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Autoreferát disertační práce

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Elektronický systém pro podporu provádění klinických studií s možností zpracování dat pomocí umělé inteligence

Electronic clinical study management system with artificial intelligence-based data processing capabilities

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

Abstract

An increasing amount of data are collected through wearable devices during ambulatory, and long-term monitoring of biological signals, adoption of persuasive technology and dynamics of clinical trials information sharing – all of that changes the possible clinical intervention. Moreover, more and more smartphone apps are hitting the market as they become a tool in daily life for many people around the globe. All of these applications are generating a tremendous amount of data, that is difficult to process using traditional methods, and asks for engagement of advanced methods of data processing.

For recruiting patients, this calls for a shift from traditional methods of engaging patients to modern communication platforms such as social media, that are providing easy access to up-to-date information on an everyday basis. These factors make the clinical study progression demanding, in terms of unified participant management and processing of connected digital resources.

Some clinical trials put a strong accent on remote sensing data and patient engagement through their smartphones. To facilitate this, a direct participant messaging, where the researchers give support, guidance and troubleshooting on a personal level using already adopted communication channels, needs to be implemented. Since the process of such support is very time-consuming and often difficult to assure quality, it calls for revisiting methods for performing a randomized control trial.

A system named *Hubro* for electronic management of clinical studies to address many of the identified challenges has been created. The system supports following processes throughout the study: recruitment, randomization, follow up via messaging, automatic usage data collection and patient self-reported data collection through electronic questionnaires – all accessible from one single user interface. Data collected through tailored questionnaires is what is essentially defined as electronic patient-reported outcome per today, which is currently on the rise in a health research setting.

The modular design of the presented system assures the possibility of functionality enhancement in various levels of the data processing chain. The system has loosely coupled architecture and utilizes pluggable computation modules, with support of artificial intelligence.

Therefore, the system can be extended with additional sources data, but also with data post-processing capabilities, which is useful when discovering various insights or detecting specific patterns.

So far, two studies have used this system – with 50 and 8 participants. The Hubro electronic study management system has significantly improved the feasibility of these interventions through streamlined workflow, electronic messaging and data collection support. The Hubro system has saved a considerable amount of time to researchers when managing the study. The usability of the administration interface of the system on various devices such as smartphones and tablets also allowed a quick turnaround when reacting on requests of participants. Although, researchers have reported a steep learning curve for third-party tools integrated with Hubro that are used for usage analytics and questionnaire distribution. Also, as primary candidates for updates in future revisions, they identified an expansion of existing communication capabilities by a secure communication channel directing from participants to researchers; implementation of tools assisting data extraction and formatting; and introduction of reminders and recruitment planning functions.

Abstrakt

Objem dat, který je generován nositelnými zařízeními v průběhu ambulatorního i dlouhodobého snímání biologických signálů, adopce pervazivních technologií a dynamika předávání informací v rámci klinických studií – to vše mění způsoby, kterým mohou prováděny klinické studie. Více a více aplikací, které přicházejí na trh se stávají pomůckou v denním životě lidí po celém světě. Všechny tyto aplikace produkují obrovské množství dat, jež je obtížné zpracovat tradičními metodami, a vyvstává tak nutnost využití pokročilých metod.

Je také možné sledovat odvrat od tradičních metod náboru pacientů, k moderním komunikačním platformám jako sociální sítě, které usnadňují přístup k aktuálním informacím. Tyto faktory činí postup v klinické studii náročným s ohledem na management účastníků studie a zpracování informací ze zdrojů dat.

Některé klinické studie kladou velký důraz na sběr dat ze senzorů a zapojení pacientů do studie prostřednictvím jejich mobilních telefonů. Pro usnadnění tohoto přístupu, je nutné využít přímou komunikací s pacientem, kdy administrátoři studie poskytují podporu a pomáhají řešit problémy, které se mohou v průběhu studie vyskytnout, a to za pomoci moderních komunikačních platforem a elektronických zpráv vedených přímo s účastníkem studie. Celý tento postup je nicméně časově náročný, a je tedy nutné přehodnotit způsob provádění randomizované kontrolované studie.

Byl vytvořen elektronický systém *Hubro* pro podporu provádění klinických studií, který adresuje tyto nově vzniklé požadavky. Tento nově vyvinutý systém podporuje: nábor účastníků, randomizaci, zasílání zpráv, automatický sběr dat o používání aplikace a uživatelských skrze online dotazníkový systém – tato funkcionalita je integrována v rámci jednoho uživatelského rozhraní. Data, shromážděna z elektronických dotazníků, jsou v zásadě obdobou elektronických formulářů výsledků hlášených pacientem, jako způsobu sběru dat, který je v současné době na vzestupu v oblasti výzkumu eHealth.

Modulární design zajišťuje možnost rozšiřitelnosti funkčnosti na různých úrovních řetězce zpracování dat. Architektura systém je postavena na volně vázaných komponentech, a používá zásuvné moduly s podporou umělé inteligence. Systém tak může být rozšířen o dodatečné

zdroje dat, ale také o možnost post-processingu dat, který napomáhá při zpracování úloh typu detekce vzorů.

