

Designing, implementing, and testing a modern electronic clinical study management system

The Hubro system

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Abstract

Clinical trials need to adapt to the rapid development of today's digital health technologies. The fast phase these technologies are changing today, make the clinical study administration demanding. To meet this challenge, new and more efficient platforms for performing clinical trials in this domain need to be designed. Since the process of following up such trials is very time-consuming, it calls for revisiting several of the methods for performing both randomized, and other clinical trials. We present system for electronic management of clinical studies that addresses many of the time-consuming challenges, which additionally address many of the quality assurance aspects. We also present results from testing the system in two studies with 50 and 8 participants.

Keywords

RCT, clinical study, Kubernetes, GDPR, privacy, automatic data collection

1 INTRODUCTION

Randomized control trials (RCTs) are still the gold standard for the evaluation of health interventions, including evaluating technologies being introduced into healthcare providers' clinical practice and patient care. However, because clinical trials operate off of an established standard of meticulous and manufactured testing environments, they are often unable to produce results on schedule (delayed 86% of the time), demonstrate efficacy (57% were not able to) [1] or provide patient-relevant outcomes [2]. This is especially relevant in studies involving the rapid developing digital health technologies, e.g. mobile apps, wearables and sensors for recording and self-registering of patient data.

Today's tools for managing RCTs, and clinical trials in general, are simply too slow and ill equipped to evaluate such technologies. Clinical trials need to adapt; the most time-consuming phases of trials, i.e., recruitment, participant management and data-collection, need to be streamlined. In fact, companies such as CRO Analytics [3], CenterWatch [4] and the FDA [5] have echoed that a clinical trial's adherence to their stated objectives and schedule – as a justification of funding - requires that investigators become more adaptive to real-world impacts upon their trial [6].

An increasing number of clinical trials put a strong accent on remote sensing data, self-management, and patient engagement through their smartphones. To facilitate this, researchers need to provide more advanced and direct participant support including guidance and troubleshooting compared with traditional clinical trials. Since the process of such support is very time-consuming and often difficult

to assure the quality of all adopted channels, it calls for revisiting methods for performing clinical trials, including the variety of types of studies, from feasibility studies to randomized control trials.

Two critical issues with studies involving personal smartphones and sensors are privacy and data security. The apps and software involved must fulfil several legislative requirements, where a major one was issued in July 2020 by a judgment made by the Court of Justice of the European Union (CJEU), commonly known as Schrems II [7]. This invalidated the EU-US Privacy shield and enforced the integration of additional privacy-focused measures. In Norway, Schrems II has been a showstopper for the national project *Health Analytics Platform* [8].

From the perspective of software infrastructure, Schrems II's judgment restricts which cloud vendors can be used to deliver compute-, or storage services. Even though many of these providers have widespread local data centers, their utilization is limited by the fact that a use of these services may liaise with auxiliary services in the technology stack of the cloud provider (e.g. authentication service) that may send metadata to US-based servers.

The range of public cloud providers is enormous, and the spectrum of their managed services significantly facilitates integration of the system in various aspects. The convenience of use may also act as a double-edged sword due to violation of regulations like Schrems II. Therefore, it is necessary to validate compliance with legislative requirements not only with regards to GDPR, but also with other regulations that may influence the software architecture design and implementation.

The 18th Scandinavian Conference on Health informatics, Tromsø, Norway, August 22-24, 2022. Organized by UiT The Arctic University of Norway. Conference Proceedings published by Linköping University Electronic Press at <https://doi.org/10.3384/ecp187>. © The Author(s). This work is licensed under the Creative Commons Attribution-NonCommercial 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc/4.0/>

For study administration, researchers typically have to use several different disjointed tools for each stage of the project. Because these tools are siloed, they do not communicate directly, leaving the researcher to separately access, format and translate the information between systems. An example from our own research portfolio demonstrates this point well. In 2010-2013, our research team was part of the Norwegian arm of the REgIONs of Europe WorkINg together for HEALTH (RENEWING HEALTH) EU-project, a three-armed prospective randomized controlled trial (RCT) with data collection from questionnaires, a mobile phone app, and qualitative interviews [9]. Individuals with type 2 diabetes (T2D) were recruited through their general practitioners (GPs) using paper handouts for informed consent, participation and study information. The intervention involved participants using a diabetes app on a smartphone to self-manage their diet, physical activity, goals and blood glucose over the course of a year. Randomization was performed using a separate system, the WebCRF (Case Report Form), through an external group. Participants were trained on the use of the app during in-person meetings. The data that participants registered in the app and their usage logs were automatically and continuously and stored into a secure server. Self-reported outcomes were collected via standardized questionnaires in paper formats, and clinical measures were manually reported by GPs from medical records, documented in a paper-based study protocol. This is all in addition to patients' feedback and healthcare perspectives collected from the GPs via interviews [9]. The main challenges were the coordination of using all these different systems; we needed to open a key-locked cabinet to access the names and addresses when needing to send out invitations to meetings, and when we wanted to connect the different extracted data, from a look-up table of the different IDs of the different data sources. We also had to

