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Brief Communications

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Development and utility of a clinical research informatics application for participant recruitment and workflow management for a return of results pilot trial in familial hypercholesterolemia in the Million Veteran Program

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Abstract

Objective: The development of clinical research informatics tools and workflow processes associated with re-engaging biobank participants has become necessary as genomic repositories increasingly consider the return of actionable research results.

Materials and Methods: Here we describe the development and utility of an informatics application for participant recruitment and enrollment management for the Veterans Affairs Million Veteran Program Return Of Actionable Results Study, a randomized controlled pilot trial returning individual genetic results associated with familial hypercholesterolemia.

Results: The application is developed in Python-Flask and was placed into production in November 2021. The application includes modules for chart review, medication reconciliation, participant contact and biospecimen logging, survey recording, randomization, and documentation of genetic counseling and result disclosure. Three primary users, a genetic counselor and two research coordinators, and 326 Veteran participants have been integrated into the system as of February 23, 2023. The application has successfully handled 3367 task requests involving greater than 95 000 structured data points. Specifically, application users have recorded 326 chart reviews, 867 recruitment telephone calls, 158 telephone-based surveys, and 61 return of results genetic counseling sessions, among other available study tasks.

Conclusion: The development of usable, customizable, and secure informatics tools will become increasingly important as large genomic repositories begin to return research results at scale. Our work provides a proof-of-concept for developing and using such tools to aid in managing the return of results process within a national biobank.

Lay Summary

The Million Veteran Program Return Of Actionable Results (MVP-ROAR) Study is exploring the acceptance and feasibility of returning genetic results related to familial hypercholesterolemia (family-related high blood cholesterol) to participants in the US Department of Veterans Affairs Million Veteran Program. We developed a user-friendly computer application that can be used by our research team to help manage the process for re-contacting, re-consenting, and enrolling MVP participants into the MVP-ROAR Study. The computer application includes multiple modules that allow our research team to track where participants are in the return of results process as well as enter important operational and study data, including the recording of information related to health record reviews, recruitment and enrollment information, participant surveys, and

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genetic counseling sessions. Our experience building a computer system for managing a return of results process may be important to future return of results initiatives in MVP and can be used as an example by other large biobanks that would like to return genetic results to their participants.

Key words: informatics; genetic testing; genetic databanks; randomized controlled trial.

Introduction

Clinical research informatics is a burgeoning domain focused on using information technologies to optimize the design and conduct of translational research.[1–3] Integrated informatics tools are vital to improving efficiency over the entire research continuum from eligibility screening through study-related and electronic health records (EHR) outcomes data capture and analytics.[4–8] In parallel, the development of workflow processes associated with re-engaging biobank participants has become necessary as genomic repositories increasingly consider the return of actionable genetic information.[9–11] The development of such processes might involve myriad factors including genetic variant selection, re-contact and re-consent, biospecimen collection, disclosure processes, the integration of confirmed results into clinical care, and data curation, management, and security, among others.[12–17]

The US Department of Veterans Affairs (VA) Million Veteran Program (MVP)[18] has begun to address some of these ethical, procedural, and technological challenges to explore returning individual research results to its participants. One such initiative is the MVP Return Of Actionable Results (MVP-ROAR) Study, a nationwide randomized controlled pilot trial returning genetic results associated with familial hypercholesterolemia (FH).[19] To support this unique pilot study, we developed a flexible informatics tool to aid in the re-contact, re-consent, and enrollment management for one of the first initiatives to engage MVP participants in the process of returning actionable genetic results.

Objective

Here we describe the development and utility of an informatics application for participant recruitment, enrollment management, and data collection for MVP-ROAR. The application serves as a proof-of-concept for streamlining return of results processes and providing real-time status updates for individual enrollees and for the study as a whole. The application utilizes open-source software that can be adapted and scaled to a variety of return of results and clinical trial use cases. Base code for the application is available for review and re-use for other VA and non-VA projects (https://github.com/Genomes2Veterans/mvp-roar-app).