Systém Hubro byl prozatím využit v rámci dvou studií – s 50-ti a 8-mi účastníky. Tento systém výrazně usnadnil provádění těchto klinických studií díky zjednodušenému modelu administrace studie, systému pro zasílání zpráv a podpoře pro sběr dat. Používání systému Hubro zároveň ušetřilo množství času při administraci studie, díky použitelnosti administračního rozhraní na různých typech zařízení (smartphone, tablet, PC), které umožnilo rychlejší reakce na požadavky. Výzkumníci, kteří tento systém používali, nicméně zaznamenali poměrně strmou křivku učení při používání nástrojů třetích stran integrovaných do systému Hubro, které jsou používány pro sběr uživatelských dat o používání aplikace a distribuci dotazníků. Zároveň byly výzkumníky navrhnuty následující vylepšení – dvoucestná komunikace integrovaná v systému Hubro, implementace nástrojů usnadňujících následnou extrakci dat a formátování a implementace funkcí pro plánování náboru účastníků studie.

Klíčová slova: mHealth, klinická studie, automatický sběr dat, mobilní aplikace, elektronický dotazník, nositelné zařízení

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Introduction

The conducted research has been described and interpreted in detail in separate publications.

- M. Muzny, A. Henriksen, A. Giordanengo, J. Muzik, A. Grøttland, H. Blixgård, G. Hartvigsen and E. Årsand, "Wearable sensors with possibilities for data exchange: Analyzing status and needs of different actors in mobile health monitoring systems," *International journal of medical informatics,* vol. 133, 2020. IF 3.025. [1]
- E. Årsand, M. Muzny, M. Bradway, J. Muzik and G. Hartvigsen, "Performance of the first combined smartwatch and smartphone diabetes diary application study," *Journal of diabetes science and technology,* vol. 9, no. 3, pp. 556-563, 2015. [2]
- E. Årsand, M. Bradway, H. Blixgård, M. Muzny, A. Giordanengo, A. Grøttland and G. Hartvigsen, "Experience from using a dynamic study management service for an mHealth diabetes type 2 RCT," *DIABETES TECHNOLOGY & THERAPEUTICS,* vol. 20, p. 73, 2018. [3]
- A. Henriksen, M. H. Mikalsen, A. Z. Woldaregay, M. Muzny, G. Hartvigsen, L. A. Hopstock and S. Grimsgaard, "Using Fitness Trackers and Smartwatches to Measure Physical Activity in Research: Analysis of Consumer Wrist-Worn Wearables.," *Journal of medical Internet research,* vol. 20, no. 3, 2018. IF 5.03. [4]

The diversity of various mobile health (mHealth) -enabled clinical trials puts a strong accent, especially on the possibility of individual handling of participants data in different stages of a study. In ordinary cases, this need is covered by direct participant messaging, which supports the guidance and troubleshooting on a personal level using already adopted communication channels. The situation calls for a revisit of methods of performing randomized controlled trial (RCT) [5].

Multiple observables are forming the input when performing a mobile health intervention. Examples of these observables are electronic patient-reported outcome (ePROs), mobile application usage data, self-registered data and health data collected from connected wearable devices with possibilities for data exchange. While usage data and self-registered data collection and processing is a deterministic task, to better understand wearable device's data

exchange, it is first necessary to establish a framework that describes current data exchange possibilities due to heterogeneous capabilities of various wearable devices.

To set a foundation for documenting data exchange possibilities, we have identified a framework [1], that describes data flow between different data collection systems. The basic block of the framework is the wearable device as a source of data. The framework also contains systems such as Health platforms (Google Fit [6], Apple Health [7]), third party fitness services, device's cloud service, middleware and Electronic Health Record (EHR). Device's data transfer capabilities are, however, often influenced by made-by-design constraints. Manufacturers tend to implement their own proprietary Application Programming Interfaces (API) for transferring the data. In a world of mobile applications backed with cloud support, this allows device producers to control the flow of data from the initial point of transmission, leaving out a possibility for implementation of e-health solutions through standardized protocols.

Based on the findings, we have identified and addressed the following challenges:

- the current status around wearable devices signalizes lack of systematic health data exchange capabilities. Wearable devices generate a vast amount of data from their integrated sensors and are an essential input of mobile interventions. However, the support for exchange of this data is limited

- commercially-available wearable devices do not fit into the framework of mobile electronic health (eHealth) self-management tools only as a passive source of health data. However, in some cases, they can complement the functionality of a mobile device and improve patients comfort when dealing with a chronic disease such as diabetes. To prove this, we have designed, developed and tested the usability of the first combined smartwatch-smartphone diabetes diary application

- there is a need for updated evaluation approaches for eHealth and mHealth interventions, that would provide not only survey-based instruments but also integrate a data collection framework, that would support researchers addressing the challenges above. To address this issue, we have created and tested a research tool for the management of mHealth and eHealth studies

Hypothesis and Research Objectives

The aim of our research was to:

- identify health data-exchange capabilities of wearable sensors
- demonstrate the application of wearable computing in personal health care on a specific use case of a novel combined smartwatch-smartphone application for diabetes self-management
- design and implement a clinical trial support tool, with support for data-collection from wearable devices and use of artificial intelligence for data processing

Within the evaluation and testing phase, we aimed to:

- evaluate the usability of the combined smartwatch-smartphone application on a small sample of T1 diabetes patients using questionnaires
- perform two studies using the Hubro tool, and evaluate the usability of the system using questionnaires that have been responded by the study manager

Methods

We have designed and implemented a system for electronic study management, Hubro, and also newly developed accompanying smartwatch application. We have demonstrated its usability with an existing smartphone application *Diabetes Diary* [8]. Diabetes Diary is a self-management tool for patients with diabetes, developed by the Norwegian Centre for E-health Research (Tromsø, Norway) in cooperation with Spin-off Companies and Research Results Commercialization Centre, The First Faculty of Medicine, Charles University in Prague (Prague, Czech Republic). Its primary function set consists of glucose, carbohydrates, insulin, medication and physical activity self-tracking; visualization of the data; decision support through insulin dose recommendation based on similar situations and integration with the

RunKeeper fitness platform [9]. The Diabetes Diary is currently available worldwide. Although the application supports both the iOS and Android platform, the functionality slightly differs.

