THE FDA MYSTUDIES APP: PATIENT CENTERED OUTCOMES RESEARCH TRUST FUND ENABLER FOR DISTRIBUTED CLINICAL TRIALS AND REAL WORLD EVIDENCE STUDIES

COLLECTION OF PATIENT-PROVIDED INFORMATION THROUGH A MOBILE DEVICE APPLICATION FOR USE IN COMPARATIVE EFFECTIVENESS AND DRUG SAFETY RESEARCH

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October 10, 2018

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. This project was funded by the Office of the Secretary PCORTF under Interagency Agreement #750115PE060034 with the FDA.

The FDA MyStudies App: Patient Centered Outcomes Research Trust Fund Enabler for Distributed Clinical Trials and Real World Evidence Studies

Collection of Patient-Provided Information Through a Mobile Device Application for Use in Comparative Effectiveness and Drug Safety Research

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I. BACKGROUND

The FDA MyStudies App is designed to facilitate the input of real world data directly by patients which can be linked to electronic health data supporting traditional clinical trials, pragmatic trials, observational studies and registries. It was developed by the FDA and private sector partners, but source code and documentation is being released to the public so the app and patient data storage system can be reconfigured and rebranded by other organizations conducting clinical research. The FDA MyStudies App has several important features. The data storage environment is secure and supports auditing necessary for compliance with 21 CFR Part 11 and the Federal Information Security Management Act, so it can be used for trials under Investigational New Drug oversight. The app is configurable for different therapeutic areas and health outcomes which reduces software development hurdles for non-FDA users. The data storage environment is partitioned to support multi-site trials or "distributed database" studies. The code for MyStudies will be open source so software developers can improve upon its capabilities.

II. INTRODUCTION

A. PROBLEM STATEMENT

The proliferation of "Big" electronic health data sources offer several potentially positive attributes for comparative effectiveness and drug safety research. Data sets with "breadth," large numbers of individuals, may reduce selection bias by capturing a larger percentage of the underlying source population targeted for study. As more and more health data elements are recorded electronically for each individual, "depth" increases which improves the chance that relevant exposures, outcomes, and confounders are recorded. Finally, different types electronic healthcare data have the potential to increase "diversity" and enable "cross-checking" which might improve accuracy.

Despite the aspirational "big data" vision, currently most comparative effectiveness and drug safety research in the United States relies on healthcare claims for payment or electronic health records used to document care. Healthcare claims provide breadth and consistent capture of person-time during enrolled periods because most medically-attended health events trigger claims for payment. In contrast, electronic health records provide increased depth, but except within integrated care delivery and payment systems, they do not capture consistent person-time. Care which is recorded in a separate electronic health record system will not be visible in the primary electronic health record system that is being used as the data source for research unless the systems are linked. Even when claims and electronic health records are linked, important information potentially affecting outcomes is typically not captured. Examples of such information include but are not limited to adherence to prescription medications or therapies, health outcomes that are not medically attended, and characteristics which are inconsistently recorded in electronic health data such as illicit drug use, tobacco use, vitamin and supplement use, race, socio-economic status, educational attainment, and over-the-counter medication use.

Neither claims nor electronic health records directly capture the patient perspective, and effectiveness studies often have endpoints such as functional status scales that depend on patient input. Furthermore, when treatments are compared it is important to follow patient reported and electronic health outcomes in a prospective manner and calculate rates among cohorts that have provided informed consent. While claims and electronic health records have provided access to secondary data

from large populations, enrollment for prospective studies, trials, or registries remains challenging given the substantial resources involved for the research team and the effort required by the patient to participate in calls, online surveys, and clinic visits. A patient-centered app-based electronic method suitable for capturing the patient perspective and linking it to existing electronic health data that is scalable, secure, configurable, reusable, compliant with clinical research and regulatory needs, and capable of supporting defined research cohorts is necessary to expand the capacity of comparative effectiveness and drug safety research.

B. SOLUTION

The Affordable Care Act of 2010 (ACA) directed the U.S. Department of Health and Human Services (HHS) to build data capacity for patient-centered outcomes research (PCOR) through the Patient-Centered Outcomes Research Trust Fund (OS PCORTF). The key deliverable of this project is a mobile device application and patient data storage environment that can securely and transparently record the patient perspective and enable data linkage to existing electronic health data in distributed or centralized studies, trials, or registries. The mobile device application and patient data storage environment are designed to support the broad range of potential healthcare outcomes research topics through a configuration portal since development of multiple similar systems on a topic-by-topic basis is resource intensive. The project was conceived by Dr. David Martin, now the Associate Director for Real World Evidence Analytics in the Office of Medical Policy at the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Funding was provided by the Patient-Centered Outcomes Research Trust Fund through a competitive application process administered by the Associate Secretary for Planning and Evaluation (ASPE) of the Department of Health and Human Services. The project was overseen by the FDA's Catalyst Program under contract HHSF223201400030I. Deliverables will be placed in the public domain to enable private and public sector organizations to adapt the system to support specific single and multi-site studies or engage in additional app development (e.g., optical capture, new active tasks, etc.).

C. IMPLEMENTATION CONCEPT

This project included development of the app and storage environment, but it also included implementation within two existing national distributed electronic healthcare systems, Sentinel and PCORnet, that support comparative effectiveness and drug safety research. The Sentinel system was developed by the FDA in response to a Congressional mandate contained in the Food and Drug Administration Amendments Act of 2007. It is a national electronic monitoring system for medical products routinely used for regulatory decisions by the FDA which relies primarily on an underlying distributed database of administrative healthcare claims data. The Patient-Centered Outcomes Research Institute was established as a result of the Affordable Care Act of 2010, and it developed a distributed database, PCORnet, consisting primarily of electronic medical records from participating healthcare delivery systems. The purpose of the implementation phase was to ensure the system could operate from both a technical as well as regulatory perspective.

III. METHODS

A. BACKGROUND

Harvard Pilgrim Health Care Institute (HPHCI) was selected by FDA and ASPE to build the generalizable mobile app platform. As proof-of-concept, this project piloted a descriptive study of exposures and healthcare outcomes among 64 pregnant women. Pregnant women were chosen as the pilot cohort for this project as pregnancy is among the most complex use cases encountered in pharmacoepidemiology and electronic health services research. Investigators generally cannot obtain complete information from claims data about gestational age, birth outcomes, medication use, supplements, tobacco use, occupational exposures, or other maternal and paternal characteristics. While the mobile device application was configured for this specific use case, it is generalizable and can be used for studies in other therapeutic areas and patient populations.

To reduce the initial implementation and design costs, minimize maintenance and enhancement costs over time, and enable future external developers to modify and expand the capabilities of the app, the project sought widely available software resources for creating mobile device studies and surveys. Apple Computer publishes an open-source tool suite called ResearchKit, which provides a variety of tools that can be used by app developers to construct survey apps for iOS devices (Apple smartphones and iPads). ResearchKit includes standard modules for eligibility and consent as well as different question types and a wide variety of response types. A roughly comparable set of capabilities for Android devices is available as ResearchStack, developed by Cornell Tech. These tool suites are commonly used to deploy mobile app based studies, which made them well suited for the platform.

As the pregnancy pilot was the first application under the FDA Catalyst Program to use mobile devices, the project consulted closely with four FDA approval bodies through the design phase: the Sentinel Audit team, the Cloud & Mobile team, IT Security team, and the Privacy team. These groups reviewed the technical architecture, including both the mobile device and the hosting architectures, to ensure the app and storage environment were aligned with emerging FDA standards for mobile applications. They also made recommendations for improvement that the project team implemented.

To maximize dissemination of the project's results, all software developed for this project will be placed in the public domain, available through GitHub.

B. VENDOR SELECTION

HPHCI does not have app development capabilities in-house, so two requests for proposal (RFP) were issued, a developer RFP for the mobile app and an RFP for the supporting infrastructure. Recent mobile apps built on the ResearchKit and ResearchStack suites were reviewed to identify potential respondents. Companies could respond to one or both RFPs. Three organizations responded to the developer RFP alone, two responded to the infrastructure RFP alone, and two responded to both.

Boston Technology Corporation (BTC) was selected as the developer of the mobile app. BTC displayed the best understanding of our objectives and had considerable expertise using ResearchStack as well as ResearchKit. Other potential vendors had experience with ResearchKit, but had little or no experience using ResearchStack. LabKey Corporation was selected as the infrastructure provider. They offered the most flexible infrastructure purpose-built for biomedical research.

Coordinating between two separate vendors required additional effort as BTC and LabKey used different development methodologies. The end user tools were built from the ground up by BTC via a waterfall process that necessitated extensive requirements gathering before development. The storage

environment was built on an existing product offered by LabKey, so additional modules and functionality were added via an agile development process. However, this approach utilized strengths of the two strongest candidates.

C. DATA PARTNER SELECTION

A data partner was also required to conduct a study as proof of concept of the mobile app platform. A workgroup opportunity statement was circulated to all Sentinel Data Partners. The key attributes of the desired partner included: (a) current Sentinel Data Partner; (b) can include an obstetrician with an active panel of patients in the workgroup, where the obstetrician need not be affiliated with Sentinel; and (c) the Data Partner's Sentinel database includes information on patients in the obstetrician's panel.

The criteria also favored Sentinel Data Partners that were also PCORnet Data Partners. Kaiser Permanente Washington (formerly Group Health Cooperative), and its Health Research Institute, best met these criteria and was chosen as the Data Partner. KPWHRI had extensive experience in studies of pregnant women specifically, offered capabilities for developing recruitment materials and conducting outreach via phone and email, and could enlist the participation of patient representatives. As an integrated healthcare delivery system, they have both claims data and EHR, which allowed for additional data matching opportunities.

D. DESCRIPTION OF WORKGROUP

The organizations participating in the workgroup included the FDA, Harvard Pilgrim Health Care Institute (HPHCI), Kaiser Permanente Washington Health Research Institute (KPWHRI), Boston Technology Corporation (BTC), LabKey Corporation, and an investigator from the UCSD component of the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS).

