, and helped facilitate compliance with GDPR.

To ensure equity, sites were provided with smartphones to offer anyone wishing to take part in the study but who either did not own a smartphone or owned one that did not meet the minimum system requirements. Based on rates of smartphone ownership in young people nearing 90%[26] and nearly 100% in the general population (Pew, 2023[24]), we estimated the number needing a smartphone to be minimal.

Active data

Daily surveys. The daily surveys are intended to capture self-reported emotions, thoughts, and behaviors of the past day as daily assessments are most commonly utilized in digital phenotyping research (Bufano et al. 2023[48]). Given the challenges of prolonged engagement, the goal was to ensure that daily surveys could be completed within five minutes. A 2023 systematic review and meta-analysis of methodological characteristics and feasibility of ecological momentary assessment studies in psychosis found no consensus and rather a high degree of variability between measures (Bell et al. 2023[49]) necessitated creation of questions for this study. Adopting a delphi approach, ProNET and PRESCIENT each selected a number of questions to include in the daily surveys and then shared their suggestions. Over a week, all collaborators involved in the digital component of the project voted on which questions were deemed most important as well as which were overlapping. This process was repeated twice until there was consensus on a final battery of 30 questions. There was also an initial plan to cover this battery in two modes: one burst mode, where the participants would engage multiple times per day for two weeks, and one baseline mode, where they would only complete the survey three times per week. This plan was abandoned due to complications with implementation. The decision was made to instead offer the surveys once per day across the entire study, and this was approved by the AMP SCZ steering committee. In addition, we tested how to display the questions for optimal ease and use on the smartphone app. The 30 items assessed are listed in Table 1. No items assess risk of self-harm or suicide in this study. All items are scored using a 7-point Likert scale, capturing intensity over the course of the day. We also considered a visual analog scale (VAS, ranging from 0-100), yet the Likert scale was selected as it was visualized more clearly on smaller screens. Prompts before taking any survey review that no responses are reviewed in real-time and offer instructions for reaching study staff for seeking immediate help. According to the protocol, the participants receive a notification every evening at 8 pm to complete their daily survey. They are instructed to complete the survey between 8 pm and the time they go to bed. The surveys expire overnight at 2 am, 6 h after being sent.

Table 1. Items of the daily surveys.

No	Item	Explanation provided by the RA at briefing
1	I felt cheerful	How happy and joyful did you feel today?
2	I felt stressed	Did you feel stressful or tense today?
3	I felt down	Did you feel unhappy or low today?
4	I felt strange	Did you or the world around you seem weirder than other days, today?
5	I felt content	Did you feel satisfied with how things turned out today?
6	I felt suspicious of others	Did you find it hard to trust other people today?
7	I felt relaxed	Did you feel calm and peaceful today?
8	My thoughts were racing	Were your thoughts going very fast, or too fast in your mind, today?
9	I felt enthusiastic	Did you feel excited about things today?
10	I heard things that others could not hear	Did you hear sounds or voices that others did not seem to notice today?
11	I felt empty	Did you feel hollow or vacant today?
12	I felt anxious	Did you feel nervous and uneasy today?
13	I could concentrate well	How well were you able to focus on things you needed or wanted to do today?
14	I felt irritable	Did you feel grumpy, short-tempered, or easily annoyed today?
15	I felt worried	Did you feel troubled or concerned today?
16	I could enjoy nice things when they happened	How well were you able to experience positive feelings when nice events happened today?
17	I felt that others could read my mind	Did you feel like other people could access your thoughts directly today?
18	I felt lonely	Did you feel alone today?
19	I felt very special	Did you feel like you were different from other people today?
20	I felt energetic	Did you feel like you had the energy to do things today?
21	I felt that others could control me	Did you feel like you were under other people's control or direct influence?
22	I felt motivated	Did you feel like doing something or being active today?
23	I felt like my thoughts were confused or blocked	Did you feel like your had difficulty following your thoughts or that you had a hard time thinking clearly?
24	I saw things that others could not see	Did you see people or things (like shadows, animals, or lights) that others did not seem to notice today?
25	I could handle what came my way	How well were you able to cope or deal with things today?
26	I was able to function well	Did you feel like you could do what you needed or wanted to do today?
27	I spent time with other people (live)	How much time did you spend in the company of other people, face-to-face?
28	I spent time with other people (online/ digitally)	How much time did you spend in the company of others online (e.g., via FaceTime, WhatsApp or Zoom)?
29	I experienced a negative or unpleasant event	How many times did you experience something which you found negative, stressful, or unpleasant?
30	I experienced a positive or pleasant event	How many times did you experience something which you found positive, nice, or pleasant?
	Feel free to go to the voice diary	This final item is an invitation to tell us something about how you have been doing or feeling lately in the voice diary. Here you can simply talk about what's on your mind.