Materials and methods

MVP is one of the largest genetic and health-related research initiatives in the world, having enrolled more than one million participants to date.[20] Participants provide a blood specimen, complete health and lifestyle surveys, and give permission for access to their health records. This includes records from the Veterans Health Administration, an integrated health care system comprising nearly 1300 facilities that serves approximately nine million Veterans across the US annually.[21] Additionally, as part of enrollment, MVP participants agree to be contacted for future voluntary research activities. They are also informed that their genetic information will not be returned to them nor made available in their health records. Genetic and health data from MVP enrollees have almost exclusively been used to date to conduct large-scale genomic discovery association studies.

To better understand the potential for providing individual-level data back to participants, MVP has launched pilot work designed to re-contact MVP participants for recruitment into return of results research. MVP-ROAR, one of these pilot projects, is exploring the feasibility of returning results to MVP participants and documenting the associated process- and health-related outcomes. MVP-ROAR focuses on the return of genetic information associated with FH, a monogenic disease affecting approximately 1 in 250 adults.[22] FH is characterized by severe elevations in low-density lipoprotein cholesterol (LDL-C) and markedly increased risk of premature coronary artery disease.[23] The project involves genotype-first identification of MVP participants suspected of harboring FH-related variants. Prior to participant outreach, the MVP-ROAR team works closely with MVP Core research staff to curate eligible FH-related variants, as determined actionable by the Clinical Genome Resource (ClinGen) FH Variant Curation Expert Panel.[24] MVP Core research staff use this information to identify eligible MVP participants and conduct initial re-contact efforts to inform them about MVP-ROAR. Participants who do not opt-out of being contacted are recruited by MVP-ROAR, with enrollment involving a separate consent process, genetic result confirmation via next-generation sequencing, and disclosure of the genetic confirmation test and genetic counseling either immediately or after 6-months to a projected 200 participants and their health care providers at VA facilities nationwide. The primary outcome is change in LDL-C from study baseline to end of study (6-months post-enrollment), with the expectation that individuals who receive confirmation of molecular diagnosis of FH (immediate arm) will receive FH-tailored care and experience greater reductions in LDL-C compared to those who receive a genetic confirmation test after 6-months (delayed arm). Additional outcomes and processes will explore proportions of participants meeting LDL-C targets (eg, <100 mg/dL for primary prevention), medication starts, intensification, and adherence, lifestyle modifications (eg, smoking, physical activity), and number of first-degree relatives who undergo cascade screening (provided at no additional cost to participant family members by the genetic testing vendor). Both MVP and MVP-ROAR have been approved by the VA Central Institutional Review Board (IRB) and all Veteran participants provide consent to participate in each research effort. The study integrates MVP, MVP-ROAR, and historical and current clinical data from the nationally deployed VA EHR[25] system to initiate and track the entire return of results process and aid in the recording of study-related outcomes.

We leveraged the robust VA Informatics and Computing Infrastructure (VINCI)[26] to develop a custom end-to-end informatics solution to support MVP-ROAR. Conception and development of the application began in May 2021 with the first complete version placed into production beginning November 2021. The multi-user application integrates