To demonstrate the usability of smart wearable devices with physical activity tracking capabilities in a self-management of chronic diseases, we have integrated the Diabetes Diary smartphone application with a smartwatch, resulting in the development of the first combined smartwatch/smartphone diabetes application [2]. The novel concept of combined smartwatch/smartphone diabetes application enabled users to utilize the potential of the wearable device by making new registrations and having them synchronized with the smartphone; getting timely reminders for blood glucose check; having an estimated step count transferred to the smartphone and segmented into individual physical activities. The application was developed for nine months using agile development methods with three diabetes patients continuously testing the application. Agile development methods allow an incremental model, which is based on a tight collaboration within the team and stakeholders and using dynamic interactions, it provides continuous delivery contrary to traditional methods of development, such as the Waterfall [10]. In a research setting, it is desirable to adhere to dynamically changing requirements flexibly, and therefore we chose Agile. The performance evaluation of the combined smartwatch/smartphone diabetes application was assessed using a questionnaire, where users reported increased usability and provided specific suggestions for improvements. Indeed, the lack of data collection infrastructure and nonexistent usage analytics platform served as additional indicators for a need for an update of research evaluation methods.

We have also shown that for consumer-based physical activity trackers and smartwatches, the number of new devices coming to the market every year is high and increasing [4]. With analysis interoperability, we have documented data-exchange capabilities of 362 wearable devices in terms of data transfer protocols, communication interfaces, integration with PC/smartphone, access to user data, developer-access to the device, and market status. Based on this analysis, we created a framework, which we further use to describe relations between different components in terms of communication capabilities. This framework allowed us to better understand issues with interventions using mobile and wearable devices, from the standpoint of different actors in mobile health monitoring systems: EHR providers, software developers, and patient users.

Piwek et al. identified three reasons that limit the extensive growth and further use of mobile devices for research [11]:

- programming barriers
- consenting issues
- concerns regarding privacy and data security

The new Hubro platform was created based on needs to perform studies dynamically and fully electronically. With a massive use of social networks, email and electronic communication in general, the online recruitment process can be much more time-effectively than during an ordinary RCT. We can reach potential participants through electronic channels and provide them with a link to an electronic resource (website) where they can get more information about the study and show their interest to participate if they find the study relevant. From this point, the study manager can guide the participants through the whole study process by directly sending them personalized messages. Participants can be randomized into different groups by a built-in block randomization routine or manually by the study manager. The study manager is also able to provide participants with electronic questionnaires in different phases of the study. Hubro research platform also provides tools for a data collection from the software which study participant uses during the study, i.e. the subject of intervention (e.g. smartphone application). The potential of Hubro research is in its' modularity, expandability and re-usability for different intervention types.

Figure 1. illustrates all steps of study:

1. Electronic recruitment of participants through e-mail, social networks, web and other media

2. Informed Consent forms, distribution and reception of answers

3. Randomization via a built-in and adjustable algorithm

4. Questionnaires: creation, individual delivery and collection

5. Remote distribution of intervention, e.g. through mobile apps, web-URLs or user-logins

6. Follow-up of participants during and after the trial, i.e. reminders, user-support

7. Data gathering, automatically and continuously, including health parameters and usage logs from intervention tools, e.g. sensor data, app data or website input

8. Data analysis, i.e. regular and continual analysis, and data-grouping for later advanced analysis

9. Study closure, patient follow-up, reporting and delivery of expected results and insights
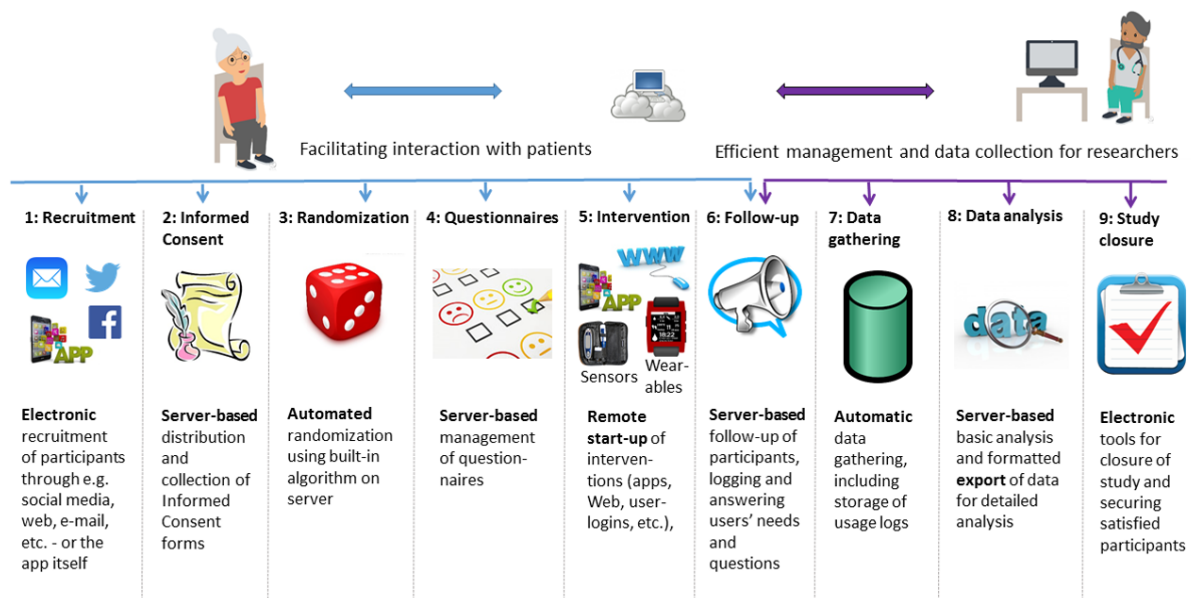
Figure 1. Hubro - electronic study-management system.