Voice diaries. The voice diaries offer participants the possibility of recording up to 2 min of free speech to talk about any topic they wish. This voice diary was not included in the initial protocol but was suggested by a parallel team focusing on speech and voice analysis [journal to add citation to Bilgrami et al. paper please]. There were some concerns about offering participants the option to provide speech samples at random times throughout the day versus prompting participants at predefined times. Guided by privacy concerns, the committee opted for the latter, and a new voice module was created in mindLAMP, which prompts for a voice sample once per day at the same time as the surveys. In response to concerns raised by institutional review boards, careful instructions were created around the prompt so users would understand what not to disclose in their audio recordings Prompts before taking any voice diary also review that no responses are reviewed in real-time and offer instructions for reaching study staff to seek immediate help.

Passive data

Platform selection. PRESCIENT originally selected Aware (https://awareframework.com/) as their preferred platform to collect passive data, whereas ProNET opted for mindLAMP (https://www.digitalpsych.org/lamp.html). Given the overlap in functionality between both platforms and the preference to use the same app in both networks, in order for data collection to be harmonized, mindLAMP was selected by both networks as it had better integration with Apple Health/SensorKit and Google Fit/ Health. While Apple and Google's novel data streams are not part of the study, this functionality in mindLAMP offers potential redundancy that will future-proof the study for any potential changes to how this type of data can be collected over the course of the study.

Domains of passive data. While there are many domains of passive data that smartphones can collect, three domains were selected for this study because of their commonality across all smartphones and operating systems (Apple and Android), clinical/ scientific potential, and ease of collection. The three domains of passive data selected were: 'Geolocation', assessing raw global positioning system (GPS) coordinates collected at a frequency of 5 Hz, 'Accelerometer,' assessing motion at 5 Hz, and 'Screen state,' which records whether the phone screen is on or off (but no screen content related data). These passive data streams are collected continuously throughout each day. While technically feasible, metrics related to specific screen activity (e.g., types of app used) or phone activity (e.g., call number and text content)

were not included as they violate Apple and Android terms of service, creating ethical, legal, and scientific challenges. Through Apple SensorKit, screen-related metrics can be selected for collection but this functionality is not yet supported by Android smartphones. Thus this study did not collect phone or screen activity data. Instead, domains were picked that were accessible on all devices (Apple and Android) and did not violate terms or conditions.

The GPS sensor measures the longitude and latitude of a user at a designated frequency. As a requirement for smartphone apps to be running in the background and collecting any passive sensor data, GPS collection permissions must be accepted to obtain high-frequency data from any sensor, even if the mindLAMP app does not request or capture GPS. The accuracy of the GPS data will vary based on phone model and open-sky conditions but for most smartphones will be between 5 and 20 m. This enables the creation of metrics around mobility patterns, hometime, and environmental exposures. This also means the GPS data contains potentially identifiable data and warrants the strong technical, legal, and ethical protections put in place to protect confidently in this study.