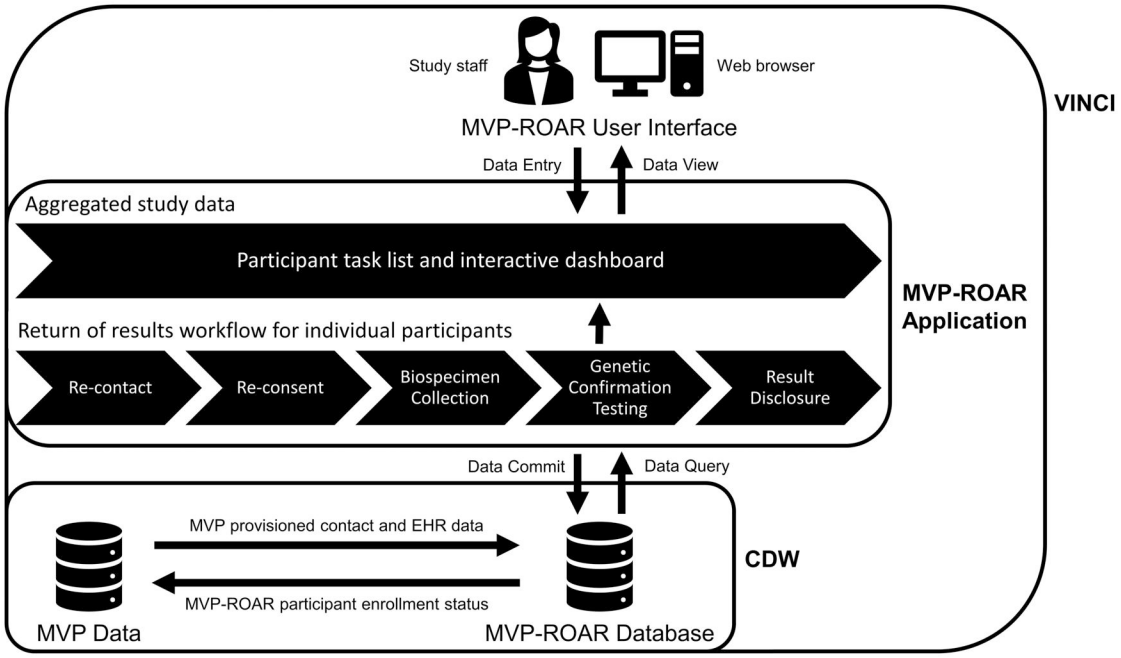

Figure 1. Generalized MVP-ROAR application framework and computing environment infrastructure. MVP identifies participants with actionable genetic information and provisions contact and other data to MVP-ROAR Study team after a brief opt-out period. Once data are provisioned, MVP-ROAR staff initiates pilot trial recruitment, enrollment, and return of results process with informatics support via a secure and user-centric web-based application. Abbreviations: CDW, Corporate Data Warehouse; MVP, Million Veteran Program; ROAR; Return of Actionable Results; VINCI, VA Informatics and Computing Infrastructure.

nationwide clinical and administrative data, electronic data capture, and dashboard analytics via a combination of commercial and open-source software. The application is housed within a secure virtual server, is password protected, and accessible only to IRB-approved and system authenticated study staff from within the VINCI environment. Study data from non-opted out participants are queried from VA Corporate Data Warehouse (CDW)[27,28] views or entered by study staff and stored within dedicated study tables easing data access for the study team and providing systematic structure and secure storage of trial data for eventual data analysis and sharing. An entity relationship diagram of the entire database structure required for the application is presented in the Supplementary Material. We rely on a task-based workflow structure (Figure 1) to transition participants through the application as return of results and other trial tasks are completed by study staff and participants in real-time.

The application is developed in Python (v3.8.14)[29] and uses the Flask micro web framework (v2.0.0)[30,31] along with libraries supporting data extraction, manipulation, and visualization,[32–36] to provide study staff with detailed views, task lists, and data entry and editing capabilities via a standard web browser. Relevant software and supporting packages required for the application are presented in Table 1. Development and maintenance of the application is managed by two members of the study team entirely within a VINCI-supported development environment. Initial development of the application was completed by one part-time developer (~0.25 FTE) over approximately six months. General management of the fully developed application, including application and database maintenance, requires approximately 2 hours per week of staff time. Patient-facing study staff with access to the application include a board-certified genetic counselor and two research coordinators.

Table 1. MVP-ROAR application development software and package infrastructure.

Application system	Software and supporting packages
Database system	• Microsoft SQL Server 2019 (v15.0.4261.1)

Server	• Red Hat Enterprise Linux Server (v7.9)
	  • Apache httpd Web Server (v2.4.6)
	  • ODBC Driver 17 for SQL Server

Backend software and development infrastructure	• Python (v3.8.14)[a]
	  • Flask (v2.0.0)
	  • Flask_login (v0.5.0)
	  • Numpy (v1.20.3)
	  • Pandas (v1.2.4)
	  • Plotly (v4.14.3)
	  • pyodbc (v4.0.30)
	  • sqlalchemy (v1.4.15)
	  • Waitress (v2.0.0)

Frontend software and development infrastructure	• Bootstrap (v4.5) • HTML[b] • Javascript • Plotly (v2.2.0)

[a] Standard libraries and package dependencies not listed.
[b] Layouts templated using Jinja2 (v3.0.1).