Hubro addresses identified issues in the following way. It reduces the programming barriers by isolating some of the system functionality from its tight integration into the smartphone, resulting in the usability of the Hubro system, i.e. by using an only partial set of functions when performing the study. The integrated survey system is eliminating the need for by providing a generic web-based surveys/consent forms, usable on PCs, smartphone, tablets and other devices that enable interactive input from study participants. Privacy and data security measures include decoupling identity database from the depersonalized data, where the only link is the password-protected translation function.

Results

Identifying Health Data Exchange Capabilities of Wearable Devices

To describe current health data-exchange capabilities of wearable devices in detail, we have carried out a review of 362 wearable devices [1]. As a primary source of data, we have used Vandrico database [12], which is a structured database of wearable devices. From the total count of reviewed devices, 310 were included from the Vandrico database, and the rest of the devices

were identified based on information from other sources (i.e. Google search, manufacturer's website linked back from Vandrico).

Identified devices were described using 13 main attributes that are listed in Table 1. We have further tracked six descriptive attributes, that identify device's manufacturer, description, source URL, keywords, system variety and source of information.

Attribute	Attribute description
Type of wearable system	Device classification
Communication interfaces	Set of integrated communication interfaces for transmitting data
Data protocol	Indicates whether the device uses proprietary or standardized/open data protocols
Smartphone/PC integration	Types of systems the devices can be connected to
Direct integration with health platforms	Indicates whether the device supports direct import of data to Google Fit or Apple Health
3rd party integration with health platforms	The device can be connected to one or more health platforms via a third-party provider
Connection to Health Care System/Middleware	The device supports import of data to a health care system/middleware
Health data types	Enumeration of types of physiological data extracted from integrated sensors
Integrated sensors	Enumeration of sensors integrated within the device
Medical device	Indicates a certification or approval by corresponding agencies/authorities
User data access	Collected data are accessible either by directly inquiring the device or via a cloud solution
Developer access	Indicates support for the development of custom applications running on the device
Device availability	Indicates the production status of the device

Table 1. Collected attributes for wearables [1].

Based on the collected data, we have concluded the following:

- only a few producers are using standardized transmission protocols/APIs to enable third parties to transfer a data from a wearable device

- Bluetooth compatibility issues may hinder the integration of wearable devices with a full spectrum of smartphones

- Google Fit integrates directly with slightly more devices compared to Apple Health. However, 87% of the reviewed devices do not connect with any health platform

- connection to Health Care Systems/Middleware is sparsely supported

- majority of identified health data types were formed by accelerometer-derived data (physical activity, sleep data)

- only a few wearables covered in the review integrate advanced sensors of physiological health parameters such as ECG, EEG or blood pressure

- the wearable devices consumer market comprises of a small number of certified devices

- there is a need to use a standardized data exchange format to improve interoperability

- only a few devices provide developer tools that allow creating applications running directly on the device

Combined Smartwatch/Smartphone Application for Diabetes Self-Management

We have proposed a novel concept of a diabetes companion application running on a smartwatch [2]. This application aim is to facilitate the use of digital diabetes diary on the smartphone and add several new features. We mainly focus on the integration of physical activity tracking capabilities, and we investigate how these capabilities affect the compensation of diabetes patients. Our solution delegated commonly used functions of a smartphone-based diabetes diary to the smartwatch and added physical activity processing of accelerometer data on a smartphone.

As a candidate for the implementation, we selected Pebble smartwatch [13]. Pebble supports a desirable set of functionalities that we have identified during the review of wearable devices. Mainly it is the possibility to develop own applications running on the device, access to the raw

sensor data and compatibility with both leading smartphone operating systems – Android and iOS. Testers in the evaluation phase have appreciated the device's features like a simple user interface, long battery life and well-readable monochromatic display.