- FDA
    - David Martin, Associate Director for Real World Evidence Analytics
    - IT Security, Privacy, Cloud & Mobile, Sentinel Audit Team on a consulting basis
- HPHCI Staff
    - Jeffrey Brown; Associate Director, Therapeutics Research and Infectious Disease Epidemiology Group (TIDE)
    - Chayim Herzig-Marx; Director, Center for Distributed Analytics and Informatics Systems
    - Zachary Wyner, Senior Health Informatics Analyst
    - Juliane Reynolds; Senior Project Manager
    - Alison Kawai; Epidemiologist
- KPWHRI
    - Sascha Dublin; Associate Investigator, Kaiser Permanente Washington Health Research Institute
    - Predrag Klasnja; Assistant Investigator, Kaiser Permanente Washington Health Research Institute
    - Linda Kiel; Senior Project Manager
    - Ladia Albertson-Junkans, Senior Research Assistant
    - Karen Byeman, Patient Advisor
    - Kacie Washington, Patient Advisor
    - Kate Ziechner, Midwife
- Boston Technology Corporation
    - Shyam Deval, President
    - Ranjani Rao, CEO

  - Shanthala Rao, Senior Project Manager
  - Vinay Raja, Senior Programmer
  - Vasant Kumar, Senior Programmer
- LabKey Corporation
  - Adam Rauch, Vice President of Software Development
  - Susan Hert, Senior Programmer
  - Angelica Omaiye, Research Assistant
  - Brian Connolly, Customer Relationship Manager
- University of California San Diego/VAMPSS
  - Christina Chambers, Professor of Pediatrics

Responsibilities of the FDA included providing overall leadership to the project, approving all work plans and designs, leading the scientific "sub" workgroup, and serving as liaison with ASPE. David Martin was involved in all aspects of the project –software requirements, study protocol, IRB, questionnaire design, recruitment material development, app testing, data analysis, co-authorship of the final report, and reporting and dissemination in professional venues.

Responsibilities of HPHCI staff included writing and negotiating statements of work, developing functional and technical requirements for the mobile app software and the infrastructure, oversight of technical implementation, day-to-day project management, securing approval from FDA's IT Security, Privacy, and Cloud & Mobile teams, testing software and infrastructure capabilities, maintaining project documentation, quarterly reporting to ASPE, participating in questionnaire design, configuration of the mobile app platform and supporting servers, data analysis, dissemination in professional venues, and authorship of the final report.

Responsibilities of KPWHRI included securing IRB approval, leading development of recruitment materials including consent documentation, identification and recruitment of patients, maintaining the mapping that enabled linking patient-provided information with Sentinel and EHR data, participating in software design and user acceptance testing, participating in the scientific "sub" workgroup, conducting linkage and extracting data from electronic health data systems, conducting data analyses, and dissemination of findings in professional venues and publications. KPWHRI also conducted exit interviews with the patient cohort after data collection concluded to characterize the participant experience in the pilot and with the app. A summary of findings from exit interviews can be found in Appendix 1.

E. DESIGN

1. Process

Requirements gathering began in August 2016, immediately after vendor selection. HPHCI, LabKey, and BTC teams held regular meetings to document business requirements. A tool called MindMaple was utilized by BTC to capture these requirements visually. Due to an initial delay while the agency determined if it needed separate policies and procedures for FDA-Catalyst, engagement with a data partner for the project was delayed. Because the entire scientific "sub-workgroup" could not be formed without the data partner's participation, questionnaire development lagged requirements gathering and app design throughout the project. The KPWHRI principal investigator joined the workgroup in September 2016 at which time a kickoff meeting with all workgroup members was held. KPWHRI workgroup members including scientific and patient representatives were recruited over a period of several months with the last member, a nurse midwife substituting for an obstetrician joining in the spring of 2017. KPWHRI members were invited to requirements gathering meetings after the contract

was signed but requirements gathering was complete by January 2017. In late January 2017, Christina Chambers, an investigator from the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), a system for evaluating medication and vaccine safety in human pregnancy, provided epidemiologic expertise during the first meeting of the scientific workgroup. She described procedures, methods and questionnaires used by VAMPSS to obtain primary data from pregnant women. A key goal of this phase was to balance the requirements for a pregnancy-focused application with the broader mandate to deliver a generalized platform that allows for distribution of studies and questionnaires.

After finalization of requirements, the LabKey team worked extensively with the BTC team to divide up the development effort, convert business requirements into final specifications, and determine the appropriate communication protocols between system elements. LabKey was responsible for development of all aspects related to the storage environment, BTC was responsible for development of mobile app and Web Configuration Portal (WCP) described in later sections of this report. FDA and the HPHCI team reviewed and approved each specification before development work began.

2. Final Design

The system contains three elements: two functionally equivalent mobile applications (apps), based on the Apple ResearchKit and Android ResearchStack frameworks, the Web-based Configuration Portal (WCP) for configuring studies and other elements accessed via the apps, and a HIPAA and FISMA, 21 CFR Part 11 compliant storage environment from which study participant responses and consent forms can be accessed and downloaded.

The Federal Information Security Management Act (FISMA) is a law that authorizes the Secretary of Commerce to promulgate information system security standards that are compulsory for all federal agencies and commissions the National Institute of Standards and Technology to develop those standards. The most current version of the NIST document describing these standards is currently in draft form. Because the mobile application project is funded by and intended for the use of the FDA, the design, development, operation, and maintenance of the mobile app framework have adhered to FISMA security standards. These standard, or security controls, are grouped into 20 families, across three categories: administrative, physical and technical. Complying with FISMA requires both documentation of and processes to implement controls in all 20 families. This documentation is maintained by the developers of the mobile app, Boston Technology Corporation and Labkey Corporation.

Administrative controls make up the largest group and include aspects such as awareness and training, individual participation, incident response, planning, audit controls, and system and services acquisition. Physical controls include physical and environmental protection and media protection. Technical controls include access controls, configuration management, privacy authorization, and system and communications protection. How each of the 20 control families is implemented must be documented in a system security plan. Senior management is responsible for providing oversight to ensure that the documented procedures are followed.

The nature of the specific control structures and processes implemented depends upon the level of risk inherent in the business process or information system at hand. NIST standards allow systems and operations to be classified as low, moderate, or high risk. The Sentinel system is classified as moderate risk, so the FDA MyStudies app was also designed to meet the moderate risk level.

Part 11 of Title 21 of the Code of Federal Regulations pertains to criteria for determining that electronic signatures and records are equivalent to hand-written signatures and paper records. The objective is to ensure the authenticity, integrity, and confidentiality of electronic records and signatures. The regulations distinguish between closed and open systems. An open system is one in which access to the

system **is not** controlled by people who are responsible for the content of the electronic records contained in the system. A closed system is one in which access to the system **is** controlled by people responsible for the content of the electronic records in the system. The mobile app is a closed system.

The closed system criteria for determining that electronic records and signatures are equivalent to hand-written signatures and paper records can be summarized:

- The system must provide the ability to authenticate people who should have access to the system. This include both people contributing electronic records or signing electronically as well as people with analytic or reporting access to stored information.
- The system must provide the ability to protect the integrity of information stored in the system and to produce both electronic and human-readable copies of all records stored.
- The system must provide access controls to limit access to authorized parties only and to limit each party's access to appropriate information only.
- The system must provide the ability to time stamp or otherwise provide an audit trail for every electronic record or signature.

The mobile app meets all of these requirements. The mobile app, WCP and storage environment make up an integrated platform that can support multiple mobile app based studies across multiple organizations and can partition response data by study and organization. Data are linked across system elements by a study ID, unique to each study. To use this system, patients simply download a mobile app on their iOS or Android device and enroll in studies as allowed by each study's enrollment protocol. The researcher or sponsoring organization interacts with the WCP and storage environment to configure and distribute studies and analyze responses.

The storage environment consists of three independent servers: a response server to store data captured via the mobile app, a registration server to store participant PHI (email addresses and consent forms), and a metadata server. The metadata server contains all study information configured in the WCP including questionnaires, consent and eligibility content, and study resources. This design was chosen to enable the partitioning of PHI from response data. A unique set of credentials is required for each server; there is no method to combine email addresses and consent forms and response data unless one has access to two servers.

Furthermore, the response server and registration server are custom implementations of the LabKey Server, the core product provided by LabKey Corporation, designed to facilitate the storage and analysis of clinical study data. Two custom add-ons were built for this project: 1) a module that automatically creates a new database schema for every new questionnaire, eliminating the need to manually create a database scheme for each new study; 2) the ability to produce a unique token – called an enrollment token – that can be given to participants to restrict enrollment to a specified cohort or match data to external data sets. All three servers enforce role-based governance; studies are partitioned by participating organization and responses are only accessible by authorized users. Responses are accessed via direct SQL querying, downloading into SAS or R, or exporting to Excel or other common formats.

Study materials, including questionnaire content, consent forms, eligibility questions, and app notifications are configurable and distributed to the apps via the WCP. All ResearchKit and ResearchStack question types can be used in a questionnaire: scale, boolean, single/multi select, scroll wheel, value picker, image select, open text, date/time, map and email. On iOS, participants can utilize data already stored in their iPhone's Health app to answer a question. Active tasks, activities that use phone sensors or game-like mechanics to collect data, can also be distributed on iOS. The system currently allows configuration of two existing Apple ResearchKit tasks, Tower of Hanoi and Spatial

Memory. A third task, a fetal movement tracker, was custom built to provide an engagement tool for future health outcomes research involving pregnant women.

Studies can include multiple patient questionnaires with advanced branching logic and custom scheduling and recurrence. Resources such as PDFs or links to external sites can also be distributed to study participants. To enhance data validity, questionnaires can restrict answers to specific types (numeric, character, height/weight, date/time, geographic) lengths, and formats. Responses can be also be configured to require or exclude specific characters.

In the app, participants respond to questionnaires at their convenience, as responses are stored locally until submission or questionnaire expiration. Participants can visualize their own responses to specific questions over time on an in-app dashboard. This dashboard is configured by researchers using the WCP.

The system was funded by FDA, therefore FISMA level data security was required. However, all system elements are available as open source and there are many potential methods of implementation for this system, which are described in later sections of this report.

F. DEVEOPMENT AND TESTING

Development of the mobile app and WCP occurred from January to July 2017 for the initial launch. A third, preplanned development period occurred from September to December 2017 and added features requested during the testing phase that could not be incorporated by the start of data collection in September 2017. Development of the storage environment occurred from January to June of 2017. Weekly meetings were held with HPHCI, FDA, BTC and LabKey to discuss any issues or roadblocks to development. BTC and LabKey also provided weekly status updates to HPHCI and FDA.