The triaxial accelerometer measures acceleration applied to the device. Each measurement is measured in acceleration due to gravity (Gs) and is taken relative to the coordinate plane of the device. For example, a device resting face-up on a flat surface will report a measurement with the coordinate values <0, 0, 1> and face-down will report <0,0,−1>. This data enables metrics of sleep duration, sedentary/physical activity, and other motion-related features to be derived with the assumption that the phone is often on the participant's body.

The screen state sensor records when the screen is turned on or off, when the device is locked or unlocked, and any changes in battery level from charging or discharging the device. This sensor does not record the amount of time spent within specific apps, content nor how many notifications are received. This enables the creation of metrics related to daily screentime as well as patterns of phone use, with routine battery charging perhaps a potential marker of executive functioning.

Given that participant preferences for sharing data vary, a solution was found in offering three configurations of the mindLAMP app in which passive data are collected for either (1) all sensors, (2) all sensors except geolocation or (3) no sensors at all (i.e., daily ambulatory surveys and voice diaries only). This customization was feasible within the current functionality of mindLAMP. The open-source nature of mindLAMP means that others can recreate the exact configuration of the app for this study or also expand upon it by activating new sensors not utilized in AMP SCZ such as Bluetooth or the Apple SensorKit suite. The passive data collected on these three domains enable the creation of a myriad of secondary features related to behavior, mobility, and sleep. Examples of secondary features include hometime, mobility entropy, access to green spaces, local temperature, and others that can be created from the raw data. While code and an application programming interface (API) called Cortex already exists a pipeline to transform these data streams into secondary features (https://docs.lamp.digital/data_science/cortex/what_is_cortex/), offering the raw data enables research teams to use these existing functions or to develop novel methods as they choose.

Actigraphy

Actigraphy through a secondary device that can be worn continuously over extended periods allows for a more robust characterization of sleep and daytime activity that complements the movement patterns captured by the smartphone. In addition to measuring and identifying sleep epochs, continuous wrist actigraphy has the potential to capture activities of daily living, including eating, grooming, and washing, which can be of interest in individuals experiencing mental health issues.

To collect actigraphy data through a separate device, two devices were considered: GENEActiv and Axivity. Both were of interest because they capture raw data and share these data in a non-proprietary format. The lower cost of Axivity drove the final decision.

Participants are asked to wear the Axivity wristband (on their non-dominant hand) for the 1 year duration of the digital component of the study. These devices are water resistant so can be worn while bathing. Devices are retrieved and exchanged for a new sensor every 4 to 5 weeks due to battery constraints. Accelerometers are configured to collect data at a sampling frequency of 12.5 Hz and sensitivity of ±8 g on lower power mode. The raw data output is retrieved from the wristband using freely available OMGUI software and saved as raw data files containing acceleration data for *x*, *y*, and *z* movement axes for further processing using open source processing pipelines such as Deep Phenotyping of Sleep (DPSleep) (Rahimi-Eichi et al. 2021[50]). DPSleep is used in this project to preprocess and quality control the collected data. The configuration settings were selected to achieve at least 47 days of battery life which would offer some buffer between study visits when the sensor (containing the battery) would be swapped.

Procedure of protocol development

Combining all the above-described elements, the study procedure was developed to optimize customization to participant preferences, the range of data collection, and study feasibility. Through a series of open meetings, iterative plans were shared and updated. The protocol was also refined through feedback from participants and discussions with research staff around procedures. This included members of the AMP SCZ Executive Committee with lived experience of CHR and additional meetings with this committee were convened to discuss privacy and ethical considerations around the digital phenotyping aspects of the study. Numerous adaptations were made to the mindLAMP app based on both participants' and researchers' feedback to ensure survey assessments were easy to engage with, instructions were clear, and data could be shared back in a meaningful manner. These ranged from user interface/user experience (UI/UX) improvements, creating new features like a voice diary, translating the app into numerous languages (Spanish, Korean, Italian, French, German, Korean, Chinese Simplified, Chinese Mandarin), improving the consent procedures around the app, and creating new pathways to share data back, among others. Finally, the AMP SCZ Steering Committee also offered input on the final protocol.