The basic set of our smartwatch application's functions included insertion of new carbohydrates/insulin/glucose recordings with a decimal precision (Figure 2. – A-C), presentation of prior registrations (Figure 2. – D), recording of physical activities (Figure 2. – E), reminders for glucose measurement and steps counting (Figure 2. – F). Pre-processed physical activity data was continuously transferred to the smartphone, where it was further transformed into physical activity segments and presented with the rest of the data to the user.
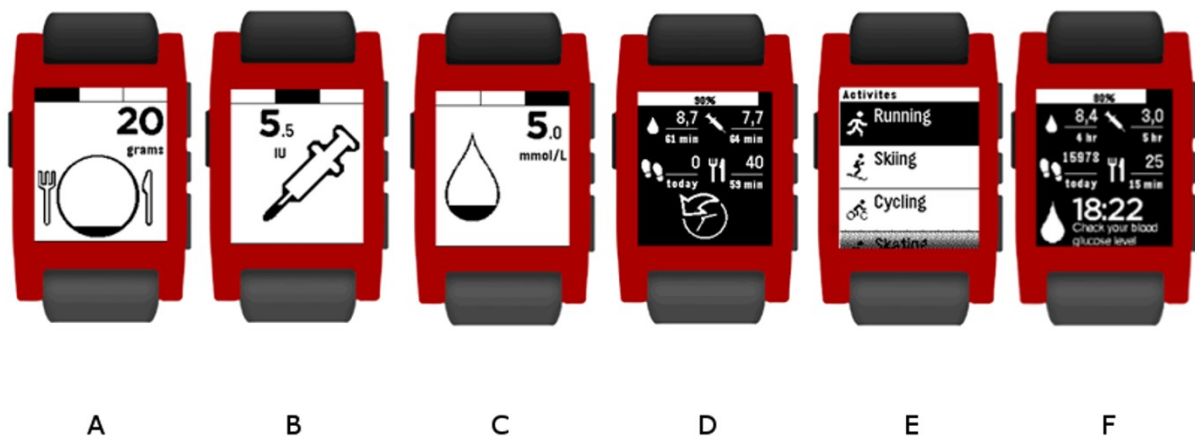

Figure 2. Diabetes Diary application on a Pebble smartwatch [2].

Evaluation of Combined Smartwatch/Smartphone Application for Diabetes Self-Management

The testing population consisted of 4 males and 2 females with type 1 diabetes. Test participants received a pre-test questionnaire, where we asked for their expectations regarding provided functionalities. Most of the identified desirable functions, such as reminders, physical activity tracking and two-way communication with the smartphone diary were already implemented during the 9-month development period and were ready to be tested.

We have used the post-test questionnaire to cover topics related to the daily usage of the application. Users have reported positive usability of the system; however, some of them have troubles understanding the advanced functions such as looking at the second latest values through the smartwatch application.

Following features received positive user feedback:

Stand-alone use of the application

To a certain extent, it is possible to use the Diabetes Diary for the Pebble smartwatch exclusively without a smartphone. This use might be an option for older people, who may find the user interface of the smartphone too complicated. In this case, the functionality of the smartwatch application is limited to show the latest and second latest registrations, track physical activity and provide alarms for an upcoming blood glucose measurement.

Possibility to use the application offline without having it connected to a phone

It is possible to use the smartwatch application for a certain amount of time offline, without having it connected to a phone. This feature may be useful when the smartphone runs out of battery. All registrations and physical activity data recorded in this offline period are consequently transferred to the phone after the smartwatch reconnection.
The smartwatch app will remember approximately 200 days of data.

Speed of making a new registration

We have compared the speed of making new registrations using the smartwatch and using the smartphone. The test has shown the average time required to make a new registration using a smartwatch was 13 seconds, on the other hand making a new registration using a smartphone took 36 seconds, which is considerably longer than in a case of the smartwatch.

The smartwatch application has been released for a public audience and gained positive feedback from its users. However, since the production of the Pebble smartwatch has been discontinued, the platform infrastructure has been unmaintained since then. The experience, however, showed the potential and improved usability of combined smartwatch/smartphone self-management application.

Design and Implementation of an Electronic Clinical Study Management System

With the ever-evolving landscape of mobile and wearable technology, it is important to empower clinical trials investigators by delivering them sophisticated tools to increase efficiency of mHealth clinical trials. While the traditional RCTs are well described, newly

emerging methods of mHealth evaluation are still being developed and their efficacy is being evaluated. In particular, for mHealth interventions targeting chronic diseases, the hypothesis that better monitoring with mobile technology will lead to better management, better outcomes and reduced disease burden has yet to be adequately tested [14]. However, we have identified lack of services/platforms, that would enable the researcher to create and manage studies with support for patient consent easily, and offer randomization, messaging and data processing with a possibility to run on-premise appliance (e.g. research organization's in-house servers).

From a high-level perspective, the Hubro consists of multiple servers, each serving a specific purpose. The responsibility has been divided in the following way:

- Questionnaire platform
- Usage logs collection platform
- Identity directories and authorization server
- Enterprise service bus
  - Identity translation service
  - Randomization service
  - Messaging service
  - Data upload service
- Web frontend for project administration
- File archive area
- REST API
- SMTP server

An initial step when performing a study is the determination of interest for participation. The generic web-based interest form is providing compressed information about the enrollment process, and it is provided for each project in the Hubro evidence. The link to interest form can be distributed via various channels. Social networks, a media with a significant outreach, can be utilized to share the link among various targeted patient groups. The interest link can also be sent out via email to existing distribution lists. Another option implemented in the Hubro system is to express an interest on behalf of a particular person. In practice, the study manager can insert one or more email addresses through the Hubro user interface, which would make these persons implicitly interested in the project.