During the first development period for the mobile app and WCP, a prototype app was made available to obtain preliminary feedback from all workgroup members. The KPWHRI team and their 7 patient representatives participated in focus groups to discuss the early prototype and provide feedback to the HPHCI team. Patient representatives were selected for the focus groups from members of the Kaiser Integrated HealthCare system who were currently pregnant or had been pregnant within the past three years.

After the development period, all stakeholders from HPHCI and KPWHRI participated in a formal two-month user acceptance testing process to ensure business requirements were accurately implemented and bugs were corrected. During this process the KPWHRI team and patient representatives were given a near final test version of the application to download to their personal smartphones. The KPWHRI study team provided consolidated user feedback to the HPHCI team on a weekly basis. HPHCI entered any bugs and enhancements found or requested by the KPWHRI team in to a software bug tracking system called Redmine. The BTC team corrected the bugs and published latest version of the test app approximately twice per week during the UAT period. Any bugs directly related to the storage environment were entered into the LabKey ticketing system and corrected based on priority.

Involvement from the KPWHRI team and patient representatives during UAT was instrumental in getting the app ready for production use. They identified areas for improvement in the app study dashboard and identified several bugs that would otherwise not have been identified or corrected. See Appendix 2 for a description of user acceptance testing feedback.

G. IMPLEMENTATION – THE PILOT STUDY

To demonstrate that the platform is a viable data collection tool in a real-world setting, the team developed a pilot study to examine medication use and healthcare outcomes of pregnant women. As described earlier in this report, the study team contracted with Kaiser Permanente Washington Health Research Network (KPWHRI). KPWHRI assisted in five components of the pilot study: 1) the design of the mobile application and focus group testing for application usability as described earlier in this report; 2) study questionnaire design; 3) mobile application testing; 4) recruitment of the study cohort 5) data analysis, and 6) exit interviews of the study cohort. The KPWHRI team enlisted patient representatives and a midwife to contribute to the focus groups, questionnaire design, and development of consent and recruitment materials.

After initially targeting a data collection period of approximately 4-6 months to test the FDA MyStudies application and the feasibility of matching mobile device reported data to Sentinel data, the actual data collection period ended up lasting thirteen weeks. Several factors impacted the timeline.

First, the user acceptance testing phase took longer than expected. The complex nature of the generalized system resulted in more software defects than expected and thus required more time for correction and verification. Second, questionnaire configuration took longer than expected. The study design required more time for configuration and testing than was expected. Third, IRB submission for this novel data collection system required additional documentation related to both the mobile technology as well as to sensitive questions such as illicit drug use history, and it involved three institutions.

Finally, the Apple App store rejected a final update to the app days before the mailing of recruiting materials on the planned start date. This development was completely unexpected since earlier versions of the app were present in the app store and were successfully utilized for user acceptance testing. The team learned that Apple's App store approval process became stricter during the lifecycle of the project, and Apple would now require apps to have branding consistent with the branding of the publishing organization in the App store. This meant HPHCI or BTC could not publish an FDA branded app from the HPHCI or BTC Apple Developer Account. To move the study forward, Apple agreed to allow the FDA MyStudies application to appear in the App Store for the thirteen weeks of data collection period of the pilot study with the understanding that the HPHCI and FDA team would address branding issues before launching future studies.

To mitigate the impact of a short timeline, the KPWHRI team sought to recruit women across all three trimesters to increase the probability of capturing pregnancy outcomes while also demonstrating the capacity to engage with women in the first and second trimesters.

Because the mobile application was funded through the Sentinel base contract under the FDA-Catalyst program, it operates under an approved privacy impact assessment for Sentinel. Because the app supports biomedical research it was exempt from the requirements of the Paperwork Reduction Act.

1. Questionnaire Development

In parallel with software development, study questionnaires were developed by a study workgroup including members from FDA, HPHCI, KPWHRI, and VAMPSS. This workgroup team outlined target areas for medication use and pregnancy outcomes which would be helpful to investigate in this study. The team used template VAMPSS questionnaires provided by Christina Chambers as a starting point. Questionnaire design was a five-month process that determined appropriate content areas, question wording and frequency as well as length and volume of study questionnaires. Drug and medical

condition lists were also assembled and curated to enable targeted options for respondents. Patient representatives in the workgroup were key contributors to this work providing helpful feedback on question content, language, and the best length for each questionnaire. KPWHRI also enlisted a midwife from their network to provide a clinician perspective on the study questionnaires. Study questionnaires are included in Appendix 3.

Once study questionnaires were finalized, the KPWHRI team completed the necessary documents for IRB review, including participant consent and recruitment materials (see Appendix 4). Patient partners participated in the review of these materials along with workgroup members from FDA and HPHCI. Prior to IRB review, the KPWHRI team needed to obtain approval from their legal compliance team to determine that an electronic signature for participant consent in the mobile application would provide appropriate confirmation of consent under laws of the State of Washington. The KPWHRI legal team confirmed that electronic consent was acceptable with the requirement that KPWHRI send the consent form in mailed recruitment materials and maintain a copy of the electronically signed consent form in their records. KPWHRI acted as the lead IRB for the pilot study with HPHCI and FDA ceding IRB review to KPWHRI's IRB.

During the development of the KPWHRI IRB application, the team described the data storage environment and who from the study team would have access to participant data reported in the mobile application and data from the Sentinel system at KPWHRI. During the project, HPHCI required initial access to the data storage environment to assign roles to KPWHRI and to orient the KPWHRI analyst. After the KPWHRI analyst received access, HPHCI assisted with early data analysis with full knowledge of the entire team who reviewed results on the call until one member of the team rechecked the protocol which stated that only KPWHRI would engage in data analysis. This was reported to the KP Washington IRB and it was classified as a protocol violation. However, the violation did not deviate from the informed consent documentation so an IRB modification was submitted and approved by the KP Washington IRB to allow this practice. A key learning from this experience is that the role of administrator staff requires some level of data access to assign roles to and train other users, but the extent of the analysis services provided by administrator personnel can and should be tailored to the needs of each study. Especially if data analysis services are not included or are circumscribed in some way then it is critical for study teams to be very clear about data access roles and responsibilities when developing a protocol. Due to the inherently distributed nature of the app and existing electronic health data, study teams should review the approved IRB application prior to study initiation to re-orient the team to their respective roles and responsibilities.

2. System Configuration

As recruitment materials were being prepared, the HPHCI team entered all study content, including questionnaires, the consent form, study resources and images into the WCP. Final study content was published periodically to a test version of the mobile app for review and approval by the KPWHRI team.

The storage environment was configured by HPHCI to ensure that patient responses and consent forms would be transmitted to the appropriate folders on the response server and registration server respectively. After both servers were configured, access was granted to a data analyst from KPWHRI and access for the HPHCI team was revoked. No other member of the project workgroup had access to both servers.

HPHCI used the response server to create a set of unique enrollment tokens for distribution to the study cohort. HPHCI sent these tokens to KPWHRI study administrators, and KPWHRI assigned a single token to each participant as they identified and enrolled them in the cohort. KPWHRI maintained a record of

token assignments which contained the token and patient ID from the Sentinel distributed dataset maintained by KPWHRI. This mapping allowed KPWHRI to extract EHR data for participating women and link these data with app responses to support final data analysis.

After the data collection period ended, the KPWHRI team sent a de-identified flat file with dates of study enrollment, questionnaire completion, and demographic information to HPHCI, per the IRB modification. HPHCI used this file in conjunction with app metrics available in the app developer accounts to analyze patient engagement. Data tables for these analyses are provided in Appendix 9.

3. Participant Recruitment

KPWHRI contacted 1,070 randomly selected Kaiser Permanente Washington patients who were identified as pregnant based upon data in their electronic medical record (see Appendix 6 for enrollment process). These patients received an invitation letter, study consent form, and study brochure (Appendix 4). The invitation letter contained the unique participant enrollment token. Roughly half of these women received follow-up via phone call to encourage them to participate in the study. Of these 1,070 women, 64 (6%) consented to participate in the study in the mobile application. There was a 4% response from the mail-only group and an 8% response from the group which received phone follow-up. This response exceeded the original study goal of 50 participants. Women were not offered any incentive to participate, and no specific therapeutic area or medication was evaluated. All women in their first trimester of pregnancy were included in the cohort. At the time of the initial cohort pull, approximately equal numbers of women in their second and third trimesters were randomly selected into the cohort such that each trimester represented about a third of the sample. Due to project delays, the cohort was updated approximately six weeks after the initial cohort was identified. All women greater than 36 weeks gestational age as of the refresh date were dropped from the cohort and replaced with as many newly pregnant women as could be identified based on the criteria above. All women were randomly assigned an enrollment token, and half of women were randomly selected to receive a phone call in addition to the recruitment mailing. Approximately four weeks after the first sample refresh, another batch of women in their first trimester of pregnancy were identified and added

4. Study Initiation and Participant Enrollment

The mobile application needed to be approved by Apple and Google to be made available in their app stores - the Google Play Store for Android phones and the App Store for Apple iOS phones. As mentioned earlier, study initiation was delayed due to an unexpected rejection of the FDA MyStudies application from the Apple App Store.

Recruitment letters were mailed on September 26, 2017, and the first participant enrolled on September 28, 2017. To enroll in the study, participants followed these steps:

1. Download FDA MyStudies from either the Google Play Store or the Apple App Store.
2. Register for an account in the FDA MyStudies application by providing an email and password.
3. Verify email address by entering a verification code automatically emailed to them by the registration server.
4. View pregnancy study in the study list.
5. Open pregnancy study and enter enrollment token provided by KPWHRI.
6. Complete and sign study consent.

Participants received notifications of questionnaires as they were available. The questionnaire development team created a questionnaire schedule with the objectives of not over-burdening the women with too many questionnaires to answer at one time and ensuring that all questionnaires were

released before the end of the three-month data collection period. The patient representatives in the workgroup helped investigators craft a schedule which would be reasonable for participants. Questionnaires were released on calendar time which increased the perceived burden for participants enrolling in subsequent weeks because questionnaires that did not expire were sequentially added to the "inbox" on the dashboard. Currently, improvements are being developed to add the capacity to release questionnaires according to the enrollment date of each participant in future studies, and an updated version of the app code will be released.

