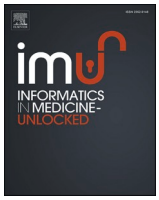
Informatics in Medicine Unlocked 30 (2022) 100931

Contents lists available at ScienceDirect

Informatics in Medicine Unlocked

journal homepage: www.elsevier.com/locate/imu



Putting digital epidemiology into practice: PIA- Prospective Monitoring and Management Application

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ARTICLE INFO

Keywords:
eResearch
Digital epidemiology
Electronic data capture system
Syndromic surveillance
COVID-19
SARS-CoV-2 pandemic

ABSTRACT

Introduction: Epidemiological data collection is often challenged by low response and, in the case of cohorts, poor long-term compliance, i.e. a high drop-out. For the correct recording of incident or recurring health events, that are subject to recall difficulties, gathering of data during the event and immediate response of the participants is crucial. This is especially true when biosampling that catches a transient biological situation like COVID-19 is involved. In addition, emerging research topics (e.g. pandemics like the current SARS-CoV-2) demand a flexible approach regarding content while allowing for complex and varying study designs. To meet these needs, we developed an eResearch system for prospective monitoring and management of incident health events (PIA).
Methods: Programming PIA focusses on IT security and data protection as well as aiming for a user-friendly and motivating design e.g. through feedback for study participants. The main building blocks of the infrastructure are identical functionalities in web-based, iOS and Android compatible application to strengthen the user acceptance of the participants. The backend consists of services and databases, which are all containerised using Docker containers. All programming is based on the JavaScript ecosystem as this is widely used and well supported.
Results: PIA offers complete management of observational epidemiological studies with six different roles: PIA administrator, researcher, participant manager, study nurse, consent manager and participant. Each role has a specific interface, so that different functions e.g. implementation of new questionnaires, administration of biosamples or management of participant contacts can be performed by different personae. PIA can be integrated in the IT system of ongoing studies like the German National Cohort but also used as stand-alone system. The software is open source (AGPL3.0): https://github.com/hzi-braunschweig/pia-system.
Discussion: Despite the abundance of existing Electronic Data Capture Systems (EDC systems), we developed our own generic tool that combines monitoring and management in order to use it for specific applications e.g. in certain pre-existing epidemiological studies or for syndromic surveillance in the current pandemic. Hence, PIA is continuously adapted to emerging requirements. Currently, systematic feedback from users is collected. We aim to improve the user experience of PIA as well as provide further feedback and additional elements like gamification in the future.

1. Introduction

1.1. Background

A major challenge in epidemiologic cohort studies is to achieve high response and long-term compliance of participants [1]. Study fatigue is especially problematic if research questions require repeated participants' responses or the collection of biosamples that aim at catching a transient biological situation. Especially studies on acute, transient infections like COVID-19 or influenza carry the challenge of requiring a participant to report on symptoms immediately at the beginning of the episode, in order to allow timely collection of biosamples for

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https://doi.org/10.1016/j.imu.2022.100931
Received 9 December 2021; Received in revised form 18 March 2022; Accepted 23 March 2022
Available online 25 March 2022

microbiological confirmation [2]. Longitudinal data capture is also required in the field of recurring health events like asthma or angina pectoris episodes.

The development of a new and specific eResearch system allows the implementation of repetitive, e.g. weekly questionnaires, without much organisational effort. The data collection can be carried out in real time, so that recall bias may be avoided.

Furthermore, the ability to use feedback and reminder functions to strengthen participant motivation for long-term participation makes such an eResearch system a promising approach to overcome aforementioned challenges and at the same time improve participant satisfaction and data quality for novel approaches in infection research [3,4].

1.2. Requirements

The main requirements for such a digital tool should focus on IT security and data privacy including separation of person identifying data from medical/questionnaire data; facilitating motivation of participants to use the tool repeatedly and possibly in long-term studies; and easy adaptability to novel research questions through generalisation. Furthermore eResearch tools should be free and open source to ensure transparency and make it re-useable for other researchers [5].