put up a separate server solution to log the user-recorded data, and their usage logs. In some cases, automatic data transfer was not completed, e.g. when users were not online at the right times for scheduled data transfer. We, therefore, required patient participants to meet in-person to download their data via cable. These processes and work-arounds took much time and was a source of errors in organizing the participant information and analysis.

The challenges that we as researchers experienced in this project helped to inspire the work described in this paper.

In this paper, we describe the iterative design, development and testing of a study administration system called the Hubro platform. The purpose of this work was to develop a single tool that would allow a researcher to administer all stages of a study using one platform instead of multiple. The aim of such a system would be to increase the efficiency, reduce errors, and give a better overview and control to the researchers performing studies involving digital health technologies. As well as an ease way to follow-up participants in the different stages of the clinical trial.

2 METHODS

We aimed to design a system that enables the researchers to do all necessary tasks in a clinical trial, including RCT, more efficiently and from one user interface – called Hubro.

Hubro was designed and developed primarily to address the need to perform studies dynamically and fully electronically. These tasks include recruitment, obtaining informed consent, randomization, distributing polls/questionnaires, distributing any intervention like an app or other software, follow-up of participants, data gathering, data analysis and closure of the study (Figure 1).

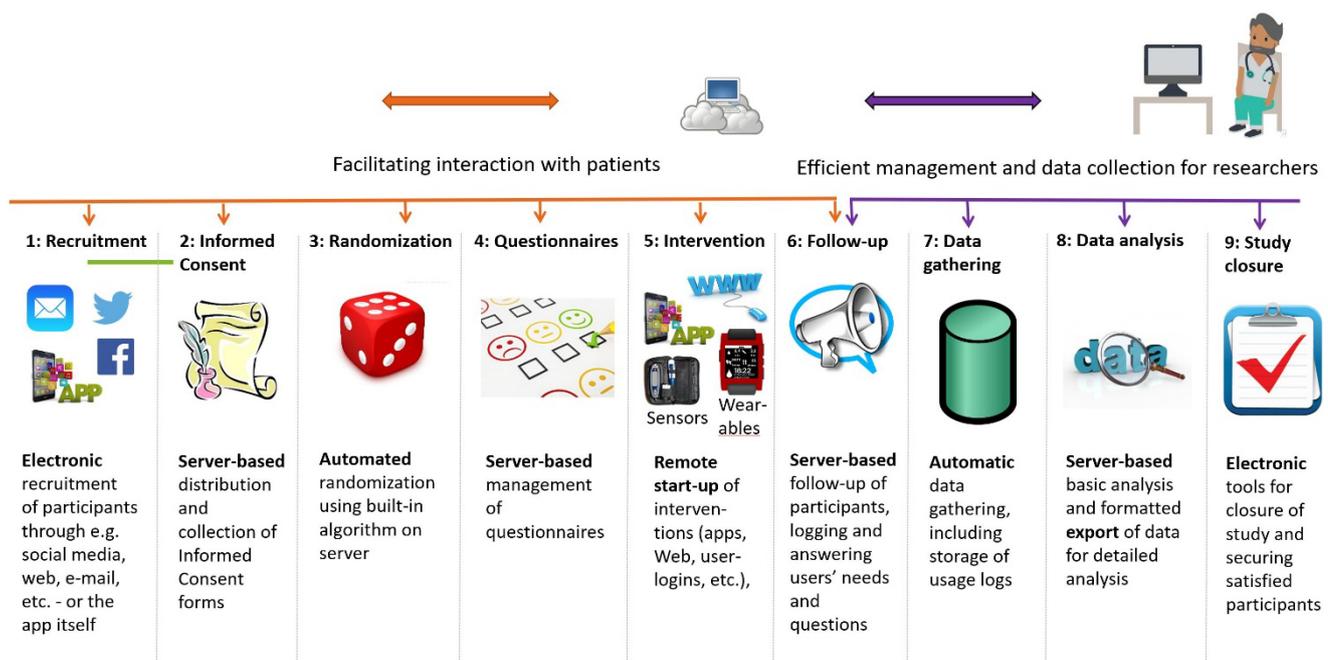


Figure 1 The introduced system for more efficient study management for clinical trials – the Hubro platform.