Engagement

Participant engagement is always of importance but deserves particular consideration in the current study for two reasons. First, the digital component is the only optional component of the overall AMP SCZ project and thus extra motivation and investment are required. Second, data collection continues for one year for each participant and thus participants are asked for long-term continued engagement. While the transparent nature of the data capture and sharing of the raw data will enable replication of data processing and analysis pipelines, missing data is common in the digital component of this study. Therefore, we took several steps to promote and encourage participant engagement designed to minimize missingness.

First, to minimize participant effort and to maximize possibilities for inclusion, the mindLAMP app was translated into eight languages noted above. This new content and language was back-translated by medical experts to ensure accuracy. As such, no translation was required by end users. This involved direct translation of all instructions in the app itself as well as translations

of all survey assessments. Local medical translation services were used and the results checked by local study teams and patients.

Second, on top of financial compensation, participants receive access to their own data. Insight into their own data has been mentioned by participants as one of the major reasons to engage in time-intensive longitudinal studies[51]. Responses to previous daily surveys can also be easily accessed in the mindLAMP app, making feedback to participants regarding their own data highly feasible. To date, there are few precedents for sharing passive data in the literature (Chang et al.[52]; Scheuer and Torous[53]. Currently, teams in AMP SCZ are working on plans to offer feedback on the passive data both in the app and at check-in visits. Each team shared their experiences around sharing data to inform strategies. The NIH All of Us Research Program (https://allofus.nih.gov/) was used as a template for the consent process, noting that feedback of the results from these digital data streams does not include diagnostic data. Of note, the study did not cover the costs of participants' smartphone data plans as the mindLAMP app only transmits data over wifi (not data). Given the high rates of smartphone ownership in this population, each study site was provided with two extra smartphones to offer in the unlikely case of a participant who may be interested in partaking but did not own a smartphone.

Third, we provided extensive protocol training and instructions to be followed by the research assistants (RAs) and highlighted the importance of building rapport with participants. We emphasized that given the one-year length of the study, it is likely that participants will need (at least some) support and encouragement to stay engaged in the project. RAs conduct comprehensive briefing sessions with study participants and contact them monthly to discuss any practical (e.g., issues with phone settings) or motivational (e.g., feeling overwhelmed or bored) issues they may be experiencing. During these sessions, the RA aims to work together to overcome any possible barriers.

Finally, as passive data collection requires active engagement with the mindLAMP app, regular use is highlighted. Trainers emphasized to research assistants and participants that active engagement is necessary for good data quality for both the daily and passive surveys. In addition, we also included specific situations to avoid in the protocol, such as the phone being placed into low power mode (which causes an immediate cessation of passive data collection) to maximize app engagement and thus improve data quality. Specific research on data quality and factors to optimize it will be important methodological outcomes of the digital component of this study.

Study procedures

Unique aspects of the study procedures include technical deployment, implementation, and data processing procedures.

Deploying mindLAMP. mindLAMP is deployed in a decentralized manner. Full details are offered on the website: docs.lamp.digital and also presented across several papers[54,55]. Each organizational unit hosts their own independent instance of mindLAMP on-premise via their organization's computing cluster, or via a supported cloud hosting provider as requisitioned by the organization. These instances of mindLAMP are deployed through Docker Swarm (https://docs.docker.com/engine/swarm/), which isolates individual components of the platform (such as the database server, web/API application, adaptive interventions, etc.) for improved fault tolerance, security, and ease of deployment. This enables mindLAMP the potential for deployment in different settings, as well as interoperability with other organizational services such as firewalls and authorization systems that use Active Directory or OAuth. While mindLAMP is optimized for Amazon Web Services, other deployments are thus possible but require specialized technical support[56]. In addition, the components of mindLAMP communicate with each other via the LAMP API, a secure encrypted protocol that also allows external tools and data science scripts to interact directly with hosted instances of the platform. The three independently deployed instances of the mindLAMP platform correspond to the associated three NIMH-supported research projects: ProNET, PRESCIENT, and PREDICT DPACC. The ProNet and PRESCIENT instances of mindLAMP are shared with their respective clinical sites, so that each clinical site has access linked to the appropriate hub. All instances of mindLAMP are also interlinked and communicate with each other using this protocol, allowing data scientists to analyze data in real time across every organization using mindLAMP.