5. Exit Interviews

At the conclusion of data collection, we invited all who were currently enrolled in the study to reach out to the KPWHRI project manager to discuss their feedback on the study by phone. KPWHRI interviewed 19 women and asked women what they liked and if there was anything they found frustrating about using the app. We also inquired about their comfort with participating in a research study on their phone though an app. While it would have been interesting to investigate why women did not choose to join the study, due to IRB restrictions, we were unable invite women who did not enroll in the study to participate in exit interviews. Declining to participate in the study was considered equivalent to declining to participate in exit interviews. The specific process and script of exit interviews is included in Appendix 1.

6. Electronic Health Record Queries

Participants consented to electronic health record and dispensing queries to provide information on exposures, outcomes, and covariates in conjunction with their responses to questions in the mobile app. These electronic health records serve as source data for the local Sentinel Common Data Model extract used by Kaiser Permanente Washington to contribute to the Sentinel distributed database. Women were identified using a pregnancy algorithm routinely utilized by Kaiser Permanente Washington Health Research Institute and the random sample of women identified was stratified by trimester. Women were identified as pregnant based on the presence of an estimated delivery date recorded by a healthcare provider within an active episode of pregnancy care. Women were included if they were between the ages of 18 and 45 (inclusive) at the time of the data pull, <=36 weeks gestational age based on estimated delivery date, English-speaking, and enrolled in a health plan (excluding Medicaid) during the preceding month. Estimated date of last menstrual period (LMP, start of pregnancy) was imputed based on the number of weeks between the data pull and the recorded estimated delivery date. Women were excluded if they had any code for possible miscarriage between imputed LMP and estimated delivery date, or if they have previously indicated that they do not wish to participate in research. Pregnancy outcomes were assessed by the presence of ICD and procedure codes corresponding to live births, miscarriages (O02xx), or abortions (O03xx) between the start and end of the study period. The ICD-10 codes used for live births can be found in Appendix 7.

Medications were identified using pharmacy dispensings and were initially classified as prescription medications if they were on the formulary. A physician on the research team curated the list and OTC-only medications were transferred to the OTC category. Medication data for acute conditions were pulled 30 days prior to an individual participant's app start date (the earliest date at which she enrolled in the study) through the end of the app. Medications for chronic conditions were pulled from Sentinel up to 110 days prior to app start date to allow for dispensings with long days' supply plus an adherence factor.

IV. RESULTS

A. PILOT STUDY RESULTS

1. Characteristics of the Cohort

There were 64 women who consented to participate in the study. Based on electronic health record data, 13% of these women were in the first trimester and 20% were in the third trimester. One objective of the pilot study was to demonstrate the ability to engage with women in the first trimester while also assessing the potential for capturing birth outcomes. Because the pilot study period did not exceed three months women were sampled from all three trimesters using electronic health record data and women were asked to provide their due date in the initial study questionnaire. Mean maternal age was 33.5 years. Among the 64 participants, three women enrolled but did not answer any questionnaires. Among the 59 women who responded (to the Initial Study questionnaire) with confirmation of an ultrasound, 93% of respondents reported that the ultrasound was accomplished during their first trimester. Of these respondents, 19% reported an unplanned pregnancy, and 92% reported no infertility treatment. Among 58 women who responded to the Initial Study and Weight questionnaire, pre-pregnancy BMI was calculated as overweight or obese by for 43% and underweight for 3% of respondents, respectively (Table 1).

Table 1. Participant Characteristics

	N	%
Maternal Race/Ethnicity	(N=48)	
Hispanic or Latina	3	6%
Black or African American	0	0%
Asian	2	4%
Native Hawaiian or Other Pacific Islander	0	0%
Native American or Alaska Native	0	0%
White	39	81%
Multiple Races Reported	4	8%
Other	0	0%
Not sure or prefer not to answer	0	0%
Maternal Education	(N=48)	
Some high school, no degree	0	0%
High school or GED	0	0%
Some college, Associates Degree, Technical Degree	3	6%
4-year college degree	16	33%
Master's Degree	17	35%
More than a Master's Degree (MD, PhD, JD, etc)	12	25%
Maternal Age	Mean (Range)	
	33.5 (23-43)	
Estimated Gestational Age at start of study	(N=64)	
First Trimester	8	13%
Second Trimester	43	67%
Third Trimester	13	20%
Pre-pregnancy BMI	(N=58)	
Underweight	2	3%

	N	%
Normal	31	53%
Overweight	13	22%
Obese	12	21%
Ultrasound	(N=59)	
Yes	59	100%
No	0	0%
Trimester of first ultrasound	(N=59)	
First Trimester	55	93%
Second Trimester	4	7%
Third Trimester	0	0%
Planned Pregnancy	(N=59)	
Yes	48	81%
No, but it was not completely unexpected	8	14%
No, it was not planned	3	5%
Infertility Treatment	(N=59)	
Yes	5	8%
No	54	92%
Any Medication Use	(N=56)	
Yes	46	82%
No	10	18%
Any Vitamin Use	(N=40)	
Yes	40	100%
No	0	0%
Any Vaccine	(N=44)	
Yes	33	75%
No	11	25%
Any Acute Condition Reported	(N=53)	
Yes	53	100%
No	0	0%
Any Chronic Condition	(N=58)	
Yes	29	50%
No	29	50%

2. Medical Conditions and Medication Use

Ten distinct chronic conditions were reported by the 58 respondents who answered chronic conditions questionnaires (Table 2). For six of these chronic conditions, at least one respondent reported discontinuing a medication. Fifteen distinct acute conditions were reported by the 53 respondents who answered acute conditions questionnaires. No respondents discontinued medications for acute conditions, and many respondents did not take medications for acute conditions.

Table 2. Conditions Reported

Condition	Women Reporting Condition	Women with Condition Who Took Any Medication	Women with Condition Who Discontinued Any Medication
Chronic Conditions (N=58 Respondents)			
Anxiety or Panic Attacks	19	11	6
Asthma	3	3	1
Attention-Deficit/Hyperactivity Disorder (ADHD)	1	0	1
Bipolar Disorder	1	1	1
Crohn's Disease	0	0	0
Depression	16	7	4
Diabetes	1	0	0
Hypertension or High Blood Pressure	2	0	0
Hypothyroidism	2	2	0
Irritable Bowel Syndrome (IBS)	2	0	0
Migraines	7	1	1
Psoriasis	0	0	0
Seizures or Epilepsy	0	0	0
Acute Conditions (N=53 Respondents)			
Cold	35	9	0
Constipation	34	13	0
Fever	5	0	0
Flu	0	0	0
Gastroenteritis	17	4	0
Headaches	34	23	0
Heartburn or Acid Reflux	36	25	0
Nausea Related to Pregnancy	38	12	0
Outdoor or Indoor Allergies	10	8	0
Pain Bad Enough to Take a Medication	3	3	0
Pneumonia	1	1	0
Sinus Infection	1	1	0
Sleeping Problems	28	5	0
Urinary Tract Infection	3	3	0
Vaginal Yeast Infection	3	3	0

Specific medications are outlined for acute and chronic conditions in Table 3 and Table 4, respectively.

Table 3. Medications Used for Acute Conditions

Condition (N Reporting Condition or Medication)	N	%
Cold	**(N=28)**	
Participants reporting taking medication	9	26%
Patients reporting not taking medication	19	54%
Acetaminophen	2	6%
Caught drops	1	3%
Chlorpheniramine	1	3%
Dextromethorphan	1	3%
Guaifenesin	1	3%
Medication not reported	5	14%
Constipation	**(N=34)**	
Participants reporting taking medication	13	38%
Patients reporting not taking medication	21	62%
Bisacodyl	1	3%
Docusate sodium	4	12%
Milk of Magnesia or Magnesium Supplement	3	9%
Polyethylene glycol	2	6%
Psyllium	2	6%
Colace	1	3%
Medication not reported	7	21%
Flu	**(N=0)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	0	0%
Fever	**(N=5)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	5	100%
Gastroenteritis	**(N=17)**	
Participants reporting taking medication	4	24%
Patients reporting not taking medication	13	76%
Fiber supplement	1	6%
Ondansetron	1	6%
Loperamide Hydrochloride	1	6%
Pepto bismol	1	6%
Medication not reported	2	12%
Headaches	**(N=34)**	
Participants reporting taking medication	23	68%
Patients reporting not taking medication	11	32%
Acetaminophen	18	53%
Ibuprofen	1	3%
Chlor-trimeton	1	3%
Sumatriptan	1	3%
Medication not reported	20	59%
Heartburn or acid reflux	**(N=36)**	
Participants reporting taking medication	25	69%

Condition (N Reporting Condition or Medication)	N	%
Patients reporting not taking medication	11	31%
Calcium carbonate	2	6%
Omeprazole	1	3%
Ranitidine	8	22%
Tums	10	28%
Medication not reported	8	22%
Nausea related to pregnancy	**(N=38)**	
Participants reporting taking medication	12	32%
Patients reporting not taking medication	26	68%
Diphenhydramine	1	3%
Doxylamine Succinate/Pyridoxine Hcl	3	8%
Ondansetron	4	11%
Promethazine	1	3%
Unisom	3	8%
Vitamin B-6	4	11%
Medication not reported	8	21%
Outdoor or indoor allergies	**(N=10)**	
Participants reporting taking medication	8	80%
Patients reporting not taking medication	2	20%
Cetirizine HCL	2	20%
Fluticasone Propionate	2	20%
Loratadine	3	30%
Medication not reported	0	0%
Pain bad enough to take a medication	**(N=3)**	
Participants reporting taking medication	3	100%
Patients reporting not taking medication	0	0%
Acetaminophen	3	100%
Pneumonia	**(N=1)**	
Participants reporting taking medication	1	100%
Patients reporting not taking medication	0	0%
Azithromycin	1	100%
Sinus infection	**(N=1)**	
Participants reporting taking medication	1	100%
Patients reporting not taking medication	0	0%
Mucinex	1	100%
Sleeping problems	**(N=28)**	
Participants reporting taking medication	5	18%
Patients reporting not taking medication	23	82%
Melatonin	1	4%
Unisom	4	14%
Medication not reported	1	4%
Urinary tract infection	**(N=3)**	
Participants reporting taking medication	3	100%
Patients reporting not taking medication	0	0%
Cefdinir	1	33%