In infectious disease epidemiology the ability for real-time response is an additional requirement e.g. because of symptomatic biosample collection. Technical flexibility, i.e. cross-platform implementation, allowing also to switch between mobile and web-application, is another important feature to enhance user acceptance. For long-term usage, the system should provide a benefit to participants. Data entries should be rewarded with (personal) health information or feedback (e.g. laboratory results).

In addition, scalability should enable application of the tool for different projects at the same time. The use of open standards should be applied wherever possible to support such scalability, flexibility and sustainability. Additionally, to assist future changes regarding user interfaces, a clear separation between data, i.e. databases, business logic, i.e. backend, and user interfaces, i.e. frontend, is needed. To avoid human error of users, automation including adjustable real-time data validation should be applied wherever possible.

Another important requirement is to address the specific roles of an epidemiologic study, e.g. researcher, participant manager, taking role-specific data protection specifications into account.

A particular challenge in meeting the requirements is, to create a stand-alone eResearch system that also can be integrated in the technical and procedural standards of already existing research frameworks such as the German National Cohort (NAKO) [6,7] or connected to other digital health systems such as SORMAS (Surveillance, Outbreak Response Management & Analysis System) [8,9] with the aim of exchanging data.

The requirements were developed in an iterative process including the product owner, future professional users of PIA and the software development team with the support of an external IT consulting company.

1.3. State of the art

Based on the defined requirements, especially for the integration into existing IT-systems and the fast and flexible adaption to upcoming research areas a customised, specific software solution is necessary. Such flexibility is not available e.g. in the well-established web-based "Grippe-Web". This is a study tool that is specifically designed for acute respiratory infections and influenza-like illness and also includes virological surveillance via self-sampling of nasal swabs [10,11]. To our knowledge, "Grippe-Web" is not designed to provide the necessary technical flexibility, and thematic modularity paramount for our envisioned research needs. This flexibility in turn is the core element of online-survey solutions like LimeSurvey [12]. This tool is flexible with respect to content of the questions to be posed, but does not allow individual, event-based surveys or other kind of feedback-procedures and is also not designed for study management.

In contrast to the systems mentioned above ECD – systems such as secuTrial [13], RedCap [14–16], castor [17] or Marvin [18] offer comprehensive study and participant management and considerably simplify the collection of clinical data, primarily by medical personal. Also well-known and in several studies implemented is "OpenClinica" [19,20]. In addition to electronic data capture via medical staff, data management, reporting and randomisation functions, participants can enter their data themselves (Patient reported outcomes - ePRO). The "Climedo" system [21] includes similar functionalities and focuses on patient participation. They have become known through their symptom diary developed in the context of the current SARS-CoV-2 pandemic, which transfers symptoms of contacts and cases to the system SORMAS [8,9].

Most of the ECD-systems offer, if any, a browser-based patient version, which is functional and expedient rather than engaging study participants in the long-term and generating fun to use.

One system that provides a separate app for participants is REDCap. The patient app as an external module is called MyCap [22]. With MyCap participants can complete questionnaires themselves and document examinations and tasks (e.g. memory tests). Unfortunately many of these systems are not publicly available, i.e. are not open source, are costly, and cannot be integrated into existing systems.

Open Data Kit (ODK) on the other hand is an open source software, which offers many possibilities regarding the integration into existing systems [23]. ODK is used for collecting, managing, and using data in resource-constrained environments. One disadvantage is that the tool is only designed for Android operating systems.

However, the focus of these electronic data capture systems is on comprehensive data collection and management (even in areas with poor network connections-offline) by professional personnel, less on participant adherence to repeated self-administered questionnaires, self-sampling of biospecimens including feedback and, hence, long-term use in epidemiological studies.

The software solutions mentioned were identified by searching databases, such as Google, Pubmed and Capterra, which offers a large catalogue of available software including feature checklists and comparison between systems [24]. All tools are comparable to PIA either through their flexible implementation of questionnaires and management functions (EDC- systems) or through their thematic commonality (Grippeweb). However, all systems cover only parts of our requirements.