Results

Main application components include a study dashboard, searchable cohort and task lists, and individual participant views and data entry modules (Figure 2). The dashboard presents users with aggregate recruitment and enrollment information as well as participant demographic, geographic, and outcomes data. Dashboard elements are fully customizable and are prioritized to offer meaningful and real-time snapshots of study progress for daily operations as well as for scheduled operational and scientific team meetings. The application includes two distinct cohort views, one including

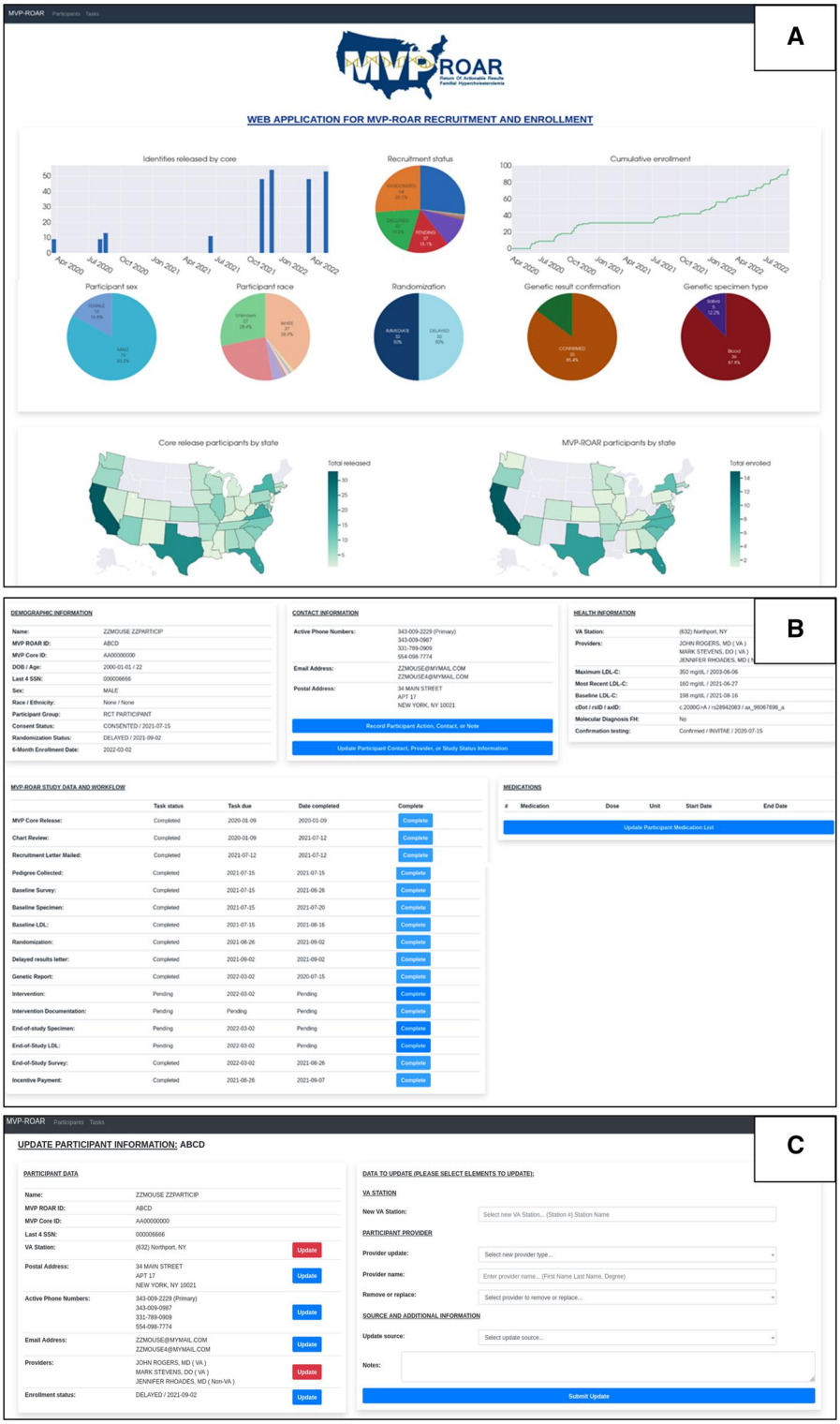

Figure 2. MVP-ROAR application user views. (A) The study dashboard including aggregate recruitment and enrollment metrics. (B) A participant detail and workflow task list available to study staff. (C) Participant demographic and study status update module.

all participants integrated into the system and a second structured by pending task whereby the research team is able to view participants according to their current status in the overall trial workflow. Individual task modules as well as demographic and contact information, relevant clinical, medication, and health care data, and an action and contact log are accessible for each individual via a participant detail page. Workflow modules are presented to application users in sequential order and display task status (pending or complete), task due date, and task completion date for efficient reference. Each task module listed in the workflow includes a button to route study staff to a corresponding web-based module for data entry or task management. Task module buttons are only made available to study staff if the prior

Table 2. MVP-ROAR application study views, data entry, and workflow modules.