Condition (N Reporting Condition or Medication)	N	%
Nitrofurantoin	1	33%
Phenazopyridine HCL	1	33%
Vaginal yeast infection	**(N=3)**	
Participants reporting taking medication	3	100%
Patients reporting not taking medication	0	0%
Clotrimazole	1	33%
Fluconazole	1	33%
Miconazole	1	33%

Table 4. Medication Use for Chronic Conditions

Condition *(N Reporting Condition or Medication)	N	%
Anxiety or Panic Attacks	**(N=19)**	
Participants reporting taking medication	11	58%
Patients reporting not taking medication	8	42%
Alprazolam	1	5%
Citalopram	1	5%
Escitalopram	2	11%
Lorazepam	1	5%
Sertraline	7	37%
Asthma	**(N=3)**	
Participants reporting taking medication	3	100%
Patients reporting not taking medication	0	0%
Albuterol	1	33%
Quavr	1	33%
Medication not reported	1	33%
Attention-deficit/hyperactivity disorder (ADHD)	**(N=1)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	1	100%
Bipolar Disorder	**(N=1)**	
Participants reporting taking medication	1	100%
Patients reporting not taking medication	0	0%
Effexor	1	100%
Lamotrigine	1	100%
Crohn's Disease	**(N=0)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	0	0%
Depression	**(N=16)**	
Participants reporting taking medication	7	44%
Patients reporting not taking medication	9	56%
Budeprion/Buproprion	2	13%
Citalopram	1	6%
Escitalopram	2	13%
Sertraline	6	38%
Venlafaxine	0	0%

Condition *(N Reporting Condition or Medication)	N	%
Diabetes	**(N=1)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	0	0%
Hypothyroidism	**(N=2)**	
Participants reporting taking medication	2	100%
Patients reporting not taking medication	0	0%
Tirosint	2	100%
High Blood Pressure	**(N=2)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	2	100%
Irritable Bowel Syndrome (IBS)	**(N=2)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	2	100%
Migraines	**(N=7)**	
Participants reporting taking medication	1	14%
Patients reporting not taking medication	6	86%
Sumatriptan Succinate	1	14%
Psoriasis	**(N=0)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	0	0%
Seizures or Epilepsy	**(N=0)**	
Participants reporting taking medication	0	0%
Patients reporting not taking medication	0	0%

**Reported medication usage is not mutually exclusive within a condition*

Table 5 lists discontinued medications and the reasons that patients provided for discontinuation. Columns correspond to the drug names selected from menus or written in free text by patients. One free text drug, "Excetra," does not correspond to a known prescription or over the counter drug. Other discontinued drugs fall into the following drug classes: beta blocker, benzodiazepine, selective serotonin reuptake inhibitor, serotonin reuptake inhibitor, central nervous system stimulant, and serotonin 5-$HT_{1B, 1D}$ receptor agonist. Six of the nine drug names corresponding to a known prescription or over the counter are labeled as Pregnancy Category C or D. Three of the nine drug names have updated FDA Pregnancy and Lactation Labeling rule sections which no longer list a category. According to the participants, healthcare providers recommended discontinuation of six of the nine drug names corresponding to a known prescription drug and also in the one free text drug that does not correspond to a known prescription drug. Patients reported making the decision to discontinue in four of the nine drug names corresponding to a known prescription drug.

Table 5. Medication Discontinuation

	Alprazolam	Concerta	Excetra	Lorazepam	Metroprolol	Methyl-phenidate	Propranolol	Sertaline	Sumatriptan Succinate	Trazadone
Reason for Discontinuation	**Total N Discontinued**									
The health condition went away	--	--	--	--	--	--	--	--	1	1
My healthcare provider recommended I switch because I was trying to get pregnant	--	--	--	--	--	--	--	--	--	--
My healthcare provider recommended that I stop because I was pregnant	1	1	1	--	1	1	--	--	1	1
My healthcare provider recommended I switch to a different medication because I was pregnant	--	--	--	--	--	--	--	--	--	--
I decided not to take it on my own because I was pregnant	--	--	--	--	--	--	--	1	--	1
I decided not to take it on my own because I was trying to get pregnant	--	--	--	1	--	--	1	2	--	--
Other reason for medication discontinuation	--	--	--	--	--	--	--	1	--	--

Table 6 displays the total Number of Women who either reported taking a medication or had a dispensing in Sentinel or both reported it and had a dispensing (concordance). Participants reported 13 times more OTC medications in aggregate than could be identified in Sentinel. Participants also reported using only 60% of the prescription medications in aggregate of those that were identified in Sentinel. As expected, there is higher concordance at the individual participant level for prescription (27%) rather than over the counter drugs (2%). Among prescription drugs, there did not appear to be a clear discordance trend by drug class.

Table 6. Medication Use

Medications for Episodic and Chronic Conditions	Patient Reported Use	Local Sentinel Data	Concordance	Total Women*
Over-the-counter Medications				
Acetaminophen	23	3	1	25
Bisacodyl	1	0	0	1
Calcium Carbonate	2	0	0	2
Cetirizine	3	0	0	3
Chlorpheniramine	1	0	0	1
Clotrimazole	2	0	0	2
Dextromethorphan	1	0	0	1
Diphenhydramine	2	0	0	2
Docusate	5	0	0	5
Doxylamine	3	0	0	3
Famotidine	3	0	0	3
Guaifenesin	1	0	0	1
Ibuprofen	3	3	0	6
Loperamide	1	0	0	1
Loratadine	3	0	0	3
Milk of Magnesia	3	0	0	3
Melatonin	1	0	0	1
Pepto Bismol	1	0	0	1
Phenazopyridine	1	0	0	1
Vitamin B6	3	0	0	3
Psyllium	2	0	0	2
Ranitidine	10	1	1	10
Tums	10	0	0	10
Unisom	7	0	0	7
Prescription Medications				
Acyclovir	0	2	0	2
Albuterol	2	2	2	2
Alprazolam	1	1	1	1
Amoxicillin	0	3	0	3
Azithromycin	1	1	1	1
Beclomethasone	0	1	0	1
Budeprion	2	2	1	3
Cefdinir	1	0	0	1
Cephalexin	0	1	0	1

Medications for Episodic and Chronic Conditions	Patient Reported Use	Local Sentinel Data	Concordance	Total Women*
Ciprofloxacin	0	1	0	1
Citalopram	1	0	0	1
Clindamycin	0	1	0	1
Effexor	1	0	0	1
Escitalopram	2	1	1	2
Estradiol	0	1	0	1
Fluconazole	1	1	1	1
Fluticasone	2	2	0	4
Fosfomycin	0	1	0	1
Furosemide	1	0	0	1
Glyburide	1	1	1	1
Ipratropium	0	1	0	1
Lamotrigine	1	1	1	1
Letrozole	0	1	0	1
Lorazepam	1	0	0	1
Mesalamine	0	2	0	2
Metformin	0	2	0	2
Methylphenidate	0	1	0	1
Metoclopramide	0	1	0	1
Metronidazole	0	3	0	3
Metoprolol	1	0	0	1
Miconazole	1	0	0	1
Nifedipine	0	1	0	1
Nitrofurantoin	1	4	1	4
Norgestimate	0	1	0	1
Omeprazole	1	1	1	1
Ondansetron	5	8	5	8
Oseltamivir	0	2	0	2
Oxycodone	0	1	0	1
Polyethylene	3	1	0	4
Prochlorperazine	0	2	0	2
Progesterone	0	2	0	2
Promethazine	1	1	0	2
Propranolol	1	0	0	1
Sertraline	10	9	8	11
Sumatriptan	2	0	0	2
Tacrolimus	0	1	0	1
Tirosint	2	6	2	6
Trazadone	1	0	0	1
Triamcinolone	0	2	0	2
Venlafaxine	0	1	0	1

**Total Number of Women who either reported taking the medication or had a dispensing in Sentinel or both reported it and had a dispensing*

Table 7 displays a detailed accounting of medication use for two chronic conditions (anxiety and depression) as well as four acute conditions (sleep problems, nausea, urinary tract infection, and pain). It separates dispensings observed in Sentinel electronic health data among three groups, women reporting a condition with medication use, women reporting a condition with no medication use, and women not reporting a condition. The acute condition "Pain" illustrates two forms of discordance. Seven prescriptions for pain medication were recorded among women who did not report pain. Of note, these prescriptions can be provided on an as needed (also known as "prn" basis). All three participants who reported taking a pain medication took the prescription pain medication Hydrocodone/Acetaminophen and none had a dispending in in Sentinel electronic health data. The acute condition "Nausea" illustrates the third form of discordance in which four dispensings for antiemetic medication were identified among women reporting nausea but no medication use. These prescriptions can be provided on an as needed (also known as "prn" basis).

Table 7. Medication Use Among Select Conditions

Condition	Women Completing Survey*	Women Reporting Condition	Medication Name	Women Reporting Use	Women Reporting Medication Use with >=1 dispensing in Sentinel	Women Reporting Medication Use with NO dispensing in Sentinel	Women Reporting NO Use	Women Reporting NO Medication Use with >=1 dispensing in Sentinel	Women Reporting NO Medication Use with NO dispensing in Sentinel	Women NOT Reporting the Condition with >=1 dispensing in Sentinel
Chronic**	**58**									
Anxiety		**19 (33%)**		**11**	**8**	**3**	**8**	**2**	**6**	**1**
			Alprazolam	1	1	0	--	0	0	0
			Citalopram	1	0	1	--	0	0	0
			Escitalopram	2	1	1	--	0	0	0
			Lorazepam	1	0	1	--	0	0	0
			Sertraline	7	6	1	--	2	0	1
Depression		**16 (28%)**		**7**	**5**	**2**	**9**	**5**	**4**	**2**
			Budeprion/Buproprion	2	1	1	--	1	0	0
			Citalopram	1	0	1	--	0	0	0
			Escitalopram	2	1	1	--	0	0	0
			Sertraline	6	4	2	--	3	0	2
			Venlafaxine	0	0	0	--	1	0	0
Acute*^	**53**									
Sleep Problems		**28 (53%)**		**5**	**0**	**5**	**23**	**0**	**23**	**0**
			Melatonin	1	0	0	--	0	0	0
			Unisom	4	0	0	--	0	0	0
Nausea		**38 (72%)**		**12**	**3**	**9**	**26**	**3**	**23**	**2**
			Diphenhydramine	1	0	1	--	0	0	0
			Doxylamine	3	0	3	--	0	0	0
			Ondansetron	4	3	1	--	2	0	1
			Promethazine	1	0	1	--	1	0	0
			Unisom	3	0	3	--	0	0	0
			Vitamin	3	0	3	--	0	0	0
			Prochlorperazine	0	0	0	--	1	0	0
			Metoclopramide	0	0	0	--	0	0	1
			Promethegan	0	0	0	--	1	0	0