We therefore developed a novel tool, which aims at offering all of the required functionalities and design features within one system. A comparison of selected electronic data capture systems is shown in Appendix 1.

2. Methods

PIA is envisioned as an extendable platform for the deployment of an eResearch system for management and capture of incident events. The software is free and open source on Github (AGPL3.0): https://github.com/hzi-braunschweig/pia-system.

The main building blocks of this infrastructure are identical functionalities in web-based and mobile applications for the participants, specific user interfaces for all roles, and a backend consisting of services and databases. We integrated end-users of all professional roles in the development approach, especially the team of the NAKO study centre, for which the system was primarily developed to ensure consideration of all necessities and aspects of their workflows. The aim was to digitize certain processes for conduction a longitudinal epidemiological study; hence, we e.g. observed processes at the study centre, wrote them down as user stories which were in turn adjusted by staff from the study centre. This process is ongoing: we priorities feedback on PIA from all professional users in our 11 studies as part of our scrum process. The highest

priority is given to data protection and IT security requirements. Other criteria are feasibility of the change requests, added value, urgency as well as time and effort required. In November 2018, we conducted the first software testing by potential study participants. 12 test users provided structured feedback via an usability questionnaire.

Prior to each study, a pre-test is conducted in which, among other things (e.g. the organisational study procedure) the usability of the system is evaluated. In addition to qualitative feedback, answers to a standardized questionnaire instrument "System Usability Scale (SUS)" [25] are assessed. Any bugs we learn about either as part of our continuous tests as product owner or via our ticket system are prioritised and fixed if necessary.

Complementary to the review of adherence with European Union General Data Protection Regulation by the "Bundesbeauftragten für den Datenschutz und die Informationsfreiheit", we commissioned external penetration tests to assess security of the system.

2.1. Architecture

The main architectural decision concerned the choice of tools and frameworks based on one common programming language. We chose to base all programing on the JavaScript ecosystem, because it is widely used and offers a large portfolio of established and well-supported tools and frameworks [26]. For reasons of platform independency, easy patching, scalability, and adaptability, we follow the approach of containerised software development using Docker containers [27]. The communication between external systems and PIA schematised in Fig. 1 is only possible via a reverse proxy as well as an API gateway and always encrypted in transit (TLS/SSL). All internal microservices and database systems are sealed off in separate Docker containers and cannot be directly reached from the outside. To further ensure data protection requirements, we separated research data into three PostgreSQL databases, which are running on disjoint virtual machines (VMs) and are located in different networks. The first one, "qPIA", consists of clinical or research data, the second one, "iPIA", contains personal identifiers such as names and addresses, while the third one, "ewPIA", contains participants' consents, and in the long-term, also withdrawals. Lab results from the laboratory of the "Hannover Medical School (MHH)" are reimported in HL7 format using a sftp server. PIA is integrated into the external EDC system NatCoEdc, the IT system of the NAKO, as an iFrame and via API-calls. Notifications to mobile devices and web browsers are sent using Google's Firebase Cloud Messaging Service (FCM) which is used in a way that respects data protection. In the context of the current SARS-CoV-2 pandemic, the architecture has been extended to connect PIA to SORMAS (Surveillance Outbreak Response Management & Analysis System) which is used for case and contact management by public health departments [8,9]. As symptom diary, health information is transmitted from qPIA to SORMAS via a dedicated application programming interface (API).

2.2. Web and mobile application

We decided to use Angular [https://angular.io] together with Node.js [https://nodejs.org] for the web application part. Angular is a well-established framework; reported together with Node.js as most widely used [26]. For the mobile application, we used the Ionic Framework [https://ionicframework.com], which is based on Angular, thus, facilitating reusability of components. The Ionic framework made it possible to build a hybrid app that runs on Android as well as iOS devices with one shared codebase. The disadvantages of this approach are possible performance losses and the lack of "native-feeling" user interface elements in comparison to natively build apps [28]. On the other hand, a shared codebase means less work, a reduction in skill requirements for software developer and, therefore, a decrease in development and maintenance costs.