Building the study protocol. The mindLAMP platform offers researchers the possibility to build their own study protocol. Prior examples of studies are cited for reference here (Shvetz et al. 2021[57]; Gansner et al. 2023[4,12,43]). Customizing the platform for the AMP SCZ study required a consensus regarding which features to use. As noted above, a consensus was reached for passive data and the decision was made *not* to utilize the 'Learn' and 'Manage' features of mindLAMP as those are more relevant to interventions as opposed to the observational nature of AMP SCZ (Chang et al. 2023[58]). For creating the survey battery, as noted previously, a consensus on the 30 items was obtained, and one protocol was built for both networks and used for all participants. This protocol contained the 30 daily survey questions listed in Table 1 and the accompanying response options. Questions and instructions were available in eight languages, covering all languages in the participating countries.

Training of research assistants (RAs). A detailed Standard Operating Procedure (SOP) was written to guide the RAs through all steps of (i) creating mindLAMP accounts for participants, (ii) onboarding participants during a briefing session in which they install mindLAMP on the phone, go through the app and the survey questions together and, (iii) a review of the overall procedure of the study throughout the year, including monthly check-ins and at the end of the study. The SOP was illustrated with screen shots for every step in the digital preparations and the onboarding. Separate instructions were shown for both the iPhone and the Android phones. The SOP is also regularly updated based on feedback from RAs and participants, and changes are made to optimize the process. The full SOP can be found via the AMP SCZ website. As an additional resource, across all sites, we deployed a number of training procedures, including an instruction video of the onboarding session, a detailed training plan for the RAs and the live training sessions done via video calls. Custom troubleshooting checklists and instructions were also deployed across all sites. The SOP will be posted on ampscz.org.

Data processing. The raw signal data captured from mindLAMP is transmitted and stored like the other smartphone data streams. Once on the secure study server, processing the data involves first transforming this raw data into primary features (e.g., number of locations visited, time at locations, number of steps taken, etc.) and secondary features (e.g., sleep duration, hometime, etc.). A detailed explanation of raw, primary, and secondary data features is presented below. This pipeline is flexible so that new primary and secondary features can be created by any team to explore new aspects of the data. As these methods are native to the mindLAMP API, researchers can directly pull data from the server and run commands to generate the following features (see Fig. 1):

1. Raw Features: A "raw" feature is a digital Cortex-compatible abstraction of a low level data stream from the LAMP Platform (for example, survey question responses or