Condition	Women Completing Survey*	Women Reporting Condition	Medication Name	Women Reporting Use	Women Reporting Medication Use with >=1 dispensing in Sentinel	Women Reporting Medication Use with NO dispensing in Sentinel	Women Reporting NO Use	Women Reporting NO Medication Use with >=1 dispensing in Sentinel	Women Reporting NO Medication Use with NO dispensing in Sentinel	Women NOT Reporting the Condition with >=1 dispensing in Sentinel
UTI		**3 (6%)**		**3**	**1**	**2**	**0**	**0**	**0**	**1**
			Cefdinir	1	0	1	--	0	0	0
			Nitrofurantoin	1	1	0	--	0	0	1
			Phenazopyridine	1	0	1	--	0	0	0
Pain		**3 (6%)**		**3**	**0**	**3**	**0**	**0**	**0**	**6**
			Hydrocodone/Acetaminophen	3	0	3	--	0	0	3
			Ibuprofen	0	0	0	--	0	0	3
			Oxycodone	0	0	0	--	0	0	1

**Answered at least one question on the survey, women answering "true" when asked whether they take a medication for this condition.*
***For chronic conditions, medication dispensings were included up to 110 days prior to a woman's app start date through app closing date.*
**^For acute conditions, medication dispensings were included up to 30 days prior to a woman's app start date through app closing date.*

3. Other Exposures

Forty-four women reported vaccine administrations during pregnancy (Table 8).

Table 8. Vaccine Use

	N	%
Women Reporting Any Vaccine	***44**	
Flu vaccine	27	61%
Tdap vaccine	10	23%
HPV vaccine	0	0%
Other	0	0%
Not sure	0	0%

**Rows do not equal 44 as some women reported vaccine use but did not indicate specific vaccine*

Forty women completed the Vitamin Use History questionnaire, and all reported prenatal vitamin use. Twenty-eight of the forty women initiated prenatal vitamins prior to the pregnancy (Table 9). Participants also reported other multivitamins, DHA, folic acid, and vitamin D.

Table 9. Vitamin Use

	Prenatal Vitamin	Folic Acid	Vitamin D	Vitamin B12	DHA	Other Multivitamin
Total Reporting Use	**40**	**5**	**5**	**0**	**5**	**11**
Started before she found out she was pregnant	**28**	**3**	**5**	**0**	**3**	**4**
Once a day	25	3	3	0	1	3
3-6 times per week	3	0	1	0	2	1
1-2 times per week	0	0	1	0	0	0
Less than once a week	0	0	0	0	0	0
Other	0	0	0	0	0	0
Started after she found out she was pregnant	**12**	**2**	**0**	**0**	**2**	**7**
Once a day	7	1	0	0	2	5
3-6 times per week	4	1	0	0	0	1
1-2 times per week	0	0	0	0	0	1
Less than once a week	0	0	0	0	0	0
Other	1	0	0	0	0	0
Not sure	0	0	0	0	0	0

Several questionnaires were used to assess exposure to alcohol, cigarettes, e-cigarettes, street drugs, and marijuana prior to and during pregnancy. The percentage of respondents reporting use of these substances decreased during pregnancy, but among some respondents use persisted for alcohol (18%), cigarettes (2%), e-cigarettes (2%), street drugs (3%), and marijuana (5%) (Table 10).

Table 10. Changes in Behavior Before, During, and After Pregnancy

Substance	Total Responding	Used Before Pregnancy		Used During Pregnancy		Stopped During Pregnancy		Started During Pregnancy	
		N	%	N	%	N	%	N	%
Alcohol	39	33	85%	7	18%	26	67%	0	0%
Cigarettes	47	2	4%	1	2%	1	2%	0	0%
E-Cigarette	45	2	4%	1	2%	1	2%	0	0%
Street Drug	39	1	3%	1	3%	0	0%	0	0%
Marijuana	39	10	26%	2	5%	8	21%	0	0%

Respondents also provided information on the frequency of use (Table 11), and some decrease in the frequency of alcohol exposure was reported during pregnancy.

Table 11. Substance Use Before and During Pregnancy

	Before Pregnancy		During Pregnancy	
	N	%	N	%
Average Drinks Per Week	N=39		N=26	
1 or less	9	23%	7	27%
2-4	16	41%	1	4%
5-7	8	21%	0	0%
More than 7	2	5%	1	4%
Not sure	0	0%	0	0%
Most Drinks in One Sitting	N=39		N=26	
1 or less	12	31%	8	31%
2-4	16	41%	0	0%
5-7	5	13%	1	4%
Not sure	0	0%	0	0%
Cigarettes Usage Frequency	N=47		N=45	
1/2 pack (5-14)	1	2%	0	0%
1-4 per day	1	2%	1	2%
1 pack (15-24)	0	0%	0	0%
More than 1 pack (25 or more)	0	0%	0	0%
E-Cigarette Usage Frequency	N=47		N=45	
Every day	1	2%	0	0%
A few days a week	0	0%	0	0%
A few days a month	0	0%	0	0%
Once a month or less	1	2%	0	0%
Street Drug Usage Frequency	N=39		N=26	
More than once a day	0	0%	0	0%
Once a Day	0	0%	0	0%
2-6 Days a Week	0	0%	0	0%
Once a Week	1	3%	1	4%
1-3 Times a Month	0	0%	0	0%
Less than Once a Month	0	0%	0	0%
Marijuana Usage Method	N=39		N=26	
Inhale smoke	5	13%	1	4%
Inhale vapor	0	0%	0	0%
Eat/ingest orally	5	13%	1	4%
Absorb through the skin	0	0%	0	0%
Other	0	0%	0	0%
Marijuana Usage Frequency	N=39		N=26	
Once a day	0	0%	0	0%
More than once a day	1	3%	0	0%
2-6 days a week	0	0%	0	0%
Once a week	1	3%	0	0%
Less than once a month	8	21%	1	4%
1-3 times a month	0	0%	0	0%

4. Birth Outcomes

None of the participants reported a miscarriage or abortion. Six women reported live births using the app (Table 12). A search of the source data for Sentinel identified 10 live births among the participants who had enrolled in the study. Of the 6 women who reported live births, 1 reported birth defects, and 5 reported normal birthweight.

Table 12. Birth Outcomes

	Patient Reported		Sentinel Data*	
	N	%	N	%
Live birth	6	9%	10	16%
Miscarriage	0	0%	0	0%
Abortion	0	0%	0	0%
No response	58	91%	N/A	
Total	*64*		*64*	

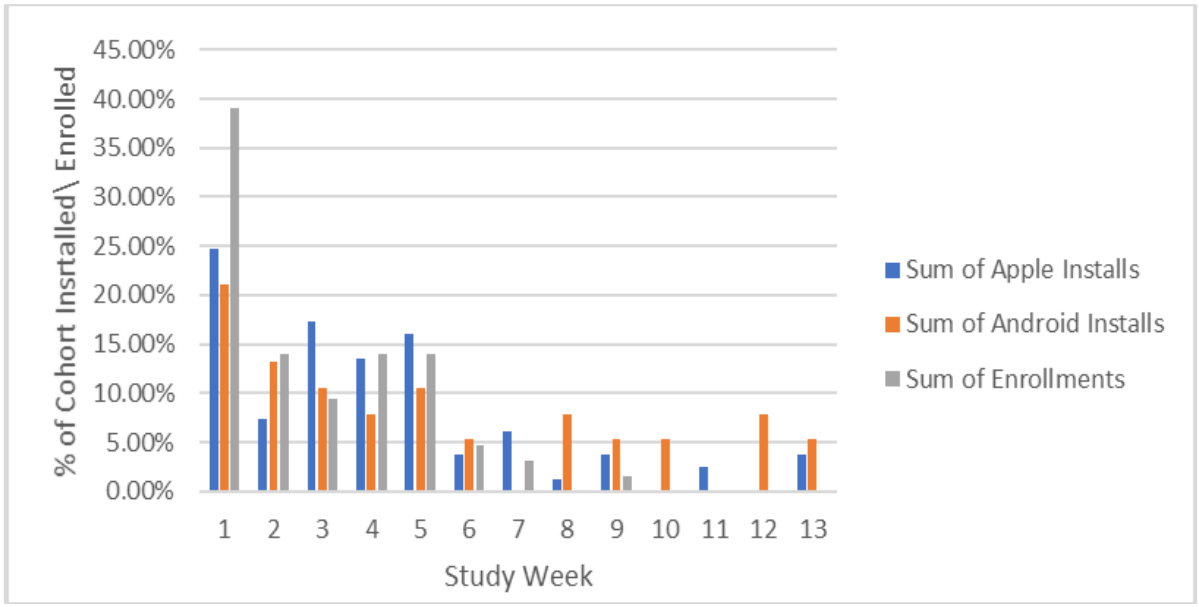
**Presence of live delivery code in Sentinel between date of app initiation and date of app closing. Some women likely stopped using the app prior to the closing date and, thus, did not report live birth outcome.*

B. APP USAGE PATTERNS AND USER EXPERIENCE

1. App Downloads and Enrollment

The app was visible in the iTunes store and Google play store, and 81 Apple users and 38 Android users downloaded the FDA MyStudies app. It is not possible to determine if all downloads were among individuals who were recruited for the specific study since there were no restrictions on downloading the app for free. As previously noted, 64 women enrolled in the study after downloading the app, and four weeks elapsed until 75% of the final cohort authenticated and enrolled in the study (Figure 1). All data tables and figures for app usage patterns are displayed in Appendix 9.

Figure 1. Installations and Enrollments Over Time



2. Completion of Questionnaires by the Cohort

Over 70% of participants provided new information ("filled in the blanks" left by electronic health records) or corroborating information ("cross checks" on electronic health records) related to key data needs for observational research in pregnancy (Table 13). They completed an initial study questionnaire which allows a researcher to establish pregnancy dating. They described existing medical conditions and medications and categorized these as arising prior to or during the current pregnancy. They also described short term illnesses that had occurred during the pregnancy and prior to enrollment. Such short term illnesses, including maternal fever, are often not medically attended and would not typically be captured in claims or electronic health records. Women also described their smoking and vaping history, weight, and demographic information such as race and educational attainment which are typically not reliably captured in claims or electronic health records.