Having the required initial amount of people who are interested in participating enrolled in the system, the study manager can start distributing informed consent forms, questionnaires and messages.

Consent forms and questionnaires are distributed through the open-source product LimeSurvey [15]. LimeSurvey is an on-line statistical survey web application, which allows to create, distribute and manage web-based surveys. The layout and design of the surveys can be modified using a template system, that makes surveys reusable in multiple different interventions.

Messages in the Hubro system can be distributed through various channels. So far, the Hubro system supports distribution of information via an ordinary email, or/and through the integrated REST API, from where the messages can be pulled by individual applications connected to the platform. For the messages delivered via REST API, we have not implemented an option for a direct response, and therefore the messages are only one-way function. Lack of option for direct response is however supplemented by a possibility to include formatted text enriched by HTML tags. This way, the study manager, can include images or website links containing additional information or interactive elements such as forms.

When planning a randomized clinical trial, careful consideration must be given to how participants are selected for various arms/treatment groups of a study. Selection bias may occur when participants are not assigned to treatment groups with equal probability. Block randomization is a commonly used allocation concealment technique in clinical trial design to reduce bias and to achieve balance in the allocation of participants to treatment groups, especially when the sample size is small. We have implemented block randomization as a default randomization method in the Hubro system, that is available for study manager.

The Hubro system uses two LDAP servers, denoted as LDAP0 and LDAP1, are used in Hubro to keep information about participants and project information. The LDAP0 identity tree structure is designed in a way, that the root level comprises of multiple project organizational units. Each project organizational unit has a set of groups that represent actual intervention groups of participants in a study. Participants remain in a project organizational unit, in a case, that the participant is not assigned the group yet.

A counterpart of LDAP0, the LDAP1, is a flat database of participant identities using an email as an exclusive, primary identifier. Essentially, every identity in LDAP1 can be linked to one or more identities in LDAP0, since every person can participate in multiple projects.

A translation service provides the translation between identities in an anonymized directory (LDAP0) and identities located in an identity directory (LDAP1).

Secure data collection service is a tool for secure, on-demand transfer of data from client to researcher. The receiving endpoint does not define any mandatory data scheme and thus leaves all data post-processing for a researcher. On the other hand, the service remains generic enough to cover most use cases of transferring various types of data from a wide range of devices (e.g. smartphones, smartwatches, wearables), when the research application is acting as a data collection hub. The data collection service can also be used as an independent component by users outside of the research study when needed, i.e. enrollment in the study is not a prerequisite for sending the data into the system.

Besides the secure user-data collection service, we have identified application usage logging as another modality, which needs to be captured to understand users' interaction with the mobile application fully. Usage logging complements questionnaire-based interventions on a more granular level of interaction tracking. These logs help us discover more profound insights into the use of the application. For this purpose, we have identified and integrated Matomo (formerly Piwik) [16], which is an open-source product, primarily designed to support web analytics.

The Hubro system can generate a vast amount of data depending on its specific application. At the time, the collected data are provided in a different format through individual services' APIs, which may hinder its batch processing in various tools. Therefore, the manual data analysis performed by researchers can be demanding in time and also in resources and needs the assistance of a person providing technical support. Pluggable modules can implement connectors with well-known and widely supported data exchange formats such as HL7 FHIR [17], or OpenEHR [18].

Another use case of utilizing decision support modules would cover smart triggering of alarms for the researcher. These alarms would be based on a decision support algorithm, generated using predefined rules set by a study administrator. These rules would consist of one or multiple conditions related to the status of patient progression throughout the study (survey completion,

delivered messages). This approach would eliminate situations, when the study manager has to frequently check for different indicators, to distinguish patients that need additional attention in terms of reminders or technical assistance.

In addition to providing collected set of unprocessed data, the Hubro system can be capable of automatic generation of additional descriptive or predictive information through pattern detection algorithms, machine learning and artificial intelligence. Implementing this feature should not be difficult due to the system's loosely coupled architecture and programming language independence. A use case that demonstrates the use of AI applied has been presented by an EHR vendor Epic, which developed a sepsis prediction module [19]. Another use case, presented by Cerner HealtheDataLab, includes HbA1c prediction for outpatient populations and heart failure prediction [20, 21].

As of now, Hubro supports a generic study workflow, i.e. manual staging of patients through multiple questionnaires combined with a continuous collection of data. While this design can present a good fit for many study protocols, it may be unusable for more complex studies or studies with many participants. As of now, study administrators have to perform many manual check-ups and interventions to keep up timely interaction with study participants in terms of questionnaire distribution and other concerns. Staying in touch is especially important during the recruitment and starting phase of the study, but after some time it may become exhausting, and thus also more vulnerable to human error. A natural expansion of the naïve approach would be an integration of a workflow manager, that would enable better, automatic control of patient staging throughout the whole study. This way, the study administrator would not need to send messages or reminders based on manual assessment of group membership, questionnaire completion or other indicators, as these would present the workflow manager's input parameters. Output actions of workflow manager would consist of questionnaire distribution, message delivery, data processing trigger and others.

Due to a loosely-coupled design of the Hubro system architecture, integration of modules with data post-processing capabilities does not require modification of existing components but instead makes use of individual services through their APIs. We have developed a proof-of-concept module that analyzes diabetes data collected throughout the study from a specific target patient group and estimates HbA1c over the last several months for each patient.