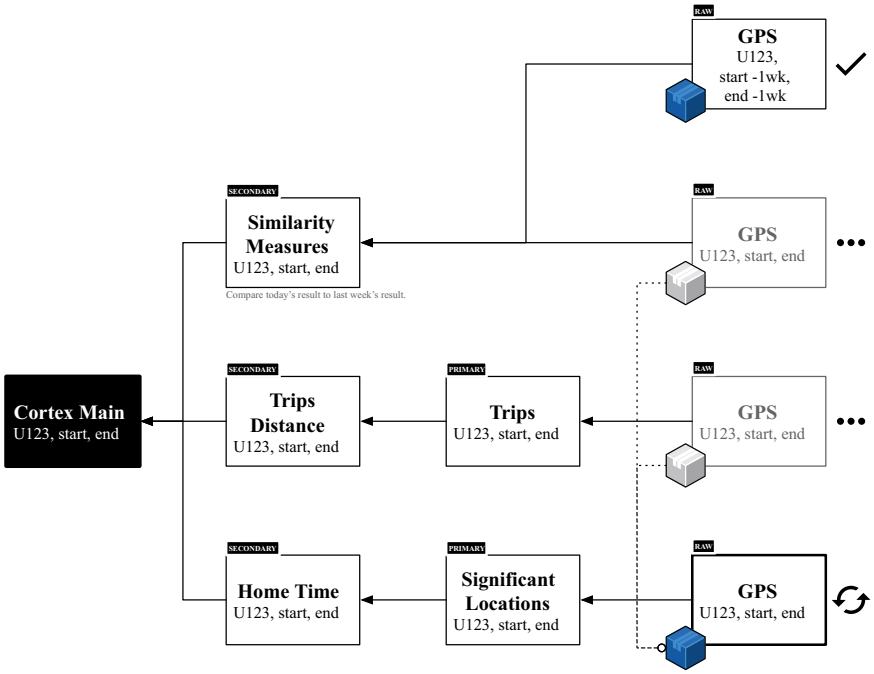

Fig. 1 Example of raw, primary, and secondary features inside the Cortex platform, which is a software pipeline that transforms digital phenotyping raw data into meaningful features. In this figure, raw data (on the far right) is GPS and primary features are trips and secondary locations. Secondary features are derived from primary features and, in this example include home time, trip distance, and similarity measures of mobility patterns across different weeks.

accelerometer data). The integration of raw features allows for simplified development of analysis code both within Cortex and outside of Cortex, by avoiding the need to switch contexts between the higher-level Cortex abstractions and the lower-level underlying LAMP Protocol when writing code. For information about raw features, please see the documentation on Feature Types in docs.lamp.digital.

2. Primary Features: A "primary" feature is a miniaturized abstraction around a raw feature that can either be used directly, or used within *multiple* secondary features and analyses. It acts as a reusable intermediate or bridge between these higher-level representations features and lower-level raw data streams. For example, Significant Locations is a primary feature that processes raw GPS data and groups these data points together into weighted traveled regions of significance.
3. Secondary Features: A "secondary" feature is a composite (i.e., summary) clinical/behavioral representation of multiple data streams, either through raw or primary features. Secondary features are additionally windowed by time resolution (i.e., "each day" vs. "each week"). For example, Home Time is a secondary feature that buckets Significant Locations by the specified resolution and determines the amount of time an individual spent at home within that time window. Additionally, Trip Distance is a secondary feature that also relies on the Significant Locations primary feature to calculate the distance traveled by an individual per time window.

Like any clinical research, the quality of the data (here represented by the degree of coverage of the sensors and lack of missingness) will determine the confidence in the resulting behavioral features. It is important to keep in mind, however, that the field of smartphone digital phenotyping for mental health is rapidly evolving and novel methods and approaches are constantly being developed. The primary and secondary features themselves likely offer value as markers of the environment (e.g., green space), sleep duration, activity levels, screen use duration, hometime, etc. Applying these primary or secondary features with statistical methods such as anomaly or change point detection may thus help to detect periods of elevated risk of adverse clinical outcomes (e.g., relapse (Cohen et al. 2023[59]) or conversion to psychosis). Related methods of anomaly detection may also be deployed directly on raw data to detect similar outcomes (D'Mello et al. 2022[60]).

DISCUSSION

The protocol described in this paper reflects the largest international effort to capture harmonized DHT-derived data collected from both smartphones and wearables in individuals at CHR for psychosis and other health outcomes. Important elements of the study include its scale, the use of a single app that is offered in multiple languages to capture both digital phenotyping and ambulatory assessments, and the availability of multiple versions of the study protocol to match participants' willingness to share their passive data. Other important elements include the direct returning of results in the app, the sharing of raw results to enable others to analyze the data, the replicability of these methods resulting from use of open-source tools, transparent protocols, and accessible analysis pipelines.