2.3. Backend service

The backend consists of several Node.js servers that are executed in Docker containers (Fig. 1). Node.js is a resource-efficient JavaScript based platform with little overhead and the only solution for containerised JavaScript services.

2.4. Storage concepts

Persistent storage is realized with PostgreSQL [www.postgresql.or/]. MySQL as an alternative would have been suitable as well; both systems perform on a very similar level [29]. The decision to use PostgreSQL over MySQL was taken due to its permissive open source license and the available developer experience.

2.5. Scalability

Horizontal scalability, i.e. scaling by adding more machines rather than increasing the machines' power, was achieved by the use of container technology in combination with stateless Representational State Transfer (REST) APIs. The REST paradigm requires a request to include all the data necessary for a server to process the request, without any additional data stored on the server, which makes it ideal for horizontal scaling.

3. Results

3.1. Implementation

We implemented six different roles: system administrator, researcher, participant manager, study nurse, consent manager and participant with specific interfaces and functions. Access is granted differentially: The researcher has access to qPIA and, thus, to all study data, i.e. medical data, including answers to questionnaires. Access to iPIA with contact data of all participants is exclusively reserved to the participant manager. The consent manager has access to a separate database (ewPIA) that contains only consents and withdrawals.

The role assignment is performed by the system administrator.

3.1.1. System administrator

The administrator sets up new studies within the app, invites new personnel into PIA and assigns those individuals with specific roles and rights within a specific study. The system administrator is also authorised to delete studies or to revoke permissions within studies.

3.1.2. Researcher

In PIA, the researcher has the possibility to implement new or change existing questionnaires including temporal scheduling of the questionnaires or defining conditions, which request participants to respond to certain questions. The researcher can set date(s), weekday, and time intervals for questionnaire display e.g. daily, weekly or monthly as well as the duration and activation time of the questionnaire. Researchers can implement algorithms for displaying a network of conditional questionnaires after specific data entry events. Researchers can put reminders as emails or in-app push notifications in place including number, timing and title of notifications to enhance participants' response. Researchers can also define conditions, after which the tool invites participants to take and ship biospecimens, including scanning of barcodes of the tubes. This can also be used to document drugs using the Pharmacy Product Number. For other documentation purposes, e.g. of vaccination cards, the invitation to take pictures can be integrated into questionnaires. The research team sees all questionnaire data, including laboratory reports, and can export them.