Hubro has been used in two studies with 50 and 8 participants, that were divided into intervention and control treatment group. Both studies aimed to test the new functions of the Diabetes Diary application. They recruited participants through the Diabetes Diary smartphone application and social networks.

The first study has lasted for 11 months, aiming to evaluate new functionality integrated into the Diabetes Diary application. The recruitment has been done online, through social networks such as Facebook and LinkedIn, resulting in 50 patients that participated in the study. Anonymous IDs have been generated for patients in both groups. Automatic self-registered data and usage data collection have been enabled by entering this ID into the Diabetes Diary application. The treatment group of patients has been provided with a new version of the Diabetes Diary via electronic distribution channels alongside with a set-up guide that facilitated the installation and data migration process[1]. Participants have been informed about the progress of the study at regular intervals using the Hubro messaging system utilizing both email and in-app messages. Same communication channels have been used to distribute questionnaires throughout the study.

During the first, pilot study the study manager spent the following amount of time on each task per participant: Informed consent delivery and collection (2-minutes); Randomization (1-minute); Delivery of the Initial questionnaire (1-minute); App distribution (4-minutes); Mid-study questionnaire (1-minute); and Final questionnaire (1-minutes). Minutes spent logging into the system, checking participant status, sending questionnaire reminders and other tasks approximately tripled these times. In total, 30-minutes have been required per user.

The second study has been conducted for 6 months with 8 patients, that were recruited through their health care providers. The research team invited the patients, that shown interest in participating in the study, by sending them a link to an interest form. Anonymous IDs have been generated for those who have signed up through the interest form. This ID linked the

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[1] Initially, the treatment groups have been using two versions of the application, and it was crucial to make the data migration process from the original version to the new version seamless and robust so that patients do not encounter any problems.

identity with both LimeSurvey and Piwik/Matomo usage analytics databases. Both emails and in-app messages were used for communication with participants. These were primarily utilized for distribution of links to questionnaires, study progression information and monthly follow-up messages.

During the period of the second study, a researcher had to actively check for responses from health care providers in LimeSurvey. These responses contained their experience with the intervention itself, and have been inserted into the LimeSurvey after every consultation with a patient, including the patient's ID. After six months, at the end of the intervention, the researcher would make sure that the patient participant had gone to the doctor by checking LimeSurvey. Once this has been confirmed, the researcher would send the second questionnaire set to the participant.

The following questionnaire has been distributed to three respondents, that have been directly working with the Hubro system, throughout the two studies.

1) Can you describe your role/competence when using the Hubro system?

2) Do you find the overall approach effective in comparison with a traditional methods approach in following aspects? Speed, reliability, management of participants, cost-effectivity.

3) What functions are you missing?

4) About which functions do you think should be implemented better/in a more user-friendly way?

5) Have you experienced any problems with the system?

6) Have you used the possibility to manage the study from the smartphone?

7) Do you find the user interface intuitive?

8) Have you got any positive/negative feedback from the study participants?

The questionnaire has been evaluated in a following way:

1) The questionnaire has been filled in by 3 respondents –PI/project manager, researcher and system developer. PI/project manager and researcher have been involved in all phases of two studies, while system developer has provided technical support (service availability assurance and data extraction support).

2) Speed, reliability, cost-effectivity and convenience of participants management were appreciated in the questionnaire answers. A concern has been expressed to a concept of two user identifiers - user ID and anonymous ID, which was hard to understand. This concept was introduced to provide study participants with a way to quickly join the study, i.e. by providing a 5 characters identifier (user ID) that was connected fully qualified GUID-based identifier (anonymous ID) in the database. Both identifiers have to be used when performing basic operations such as, e.g. extracting user data from the database, deanonymizing the user, which introduces an additional level of manual effort. In future, this concept should be revisited and implemented a more user-friendly manner.

3) Based on the feedback from researchers, following new functionalities and system updates would be appreciated: more accessible user-interface; integration of reminders; integration with more advanced recruitment capabilities other than those currently implemented; recruitment scheduling and monitoring; notifications; more secure implementation of the messaging function.

Previously mentioned connection between user-id, anon-id and data in third-party systems (Piwik/Matomo, LimeSurvey) was confusing when performing various operations such as fetching user data or exporting usage logs. Two respondents raised this issue. Another concern was expressed about the utilization of third-party tools - usage analytics platform (Piwik/Matomo) and survey platform (LimeSurvey), specifically questioning their choice due to their complexity and low user-friendliness. These tools are complex, designed to suit a wide range of use cases, and therefore they are coupled with a variety of options and settings, that might be confusing for researchers/study administrators, who only need to use a specific subset of these functions. Although, within the narrowed portfolio of alternatives, these tools stand out among other choices in terms of integration possibilities.

4) Researchers mentioned following optimizations to minimize manual efforts and frequent checkups in following ways - a better-implemented process of operating with patients, i.e. placing them into groups; easier distribution of questionnaires and tools (applications); more streamlined process of questionnaire completion checks, a user interface to interact directly with the LDAP servers (e.g. removing participants).