Despite the sensitive nature of these topics, 60% of women responded to questions regarding recreational drug and alcohol exposure and categorized exposures, if applicable, as existing prior to or during the current pregnancy (Table 13). Vaccines and vitamin use in the prenatal period or during pregnancy were also described. Since some vaccines are available at pharmacies, worksites (e.g., influenza), and other locations, full capture of vaccine administrations does not typically occur with electronic health records. In addition, these vaccine administration sites may not bill the patient's health insurance, and as a result, these administrations may not be visible in claims data. Over the counter vitamin use history is particularly important in pregnancy given the effect of folate supplementation on the risk of neural tube defects.

Recurring questionnaires to document changes in exposures during pregnancy were less frequently answered. This might be related to the frequent and repetitive nature of the update questions. For example, 19% of women who took the baseline ongoing condition questionnaire reported having no chronic conditions and did not take at least one recurring questionnaire. The most clinically and epidemiologically relevant recurring questions were related to pregnancy status, chronic and short term medical conditions, and prescription or OTC drug use. These were answered by over 60% of women.

Updating vitamin use, alcohol exposure, and recreational drug use prospectively was completed by over 40% of women. The current pregnancy outcomes questionnaire was completed by 7 women. Women were only directed to take this questionnaire if they indicated they were no longer pregnant in the weekly pregnancy status questionnaire.

Table 13. Questionnaire Completion by Name

Questionnaire Name	Women that Completed at Least 1 Run of the Questionnaire	%	*Number of Times Completed
	N=64		
Current Weight	59	92%	264
Initial Study Questionnaire	59	92%	59
Medical Condition History	58	91%	58
Pregnancy Status	58	91%	288
Short Term Illness History During Pregnancy	53	83%	54
Pregnancy History	50	78%	50
Information About You	48	75%	48
Smoking and Vaping History	45	70%	45
Vaccine History During Pregnancy	44	69%	44

Questionnaire Name	Women that Completed at Least 1 Run of the Questionnaire	%	*Number of Times Completed
Vitamin Use History	40	63%	40
Current Medical Condition Information	39	61%	106
History of Alcohol Exposure	39	61%	39
History of Marijuana or Cannabis Exposure	39	61%	39
History of Recreational Drug Exposure	39	61%	39
Recent Short Term Illnesses	36	56%	92
Current Smoking and Vaping Exposure	31	48%	45
Current Vitamin Use	30	47%	44
Current Alcohol Exposure	26	41%	26
Current Marijuana or Cannabis Exposure	26	41%	26
Current Recreational Drug Exposure	26	41%	26
Vaccine Exposure Update	13	20%	14
Current Pregnancy Outcomes	7	11%	7

**Across all recurring instances of the Questionnaire*

3. Enrollment and Engagement Patterns

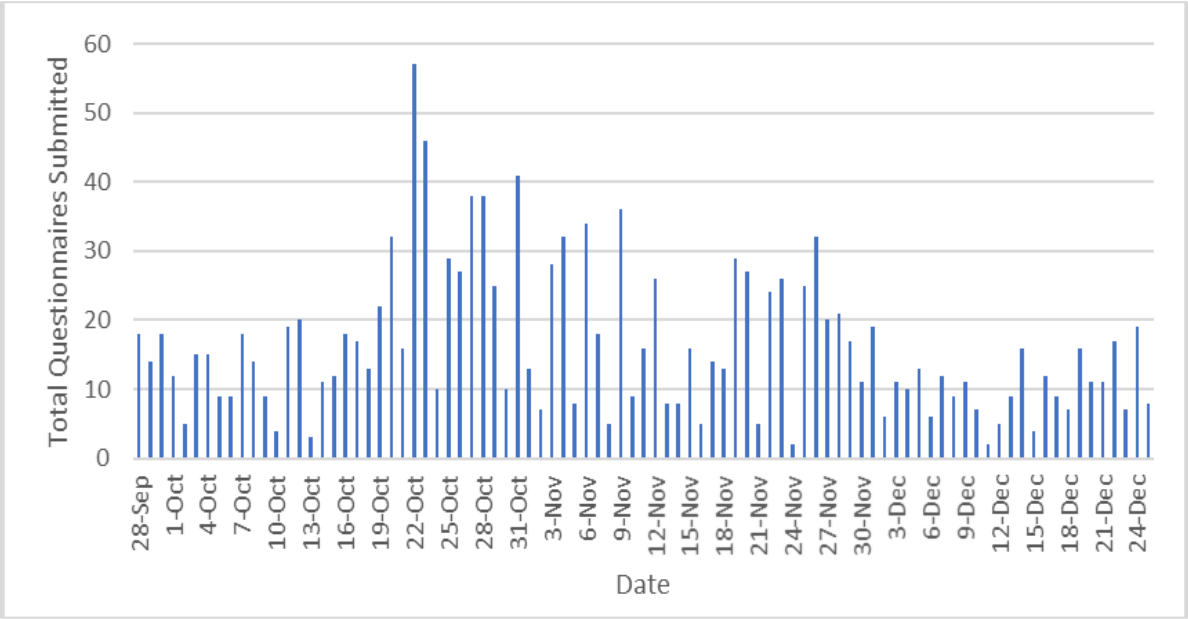
The entire study period was 13 weeks (2.75 months), and 25% of the cohort enrolled more than 1 month after the study started. 872 women were mailed invitation letters on September 25, 2017. A separate cohort of 199 women were mailed invitation letters on October 17, 2017. KPWHRI randomly identified 536 women from the first mailing for phone follow-up. One attempt to call the 536 women was made during a first round of phone follow-up between September 29th and October 13th. Beginning on October 16th, KPWHRI began a second round of phone follow-up to previously contacted women who they were unable to reach on the first call attempt. Up to three call attempts were made and up to three phone messages were left. These phone calls continued until October 27th. During the call, women were reminded of the materials mailed to them and encouraged to join the study. Women were given the opportunity to ask questions about the study and have the study described to them. The enrollment rate for the call and non-call groups was compared to determine the effectiveness of phone follow-up and is described earlier in this report. Half of the cohort (51%) engaged with the app for more than one month (Table 14) and the median period of engagement for the entire cohort was 35 days.

Table 14. Days of Engagement

Days Engaged	Number of Women	%
0-14	19	30%
15-30	13	20%
31-45	6	9%
46-60	10	16%
61-75	8	13%
75-90	8	13%
Total	64	100%

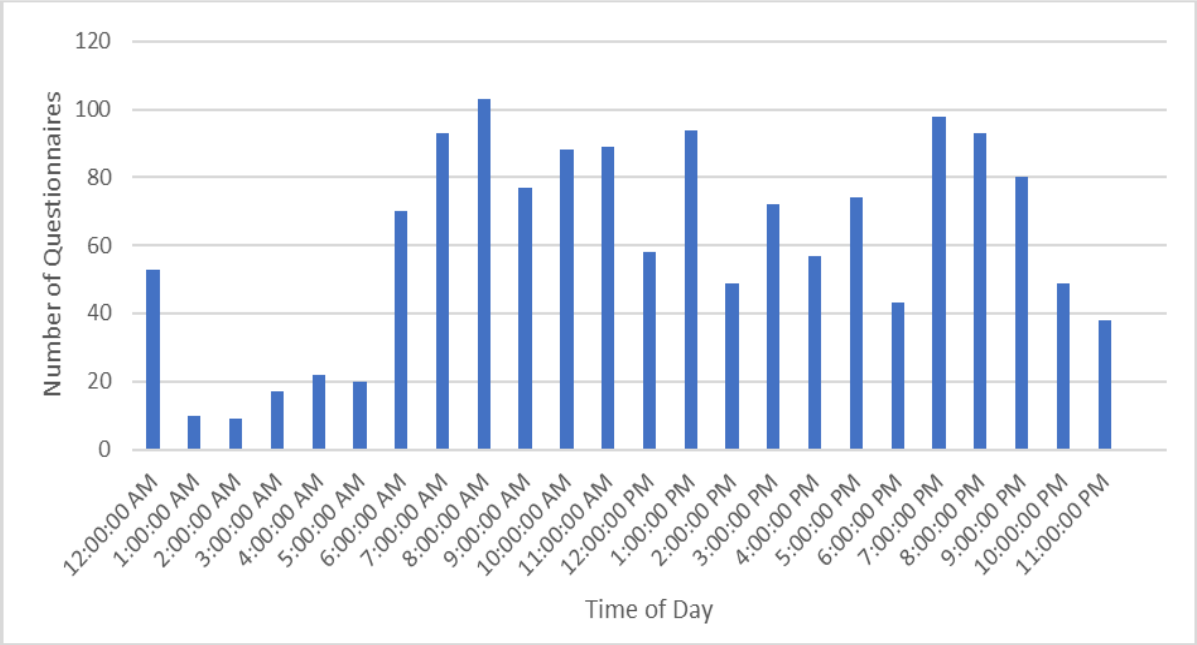
Questionnaire completion increased over the first month as enrollment grew to over 75% of the final cohort (Figure 2). As baseline surveys were completed, questionnaire completion decreased. By week 7, over 98% of the cohort had enrolled and by the end of November, all baseline questionnaires would have been completed. There did not appear to be a specific abrupt drop in questionnaire completion, but as previously described, fewer women provided updates for repetitive questionnaires relative to baseline questionnaires.

Figure 2. Number of Questionnaires Submitted



Substantial app interaction occurred outside typical working hours for a medical or research clinic (Figure 3). Interaction occurred throughout the day between 6:00am and midnight, but there was also moderate interaction between midnight and 6:00am. As described in exit interviews, participants noted the convenience of responding to research questions when this activity could fit into their schedules. Not surprisingly, women answered the one-time (baseline) questionnaires over a longer period of days than the recurring questionnaires. There was essentially an inversion with ~60% completed in the last 4 days of the week for one time (baseline) and ~60% in the first five days of the week for recurring questionnaires. The app functionality supported unlimited changes to a questionnaire within the specified timeframe for that questionnaire until the participant confirmed that her responses were complete.