3.1.3. Participant manager

The participant manager administers personal contacts with

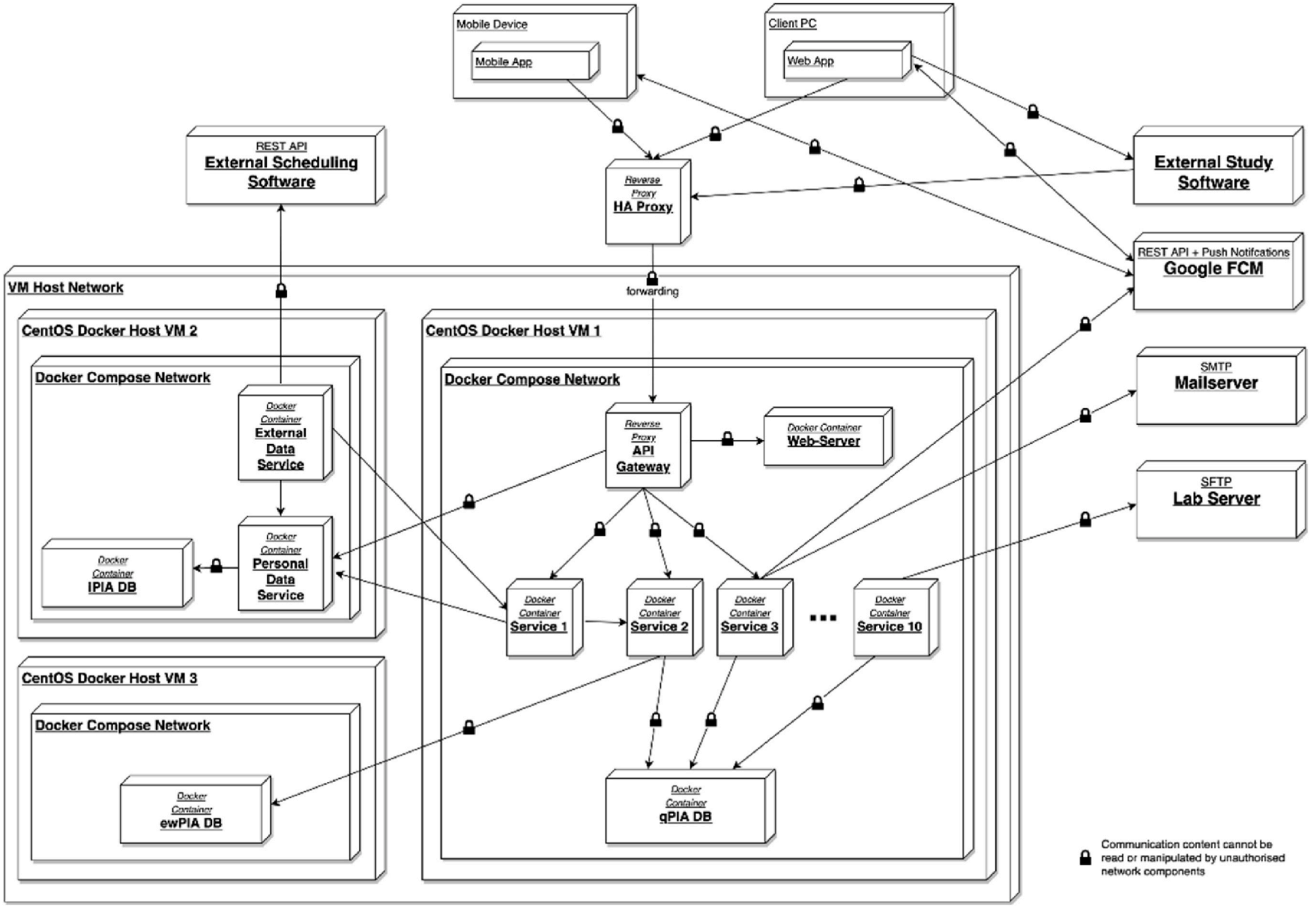

Fig. 1. Formalisation of network environment of PIA (basic version without connection to SORMAS).

participants and can enter identifying data (e.g. names). All contact events, e.g. telephone calls, are documented and can later be used anonymously for scientific analyses. An interface with a software that schedules participant visits within the NAKO [7] secures automated data transfer, while maintaining separation of research data and data that would allow re-identification of individuals. The integrated serial letters functionality within PIA also serves to send new material (i.e. biospecimen containers) to participants who are in need of new self-sampling kits.

3.1.4. Study nurse

The study nurses register new participants in PIA and generate first login data that are provided to the participants. In addition, the study nurses can store electronic case report forms (eCRF) in PIA regardless of whether the application is intended to be used by participants or by study personnel, e.g. for computer-assisted personal interviews (CAPI), or biospecimen collection in a study centre.

PIA is integrated into the IT system of the NAKO; authentication of study nurses is done in the background by exchanging a unique identifier a priori known to both system and a key not known to third parties. This has the advantage that the study nurses do not have to log into IT systems twice when registering a new participant.

3.1.5. Consent manager

Consent managers have access to PIA users' consents and in the future withdrawals in the database "ewPIA". Consents and withdrawals are stored in the "ewPIA" database for a certain period of time according to good epidemiological practice [30].