Application component	Description
Dashboard	Presents aggregated data associated with recruitment, enrollment, and randomization status, basic demographic information (participant sex, race, and geographic representativeness), and DNA specimen type (blood or saliva) and result confirmation outcomes.
Cohort view	Presents a table of all potential and enrolled study participants by study ID, name, date of birth, and study status, among other quick reference data.
Task view	Presents a filterable table of participants by study workflow task. Only active (alive, currently being recruited, or consented and enrolled) participants are included in this view.
Chart review module	A data entry and validation form for manual EHR chart review by study staff. Chart review outcomes aid the study team in determining eligibility status for each potential MVP-ROAR Study participant.
Recruitment letter tracking	A data entry tool for recording recruitment letter status and date of letter distribution.
Contact and consent tracking	A data entry tool to log each participant telephone or email communication with the study team throughout participants' entire study enrollment.
Pedigree collection tracking	A data entry tool for recording whether a participant has provided the study genetic counselor with relevant family history information. Pedigree information is collected to appropriately frame/tailor each participant's genetic counseling session and note.
Biospecimen collection tracking	A data entry tool for recording whether participants' study specimens (either blood or saliva at baseline and end-of-study) have been received by the study team.
LDL-C tracking	A data entry tool for recording participant LDL-C measurements (maximum from EHR, baseline study draw, end-of-study draw). LDL-C measurements are manually entered into the system by study staff.
Genetic report, intervention delivery, and intervention documentation tracking	A data entry tool for recording receipt of genetic confirmation report from reference laboratory, recording of results delivery and mechanism (phone, video, etc.), and that proper documentation has been delivered to participant, preferred participant health care provider, and entered in EHR.
Incentive tracking	A data entry tool for recording end-of-study participant incentive distribution.
Baseline and end-of-study survey administration	A data entry tool for study staff to record baseline and end-of-study surveys administered by telephone. Surveys include branching and other logic for differential survey instruments administered to immediate versus delayed genetic results recipients.
Randomization module	A tool for research staff to randomize study participants upon the receipt of baseline specimens. The tool utilizes both user input and data validation from the study database to ensure randomization may occur at the time the tool is used. Study team is immediately presented with the outcome and status is committed to the study database in real-time.
Participant information and status update module	A data entry tool to enter and edit participant contact information, preferred VA facility, preferred health care provider information, and unable to contact, loss to follow up, and study withdrawal status.
Medication reconciliation module	A data entry tool to record and edit current participant medications either from the EHR or directly from participants.
Action and contact log	Presents a date sorted record of all contact and study-related actions associated with each MVP-ROAR Study participant. Intended to provide research staff with a quick reference of the entire recruitment and enrollment history.

Abbreviations: EHR, electronic health record; LDL-C, low-density lipoprotein cholesterol; MVP, Million Veteran Program; ROAR, Return of Actionable Results; VA, Veterans Affairs.

workflow task has been completed and validated, ensuring proper transition of participants through the study workflow.

Application components, task modules, and data entry and editing features built specifically for the MVP-ROAR application are presented in Table 2. Information from each completed task, data entry, or data edit associated with an individual participant is logged in the study database as an "action" and presented to application users via an action log included on each participant's detail page. A staff identification number and timestamp are recorded for each action in the study database in addition to task-specific information for auditing purposes. The action log provides application users with historical information, including attempted contacts, participant notes, and task completion information by calendar date for each MVP-ROAR participant beginning with MVP data provisioning through end-of-study incentive payment ($50 for completion of end-of-study survey and biospecimen collection).