Figure 3. Number of Questionnaires Submitted by Time of Day



4. Qualitative Feedback from Exit Interviews

Feedback provided by 19 participants who consented to exit interviews provided insight into reactions to the use of an app for research as well as reactions to the specific study topic. Regarding use of an app for research, the participants expressed comfort with using an app to answer medical research questions, and they had no problems navigating the app. Push notifications from the app elicited mixed reactions with some preferring notifications and others finding them to be too frequent. Logging in after being logged off by the app was time consuming. We believe this feedback refers to the optional passcode verification, not the process to log in to the app for the first time. We expect that better communication on the ability to turn off passcode verification would minimize this complaint in future uses. The current lack of a capability for the app and the storage environment to "remember" and present earlier responses back to participants was cited as a negative attribute has been prioritized for future development. Once developed, updated app code and relevant documentation related to the storage environment will be publicly released. Regarding the study, altruism was the main motivator for participation since no monetary incentive was given. Some participants who joined the study after receiving the phone call reported that they initially did not enroll since they did not know that researchers would be interested in their data even if they were not taking prescription medications. Questionnaires were considered clear and understandable, and questionnaire length was considered appropriate.

V. DISCUSSION

A. FEATURES OF THE MYSTUDIES SYSTEM

This project accomplished its goal of developing and testing a generalizable mobile application platform and secure patient data storage environment, MyStudies, for use in clinical research. A cohort of 64 women consented to provide information through the app and to allow researchers to access their existing electronic health data, and patient provided data were linked and analyzed in conjunction with electronic health data serving as source data for Sentinel and PCORnet. Usage patterns and exit interviews indicate a general comfort with using an app to answer medical research questions within a study. The platform is built on standard mobile frameworks and the code is in the public domain so additional capabilities can be added by external app developers.

Many tools exist to create survey instruments and distribute them digitally, but they have not been designed to interact with the regulated and often distributed clinical research environment. Those that have been designed for research are typically purpose-built for one study and require significant programming expertise to reconfigure for new use cases even if they utilized utilize ResearchKit and ResearchStack. This project developed the first platform that enables research organizations to manage nearly all aspects of multiple smartphone-based multi-site clinical studies, including data collection and storage, via a point and click web-based configuration portal and a single mobile app.

The mobile app is specifically designed to collect patient reported data in a clinical study and store them in a central location; it does not interact directly with an EHR system. This design was implemented for privacy reasons – pushing or pulling data directly to/from an EHR represents a large policy change for many institutions that was outside the scope of this project. Furthermore, this design is consistent with the distributed nature of Sentinel and PCORnet. However, external organizations able to effect such policy changes could consider expending resources to develop this type of capability if they want to modify the MyStudies system for local use.

Several desired MyStudies features that could not be accommodated within the given budget and timeline. These include: 1) the ability to distribute questionnaires and organize questions according to previous responses; for example, the ability to "remember" if a user indicated they take medication X and only send questions about that medication; 2) the ability to schedule questionnaires based on actions within the mobile app or enrollment date rather than calendar time; 3) a search and auto-fill function for questions that require a long list of possible responses, such as a medication list. These features have been prioritized by the agency for follow-on development in support of another clinical study or registry, and subsequent versions of the app code and storage environment documentation will be publicly released. However, external developers could also modify the existing code for the app to accomplish one or more of these objectives.

B. INFRASTRUCTURE AND EXPERTISE FOR IMPLEMENTATION

External research organizations and app developers can implement the MyStudies system in several ways and may not need to implement the entire system depending on the use case. Vendors are mentioned below to describe roles and responsibilities but other vendors may be able to use the code and supporting documentation in the public domain to provide similar services. The front-end tools, (mobile app and WCP) have an API layer so they could be used with other storage environments. Options listed below can work with an existing single database (e.g., a single site study or a single database supporting a trial) or an existing distributed database system. The secure storage environment

and app are 21 CFR Part 11 and FISMA compliant which may or may not be necessary depending on the judgement and use case of the sponsoring organization.

1. The existing secure storage environment implementation hosted by Labkey can be used to host multiple studies to the existing gateway app with minor development for re-branding by BTC. HPHCI can manage the system and configure the studies using the web configuration portal.
2. The existing secure storage environment implementation hosted by Labkey can be used to host a single study to a single-use app (without a gateway capability) that leverages the web configuration portal to reduce app development programming compared to a *de novo* mobile app. Minor development for re-branding could be accomplished by BTC, and HPHCI can manage the system and configure the studies using the web configuration portal.
3. Organizations can independently develop a storage environment conforming to the LabKey registration, response, and WCP servers' requirements in a local environment. They can then re-brand and publish their own version of the gateway app (or a single use app) that communicates with the local electronic health data servers.
4. Organizations that do not require the linkage and authentication features of MyStudies that support cohort studies could use the system without linkage to electronic health data for "open access" studies with the Labkey storage environment or a local storage environment.
5. App Developers can use this app as the foundation for additional features including but not limited to integration with wearables, search and auto-fill functions, or optical character recognition.

A sponsoring organization and its vendors will need a variety of clinical and technical skills. An implementation workgroup should ideally include clinical experts, representatives from each software development partner, representative patient advisors, and a central coordinating staff to manage the project and handle configuration and testing. For example, a questionnaire about medical conditions in the pilot study required 150+ questions to account for the various branching paths related to medication usage for each condition. At least one analyst or informatician should have relational database experience and/or R, SQL, or SAS programming knowledge to extract and analyze data from the storage environment. Such knowledge is also important to create and store a mapping of enrollment tokens to an external dataset ID. A software developer should have experience managing and publishing an app via an app store to ensure proper testing of an app before distribution to a cohort. Interaction with clinical and subject matter experts should start prior to configuration and continue throughout the study design phase. Clinical and subject matter experts as well as coordinating staff are also needed to implement the entire study including protocol development, IRB applications, study conduct, and data analysis.

In options 1 and 2 described above, data are stored in a secure environment external to any participating site. The aim is to strictly limit access to sensitive data; for example, in a multi-site study one data partner or healthcare system would not be able to access the data from another Data Partner or system. It is not always clear what access is most useful or appropriate for other participants, such as a coordinating staff, and it will be important for organizations to carefully consider and regularly review roles and responsibilities with regard to data access and analysis among the participating parties. There are also security and privacy considerations in a multi-site clinical study using mobile devices and they may differ across sites. Use of a mobile app in conjunction with electronic health data is currently not a widespread activity. Although there are federal guidance and regulations for e-signature, data security, and privacy, there may be additional state regulations or local interpretations by IRBs that need to be

considered. A central IRB or local IRBs may need to work with legal departments at individual sites to clarify local interpretations.

An app must always adhere to the rules of the app stores in which it is available. As mentioned earlier, the workgroup discovered that the Apple App store requires apps to have branding consistent with the branding of their publishing organization. This is a relatively new change to Apple's App Store license agreement, as many app developers previously published apps on behalf of their clients' organizations. Under current Apple app store policy, a sponsoring organization that wishes to brand and utilize the MyStudies app for iOS mobile devices will need to have its own developer account from which it can publish apps to the app store. As interpreted by Apple, this does not preclude contract or third party app developers from using the developer account with permission of the sponsoring organization.[i] Thus, healthcare and research organizations that would like to use MyStudies but do not develop and publish apps as part of their routine operations may use third party app developers. To our knowledge, this issue does not affect the Android version of the app because the Google Play store, does not have the same policy.

C. IMPLICATIONS OF THE PILOT STUDY

The pilot study demonstrated that the technical, scientific, and governance procedures of the MyStudies system can operate successfully within a clinical research environment. As developed, it is FISMA compliant and also capable of supporting a 21 CFR Part 11 compliant study so it is potentially suitable to support use cases ranging from patient registries to clinical trials under Investigational New Drug oversight. Use of the app requires individuals to have an Android or iOS compatible mobile device which may influence the composition of a study population. However, smartphone and tablet usage is widespread according to data compiled by the Pew Charitable Trust.[ii]

The pilot study did not include a financial incentive for recruiting and it did not tap into an existing disease registry or patient-driven research network since it did not study a specific health condition (e.g., psoriasis or asthma). Participants in the pilot study who received a letter in the mail enrolled at a 4% rate. This rate compares favorably to the 1% "activation rate" noted in another agency study involving mailings from data partners, IMPACT Afib (unpublished data). Participants in the pilot study who received one follow-up call in addition to the letter enrolled at an 8% rate. This finding suggests that app uptake could be influenced in future studies by using even more comprehensive recruitment strategies similar to those used by clinical trials.

With respect to studies of drug effectiveness and safety in pregnancy, the study demonstrated the ability to identify women in the first trimester using electronic health data and engage with them rapidly using the mailing and app. Women reported sensitive information including continued alcohol, smoking, and illicit drug use during pregnancy. Some birth outcomes were not captured so additional outreach may be necessary in the post-partum period when participants are recovering while simultaneously caring for the infant. Further experience with a larger cohort and a more standard follow-up period approaching 12 months would be desirable to fully characterize the potential benefits of the system.

Particularly relevant to studies of comparative effectiveness or pragmatic trials in which patient reported outcomes, curation of medication use, and other information not present in the EHR are necessary, participants provided information regarding the reasons that they discontinued medications, the extend of over the counter medication use, and sensitive topics such as illicit drug use. Participants reported 13 times more OTC medications in aggregate than could be identified using electronic health records alone. Participants also reported using only 60% of the prescription medications in aggregate of those that were identified using electronic health records. As expected, there was higher concordance at

the individual participant level for prescription (27%) rather than over the counter drugs (2%). These findings, especially for prescription drugs, were likely influenced by the fact that the entire cohort was pregnant but they serve as a reminder that cross-checking adherence patterns in cohorts with different characteristics or health conditions will likely be important for real world evidence generation.

Participants reported on reasons they decided not to take prescription medications and also on self-medication with prescription drugs. Non-medically attended outcomes were also reported through the app. Given the scope of information provided by participants, the app appears capable of expanding the depth and diversity of "big" electronic health data for clinical research purposes. Over time, continued app development using information in the public domain will likely increase usability, enable integration of other real world data sources, and enhance the overall ease with which the patient perspective can be included in clinical research.

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[i] Meeting with Apple Healthcare Partnership Management staff, September 18, 2018

[ii] Pew Research Center, http://www.pewinternet.org/fact-sheet/mobile/, accessed June 30, 2018