3.1.6. Participant

Participants can choose whether to use the mobile app or the web version and switch between the two at any time. The system presents an overview of all questionnaires and their respective status to the participant (Fig. 2b). Push notifications via the app or e-mails for PIA web-users will remind participants to respond to new or overdue questionnaires. If implemented by the researchers for a specific study, complementary to scheduled or conditional questionnaires, participants can use PIA to submit a spontaneous report at any time, enabling real-time documentation of acute symptoms and timely collection of biospecimens. The barcode of which can be scanned (Fig. 2c) or entered manually. The results of the laboratory analysis are automatically reported back individually to the participant via the app using HL7 for studies conducted together with the regional university. Additional feedback like personal health information as well as gamification elements are planned. Gamification elements will include a positive text when a certain percentage of answered questionnaires has been completed and encouraging messages when only a few questionnaires have been answered. In addition we envision to graphically display statistics on the occurrence of disease in the study population over time with configurable display options for participants.

3.2. Projects with PIA

PIA is currently used in 11 projects (www.info-pia.de). In the infection cohorts "ZIFCO- Integrated DZIF Infection Cohort within the German National Cohort" [31], "App-based Infection Assessment in RESIST (iAR)", "DIMI - Digital infection monitoring in persons living with immunodeficiency" and "SMARAGD – Sensors for measuring aerosols and reactive gases to deduce health effects", PIA is used for symptom monitoring of transient infectious disease with a special focus on respiratory diseases including laboratory diagnostics.

In further projects (e.g. MuSPAD – Multi-local and serial cross-sectional prevalence study on antibodies against SARS-CoV-2 in Germany [32], RESIST – Resolving Infection Susceptibility), PIA is used as electronic data capture system for interviews and medical examinations by medical staff. In the context of the SARS-CoV-2 pandemic, PIA served as COVID-19 symptom monitoring system for hospital and nursing staff as well as a symptom diary, connected to the case and contact person management system SORMAS-ÖGD [33].

Currently, more than 140 questionnaires are implemented in PIA and about 41,000 participants registered, of which approximately 39,700 are part of the MuSPAD study.

4. Discussion

Main requirements in the development of PIA were compliance with German data protection regulations including separation of person identifying data and medical/questionnaire data, easy adaptability to novel research questions (generalisability) and the ability to function as a stand-alone app, but also be suitable for integration into existing IT frameworks of studies such as the NAKO. Further requirements were implementation of the specific roles necessary in an epidemiologic study, e.g. researchers, participant managers, study nurses and participants. The real-time collection of data as well as the collection of biospecimens immediately during the disease episode allows for microbiological confirmation that is essential in infectious disease studies. The implementation of cyclic questionnaires and the development of algorithm for displaying a network of conditional questionnaires at specific times and after specific data entry events were necessary for long-term follow-up of the participants. The implementation of these complex survey structures in combination with the desired management functions would not have been possible either paper-based or with already existing survey tools like Limesurvey. Electronic Data Capture systems such as REDCAP are being used increasingly for data collection in clinical trials. They offer a complete study management and capture various types of data. However, less attention is given to long-term use by and compliance of participants, which is crucial for epidemiological cohort studies running for several years.

By (further) developing PIA we aim at increasing participants' involvement even more. On the one hand, interest could be instigated through (more) feedback of individual results, newsfeed with e.g. study results and generally intelligible summaries of current publications of the research area [34]. On the other hand, study participants can be actively involved in the development of PIA in the context of citizen science (e.g. SMARAGD project) [35]. This encourages participants of such studies with more direct involvement to stick with the study at hand; and makes PIA potentially more attractive for participants from other projects. We are not aware of other comparable systems that aim for a participatory development approach.

Furthermore, a large number of ECD-systems are not free and open-source, which was a further requirement for us to provide transparency and digital sustainability.

Recent unforeseen developments such as the SARS-CoV-2 pandemic highlight the importance of appropriate and highly flexible systems for epidemiological research. To be flexible in our implementation, we developed our own, customised eResearch solution, which supports data entry by participants and medical staff (with all necessary roles) equally and focuses on long-term usage among the participants through user engagement with feedback components and – in future – through further implementation of gamification.