A total of 326 Veteran participants have been integrated into the system as of February 23, 2023. Overall, 3 primary users, a genetic counselor and two research coordinators, have used the application to successfully handle 3367 individual task requests involving greater than 95 000 structured data points associated with participant tracking, operational efficiency (eg, fields for staff to record VA facility specific information or to include time spent completing tasks for eventual econometric assessment), and outcomes data collection (eg, study-related LDL-C measurements or telephone survey response data). Figure 3A presents a distribution of

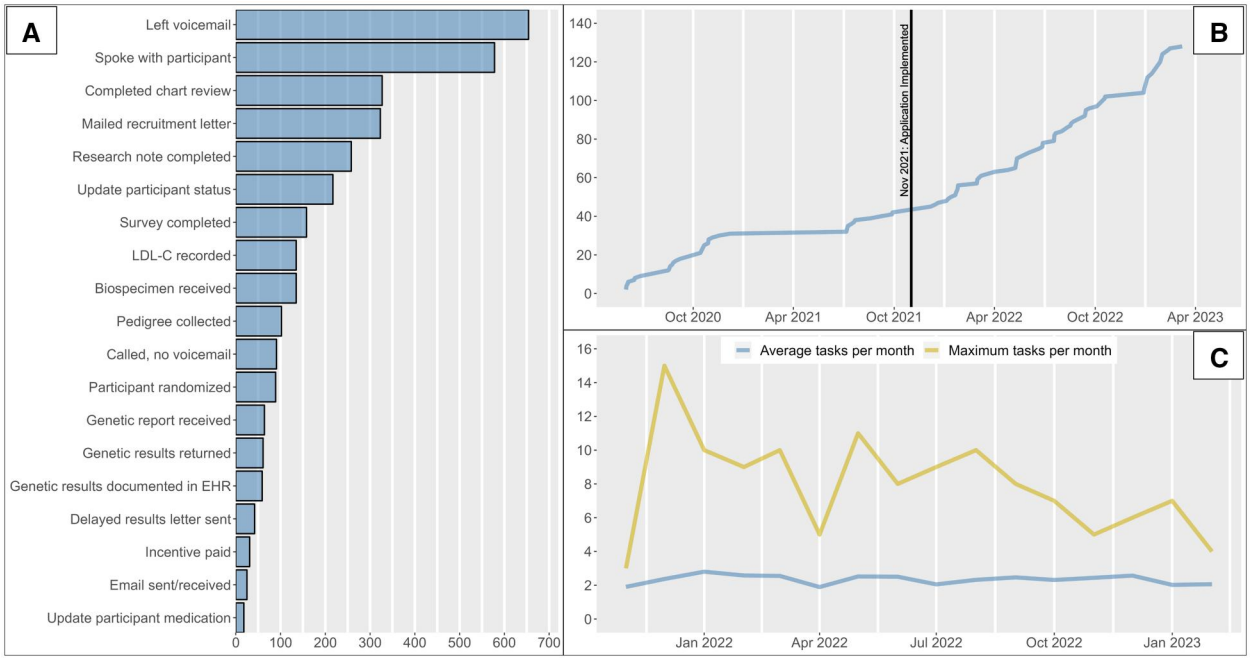

Figure 3. (A) Total return of results workflow and trial tasks completed and recorded by study staff within the MVP-ROAR application between November 2021 and February 2023. (B) Date of application implementation (November 2021) and cumulative enrollment of trial participants between July 2020 and February 2023. (C) The average number of tasks per active participant per month and the maximum number of tasks per participant per month completed and recorded between November 2021 and February 2023. Abbreviations: EHR, electronic health record; LDL-C, low-density lipoprotein cholesterol.

study-specific tasks completed by users from within the MVP-ROAR application between November 2021 and February 2023.

Operationally, transition to the application from a single-file tracking mechanism coincided with the refinement of variant selection methods and full project re-opening during the COVID-19 pandemic. Overall, the application aided the study team in re-initiating participant recruitment and has helped improve trial enrollment outcomes post-implementation (5.3 vs 3.8 average trial enrollees per month, not including periods of shutdown) (Figure 3B). From an efficiency perspective, users demonstrated acceptable usage of the application completing, on average, just over two tasks per active participant per month as well as recording greater than ten completed tasks associated with single participants across multiple months (Figure 3C). Data from each task are stored in a structured format and can be queried to inform future operational assessments associated with return of results in MVP.