5) From the researcher's point of view, one of the identified difficulties, was LimeSurvey limited export capability, that only allowed PDF exports, which was not easy to import further in a spreadsheet editor such as MS Excel. Also, it was suggested to implement a two-way messaging function, which would mitigate the necessity to use an ordinary email as a primary communication channel from patients to researchers. Also, the user interface for user's look-up based on their email addresses was perceived as a candidate for improvement, as it required a manual effort in terms of email client utilization as discussed within Question 2. Terms *Texts* and *Messages*, used in the Hubro system, were seen as potentially misleading and confusing for an uneducated researcher using the system. From the patient's perspective, a case was reported when a patient was able to only fill half of the questionnaire, due to accidentally clicking on send button, submitting it in prematurely (post-submission edit function is not implemented). Only a few cases have been reported when the patient got insufficient information or information, that was not providing enough indices on how to proceed further.

6) PI/project manager has used the Hubro functions to recruit and randomize study participants through the smartphone when travelling. The Hubro system and its third-party components are web-based and responsive so that they can be used with mobile devices such as tablets or smartphones.

7) Mixed opinions have been reported on Hubro user interface user-friendliness. An agreement has been given to complexity/steep learning curve for both main third-party components – Piwik/Matomo and LimeSurvey. The complexity of these tools was discussed in question 3.

8) Researchers stated that no negative feedback has been reported about Hubro. The primary investigator (PI) stated there the feedback was overly positive when presenting the system at conferences, workshops and other occasions.

Table 2. summarizes identified missing functions, functions that need improvement and problems with the Hubro system.

Missing functions	• Speed • Reliability • Cost-effectivity • Convenience of participants management
Functions that should be implemented in a more user-friendly way	• Easier user-interface • Integration of reminders integration with more advanced recruitment capabilities other than those currently implemented • Recruitment scheduling and monitoring notifications • More secure implementation of the messaging function
Problems with the Hubro system	• Limited export capabilities • User's look-up (deanonymization) based on their email addresses requires much manual effort • Few patients reported insufficient information on how to use the system

Table 2. Summary of identified missing functions, functions that need improvement and problems with the Hubro system.

Discussion

We have addressed identified challenges in mobile health interventions in the following ways:

- we have assessed health data-exchange capabilities of wearable devices and identified barriers, that prevent them from being integrated with existing systems
- we have demonstrated wearable devices potential to improve patients comfort when dealing with a chronic disease by the development and evaluation of the first combined smartphone-smartwatch diabetes diary application
- we have addressed a need for updated evaluation approaches for eHealth and mHealth interventions by development and evaluation of the system for electronic management of clinical studies

While some of the similar identified systems, similar to Hubro, makes it possible to plan, create and run the whole study without any programming skills, the full integration with Hubro requires certain development efforts. On the other hand, Hubro allows performing simple questionnaire-based studies with messaging support, without any need for programming skills.

We have demonstrated the usability of a wearable device on an example of a combined smartwatch/smartphone diabetes self-management application. Pebble smartwatch that has been used for this demonstration is distinct from the majority of other similar devices currently out on the market. Main differences include the monochromatic display, button controls and long battery life. These first-generation smartwatch attributes have been although highly appreciated by the testing group during the evaluation period. Currently, the application market offers more alternatives, that are implementing functionality similar to our application. These applications are utilizing various new types of input (touch display, digital crown, voice input), novel user interfaces and new sensors - all of these updates call for a further usability reevaluation of a combined smartwatch/smartphone diabetes diary application.

From a developer's viewpoint, the lack of standardized communication APIs limits portfolio of devices, that can be directly integrated with third-party mHealth software without the use of supporting cloud-based data collection service. This lack presents a fundamental motivation for the existence of several research projects, that explore and exploit off-the-record data exchange possibilities of various wearable devices. These projects are often tightly associated with Do-It-Yourself (DIY) solutions such as Nightscout [22], The Open Artificial Pancreas System (OpenAPS) [23] and similar.

When integrating a wearable device into an EHR system, we have identified three factors to consider – data reliability, data transmission risks and device certification. The last one, device certification, is aimed to ensure that the standardization, privacy and security issues are considered and adequately implemented. Essentially, legal requirements, data protection laws and regulations differ between regions, and their interpretation may be difficult as wearables represent consumer-grade devices and, at the same time, they collect personal health data.

Conclusion

The motivation behind the need to move to new evaluation methods is driven by the fact that traditional methods of interventions may provide outdated results, given the fast pace of technological advances. Therefore, it is necessary to react on and evaluate these changes promptly. Inadequate old methods are used on new types of interventions that involve the processing of vast amount of data, dynamic support and troubleshooting of potential participant's technical problems during the study and inclusion of various types of new technology. Commonly implemented clinical trial protocols are too time-consuming to provide results in a reasonable time as they are not systematically addressing identified challenges.

New types of pervasive technology become tools of daily use for many patients. They continuously adopt these technologies and collect health data from various types of sensors. These sensors can help clinicians get an objective view into a patient's lifestyle, given that the data can be transferred from the device to the clinician or the patient's EHR. However, in the current situation, the data exchange possibilities are limited, making it challenging to implement straightforward health data transfer using a standardized data transfer protocol.

The system we designed proved to be improving areas of recruitment, enrollment, engagement, and retention of participants into an RCT. Although there are several other products available out on the market, none of them is integrating such a generic toolset, aiding the process of patient recruitment, randomization, survey and consent distribution, patient follow-up, data processing and trial closure. Inconclusive clinical trials, as a consequence of clinical trial's disrupted integrity, may result in a delay of development of optimal treatment method, or an additional financial burden.

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