5. Lessons learned and conclusion

PIA is still being improved and several functions will have to be adapted in future, especially to enhance usability for all users. Additionally, new features for e.g. further study types including randomisation, are planned. Pilot usability tests and ongoing studies indicate the feasibility of the eResearch system PIA for epidemiological projects [31]. Through the implementation of new studies, new ideas and requirements arise and the scope of the system is becoming broader.

Maintainability is one of the most important criteria of software. Good maintainability makes it possible to quickly adapt to new

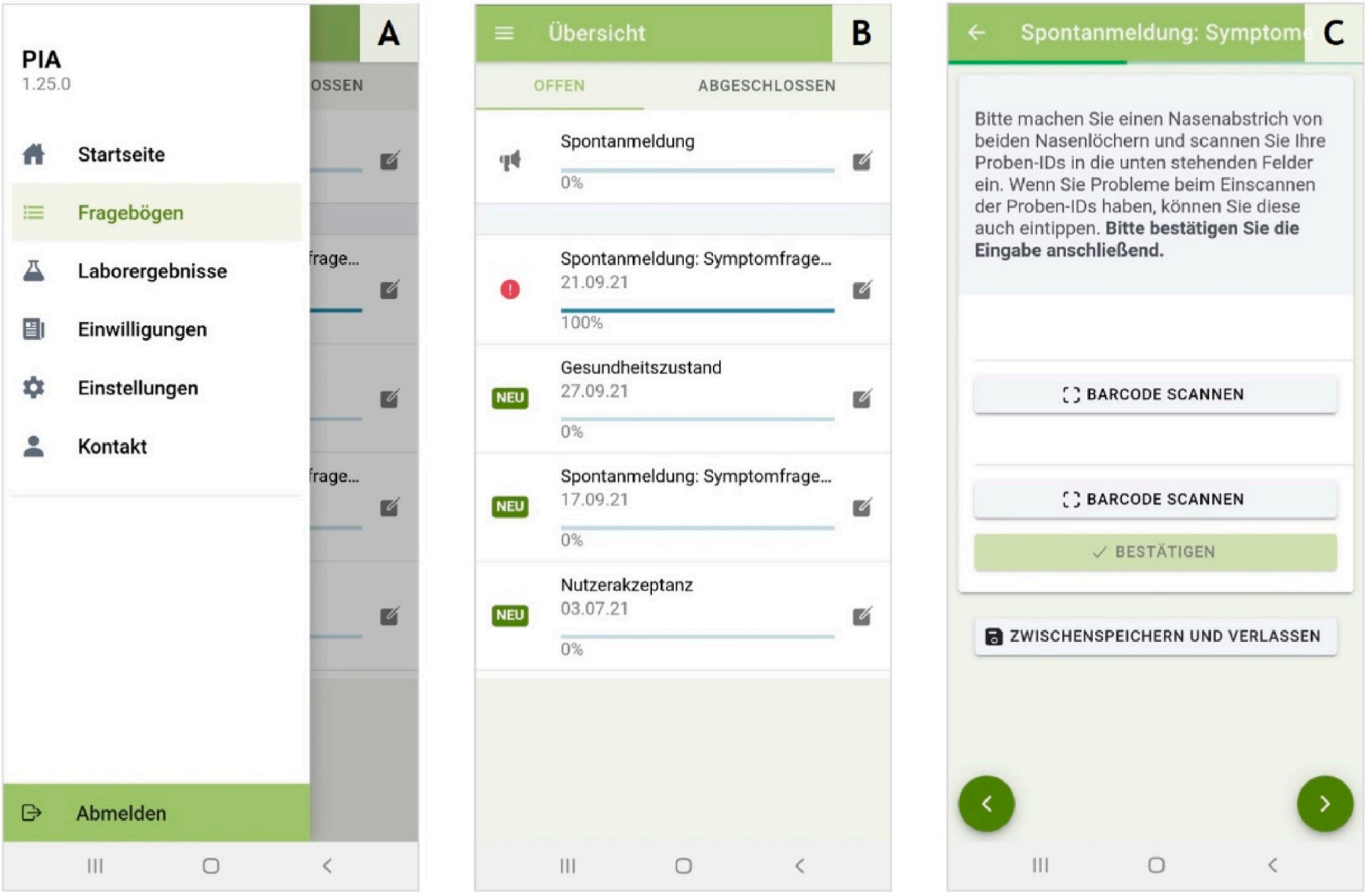

Fig. 2. **a)** PIA Menu **b)** Overview with various questionnaires. **c)** Participant interface for scanning tube barcodes after self-sampling of biospecimens.