Discussion

The development of usable, customizable, and secure informatics tools is becoming increasingly necessary as large genomic repositories have begun to consider the return of research results at scale.[37–39] While other organizations have developed informatics systems to automate pharmacogenomic clinical decision support,[40] for direct-to-patient genetic result disclosure,[41] or for complex data management and analytics systems,[42] few out-of-the-box options currently exist for workflow development and data capture involving an integrated return of results process. While some off-the-shelf products provide user-friendly and efficient informatics support for translational research generally,[43] functionality can be limited in some computing and regulatory environments such as VA.[44] Moreover, the development of a one-size-fits-all informatics solution may not satisfy the needs of individual institutions participating in genetic return of results, given large heterogeneity in workflow preferences, differences in patient populations and disease focus, and variability in EHR and data systems.[45]

Specifically, our return of results workflow and clinical trial processes require both systematic structure and individualized detail and flexibility given the translational nature of MVP-ROAR and our aim to accommodate each participant's unique personal and clinical situations. Thus, our custom-built MVP-ROAR application seeks to aid our staff in this endeavor as we navigate a first-of-its-kind initiative within MVP and the VA on a national scale. We anticipate that final process- and health-related outcomes associated with MVP-ROAR, including those learned from the development and use of our informatics system, will be informative to MVP and biobanks elsewhere for future return of results initiatives.

Primary strengths of the application, like other research and operational applications within VA,[46,47] include its security, scope, and integration with EHR data housed within the CDW. One major advantage of CDW data integration involves its standardized structure across VA facilities nationally, including the merging of our application data with EHR data conformant to the Observational Medical Outcomes Partnership Common Data Model.[48,49] Additionally, the Python-Flask framework is highly transferable, modifiable, and, depending on project requirements, can be developed, scaled, and managed by teams large or small, particularly with the availability of a well-developed and supported computing infrastructure such as VINCI.[50,51] The application offers focused and intuitive data entry interfaces and can handle multiple users as well as multiple database commit and

query requests simultaneously, which provides major advantages over single file-based participant tracking mechanisms.[52] Conceptually, the development team has greatly benefitted from input on workflow, process, and essential data elements from our interdisciplinary team of physician-scientists, research administrators, genetic counselors, data scientists, and frontline research staff.

A limitation of the application is that it requires a computing infrastructure that can securely and efficiently host web applications and some back- and front-end web development capability from members of the study team. Secondly, the application relies heavily on data entry by study staff and is not push-enabled with the VA EHR, requiring entry of genetic counseling notes and other clinical information directly into the patient medical record in order to bridge the research to clinical care continuum. Additionally, database creation, maintenance, and handling of data entry errors necessitates manual editing directly within the database by the development team, which requires additional study staff competencies in database management.

Conclusion

Our work provides a proof-of-concept for developing and using a custom informatics tool to aid in managing a return of results workflow and clinical trial process via actionable health data from a national biobank. We demonstrate the flexibility and utility of our application and provide our conceptual approach and base application code to assist other teams seeking to implement an informatics solution for returning genetic results to research participants or for conducting clinical trials in a comprehensive and efficient manner.

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Author contributions

Charles A. Brunette, Morgan E. Danowski, Alicia Harrison, Themistocles L. Assimes, Kurt D. Christensen, Joshua W. Knowles, Amy C. Sturm, Yan V. Sun, and Jason L. Vassy conceptualized and refined the return of results process. Charles A. Brunette, Morgan E. Danowski, and Alicia Harrison conceptualized the application. Charles A. Brunette led application development. Charles A. Brunette and Thomas Yi implemented and managed the application and supporting infrastructure. Morgan E. Danowski and Mark Cardellino tested and used the application to fulfill study requirements. Yan V. Sun, Qin Hui, Saiju Pyarajan, Yunling Shi, Stacey B. Whitbourne, J. Michael Gaziano, and Sumitra Muralidhar provided important MVP-related input and support for project and application development. Jason L. Vassy acquired funding and oversaw the project team. Charles A. Brunette and Thomas Yi drafted the manuscript, and all authors critically reviewed the manuscript.

Supplementary material

Supplementary material is available at *JAMIA Open* online.

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Conflicts of interest

J.G. reports a relationship with Novartis that includes grant funding. All other authors report no competing interests.

Data availability

Code and documentation for the MVP-ROAR application can be found at https://github.com/Genomes2Veterans/mvp-roar-app. Data underlying application metrics and visualizations presented in this manuscript have not been deposited in a public repository because most of the data include participant-related identifiable information. Deidentified data may be provided from the corresponding author upon reasonable request.

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