The digital component of the AMP SCZ study was designed with ethical, legal, and social implications in mind. Considering the six core domains of the Ethics Checklist for digital mental health research[61], it is possible to consider how this protocol discussed above address (1) informed consent; (2) equity, diversity, and access; (3) privacy and partnerships[62,63]; (4) regulation and law; (5) return of results; and (6) duty to warn and duty to report. The digital component is not only optional but the informed consent offers three unique ways to partake. The mindLAMP platform has been designed to support diverse populations and the protocol ensures phones are accessible to anyone wishing to partake who does not have one. Offering the app in eight unique languages also removes barriers to participation. Longstanding and ongoing partnership with patients, the open source nature of the platform,

and robust privacy protections help build trust. The protocol also complies with all local, national, and international regulations and offers innovation in secure data sharing with the NIMH Data Archive (NDA) and regulation around researcher access to the data. In addition, the mindLAMP platform is the only digital phenotyping platform with research supporting return of results to end-users (Scheuer et al. 2022[53]) in line with a recent 2023 consensus around the importance of return of results in digital phenotyping research[51]. Finally, the language within the app around each assessment and clear use of the data outlined in the informed consent and procedures with the NDA ensure that duty to warn and report is fully addressed.

The DHT-derived data collected in this project will enable us to map the experience of mental health in daily life through a high-density (volume, velocity, variance of data) lens and makes possible the potential to identify new markers for CHR. The digital collection arm is only one aspect of the AMP SCZ study. Thus, promising opportunities also lie in matching or linking DHT-derived data with other data domains. Of note here, recent reviews of digital markers for psychosis spectrum illness reveal a plethora of proposed digital markers (ref. [10], Fonseka et al. 2022[62]; Bell et al. 2023[49]), but to date none have been well validated against behavioral, cognitive, neurological, or genetic measures like those also being collected in this study. The combined and final dataset from AMP SCZ thus reflects a unique opportunity to explore the utility of these digital markers and their neural correlates in individuals at risk for psychosis.

One important issue in digital phenotyping research is reproducibility. A recent review of smartphone platforms used to study schizophrenia found that over 50% of the apps used in past research studies were no longer available (i.e., the app was removed from the Internet or from the app stores) and only 15% were publicly accessible for use today (Kwon et al. 2022[64]). This presents a threat to reproducible science. Our approach in AMP SCZ aims to solve this problem through the use of the open-source mindLAMP tool that is available on both Apple and Android platforms and already widely used in mental health research (Bilden et al. 2022[63]). The flexible deployment of mindLAMP, reflected in this protocol through hosting it at multiple institutions and customizing features, mirrors the opportunity future research teams have to validate, expand, and/or to build upon this protocol.

As with any assessment protocol, there are also challenges. Digital phenotyping methods, especially when collecting data for longer periods of time, require careful attention to data quality. Without proper setup and checking to ensure all phone settings remain as assigned (a challenge as the phone itself may suggest to the participant to disable data sharing), possibly leading to the coverage and quality of sensor data falling quickly to unusable levels. Through close collaboration with the Digital Biomarker Team in AMP SCZ, protocols and procedures are designed to detect issues early on and provide the critical feedback to the local teams on the ground to assist participants. A related challenge is thus in setting a bar for low data quality as the density of data necessary to create behavioral features will vary based on the scientific questions asked. The need for standards around digital phenotyping is clear. The results from this arm of AMP SCZ will help offer guidance around defining such standards.

DATA AVAILABILITY

The data used in this paper are available via scheduled releases at the NIMH Data Archive (NDA) AMP SCZ Data Repository (https://nda.nih.gov/ampscz).

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AUTHOR CONTRIBUTIONS

J.T. wrote the first draft. All authors edited, contributed to the writing, and approved the final manuscript.

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ADDITIONAL INFORMATION

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