requirements and continuous further development including IT security aspects. One of our lessons learned is to be more far-sighted and to take this criterion better into account. In the further process of development, refactoring work is planned to improve performance and maintainability of PIA.

Another criterion is scalability. The initial architecture was chosen to support scalability. However, the implementation of certain features, including scheduled tasks, made it more difficult to actually achieve it. We learned that the development team needs a shared vision and understanding of the software architecture to also achieve its goals in the long-term.

In addition, we aim to expand our end-to-end testing in order to detect errors at an early stage and to minimise the manual testing effort.

Furthermore, evaluations of user acceptance have shown that user navigation might benefit from an even more intuitive design. To increase long-term adherence by study participants, we plan to implement more feedback for participants and tailored gamification features.

Where possible, we assess performance indicators and user experience in epidemiological studies using PIA and results inform future software versions. During the development process, the integration of the eResearch system PIA into existing IT systems e.g. SORMAS or NatCoEDC posed a challenge due to the need for close cooperation between different IT companies and the adaption of PIA to different system structures. This should be considered in terms of time and organisation.

The main lesson learned from developing PIA includes that the integration of various experts are paramount who embody sufficient understanding in information technology, IT security, data protection, user experience, scientific methods, epidemiology and biomedicine while bridging differences in work style, methods and terminologies of these different disciplines. Their absence would result in underestimation of time and resources needed for building such a comprehensive eResearch system.

Authors' contributions

All authors have made a substantial, direct, intellectual contribution to this manuscript.

JKH and SC: Conceptualised the software as Product Owner and drafted the manuscript.

YK and SS: Advised on several features of the software conceptualisation.

ME: Designed first architecture of the software.

RD: Developed architecture of the software.

GK: Provided epidemiological expertise and advice.

All authors: Read and approved the final manuscript.

What was already known on the topic

- A variety of electronic data capture systems are available that facilitate data collection and improve data quality in epidemiological studies or clinical settings.

- For data collection in long-term studies, compliance of the participants is paramout; for specific research, the possibility for immediate response in case of incident health events or symptomatic biosampling is crucial; hence, a customised, but flexible eResearch system is needed.

What this study adds

- We present the conceptual design of the eResearch system PIA (Prospective Monitoring and Management Application) meeting the requirements of a wide range of epidemiological projects.

- The software solution is characterised by flexibility in content, comprehensive options for questionnaire implementation, many functions relevant to epidemiological research (role concept, integration of biosamples) and a high standard of data protection and IT security.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The development of PIA was funded by the Federal Ministry of Education and Research under the grant number 01KA1710 and also supported by the DZIF (German Centre for Infection Research), the Helmholtz Association, the Ministry for Science and Culture of Lower Saxony and the Ministry for social issues, health and equality (Niedersächsisches Ministerium für Soziales, Gesundheit und Gleichstellung).

We sincerely thank the "PIA Team" from Helmholtz Centre for Infection Research in Braunschweig for designing the application and for all the organisational and technical work they have done.

We greatly acknowledge the support of the Hannover study center of the Helmholtz Centre for Infection Research for enabling the conduct of the first PIA study within the German National Cohort (NAKO) and for the support in the conception of the application.

We are grateful for the work of Sven-Ove Wähling, who assisted with the conceptualisation of the basic design of the software and provided technical- organisational support.

We also thank all users of PIA (participants and professional roles) for giving us feedback.

Furthermore, we would like to thank all developers of the Conventic GmbH, who built the tool and were always available to help with technical questions. A special thanks goes to Adrian Karsten, who developed the very first version of PIA.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2022.100931.

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