The original intention was to develop a secure questionnaire data collection platform that would honor requirements by the Regional committees for medical and health research ethics (REK) for handling of personal data.

2.1 Platform design and development

We used an iterative and fluid development process involving developers and researchers with experience conducting intervention studies using digital health technologies. During the design and implementation stage, meetings were conducted between developers and researchers to 1) share past experiences with intervention study administration, 2) identify bottlenecks and 3) brainstorm solutions for the research-users' needs for conducting efficient and effective digital health intervention studies. In addition, it was a comprehensive process with communication with the Regional Ethical Committee (REK), and the Norwegian Data Protection Authority (Datatilsynet), to find solutions in order to get acknowledgement for the platform.

2.2 Platform evaluation

In the evaluation stage, the system was practically tested by using it to administer two studies using mobile health (mHealth) smartphone applications for diabetes self-management. Information from researchers who conducted the studies, was collected via a questionnaire that queried specifics about how the system was used, impressions of the system, challenges, and suggested improvements. Table 1 details the questions included.

Number	Question
1	Can you describe your role/competence when using the Hubro system?
2	What functions are you missing?
3	About which functions do you think should be implemented better/in a more user-friendly way?
4	Have you experienced any problems with the system?
5	Have you used the possibility to manage the study from the smartphone?
6	Do you find the user interface intuitive?
7	Have you got any positive/negative feedback from the study participants?

Table 1. Questionnaire to research staff who used the Hubro system during two intervention studies

Over the course of the studies, e-mails were sent to developers and informal in-house meetings were conducted to trouble-shoot use of the system in practice. Free-text responses from the questionnaires and experiences reported over the course of the studies by the research-users regarding the identified missing functions, functions that need improvement and problems with the Hubro system were summarized separately. Thematic qualitative analysis was used to identify common themes of information.

3 RESULTS

3.1 Results of the iterative development of Hubro

During the design and development process, the researchers shared with us their experiences, which lead to the addition of user-centered requirements. Users expressed the need to collect not only questionnaire data but also study participants' own self-reported data (e.g. health-related data that were recorded automatically or manually into an mobile phone application) and usage data (i.e. the data that are collected automatically and that describe patient's interaction with the application). During the development process, we as researchers identified the need to randomize and distribute patients into treatment groups and send targeted messages via e-mail or via the mHealth application itself. At the end of the development process, the software portfolio consisted of multiple self-developed components, but also included multiple 3rd party open-source software components, which are used to perform specific part of data collection process and for which re-implementation would be out-of-the-scope of the project (e.g. the questionnaire data collection software LimeSurvey [10], and the usage data collection software Piwik/Matomo [11]).

Since multiple independent services gathered the personal health information (PHI) in Hubro, it would be problematic to implement a link table operating over all these services. Instead, the approach we chose was to create an alternate identity linked with the real identity, specific study and treatment group. Therefore, implementation of a linkage table in Hubro is based on two directory services (LDAP servers) and a translation service between them. This solution was approved by REK and The Norwegian Data Protection Authority (DPA) [12] and was used across the whole system in two clinical trials at the University Hospital of North Norway (UNN).

The implementation was done solely using in-house developers, who facilitated the development process by continuously revalidating implementation of relevant user stories, worked out in close collaboration with the researchers. The system itself does not depend on any external 3rd party service and is packaged as a self-contained bundle. Consequently, the system can run on a self-serviced IT infrastructure, but also in a cloud environment if necessary.

The Hubro system consists of multiple loosely coupled applications and server components, making it a candidate for provisioning through the SaaS model [13] i.e. a software distribution model in which applications are hosted by a vendor or service provider.

To rule out potential legislative non-compliance, we have designed the system integrating essential services, not relaying on any services from the public cloud vendors. We have based the solution on Kubernetes, which is a popular open-source container orchestration platform, (Figure 2). Use of Kubernetes simplifies the deployment and provisioning process, as it becomes a standard control plane for scheduling and managing jobs in highly distributed environments. By using vanilla Kubernetes cluster, we also prevent vendor lock-in with a particular cloud provider.

Pseudo anonymization of data is secured by a translation function, that performs ad hoc mapping of anonymous identities with e-mail addresses-based list of registered participants. Translation function is accessible from all

microservices within the cluster, and the access needs to be confirmed by password or by using a service principal i.e., managed identity.

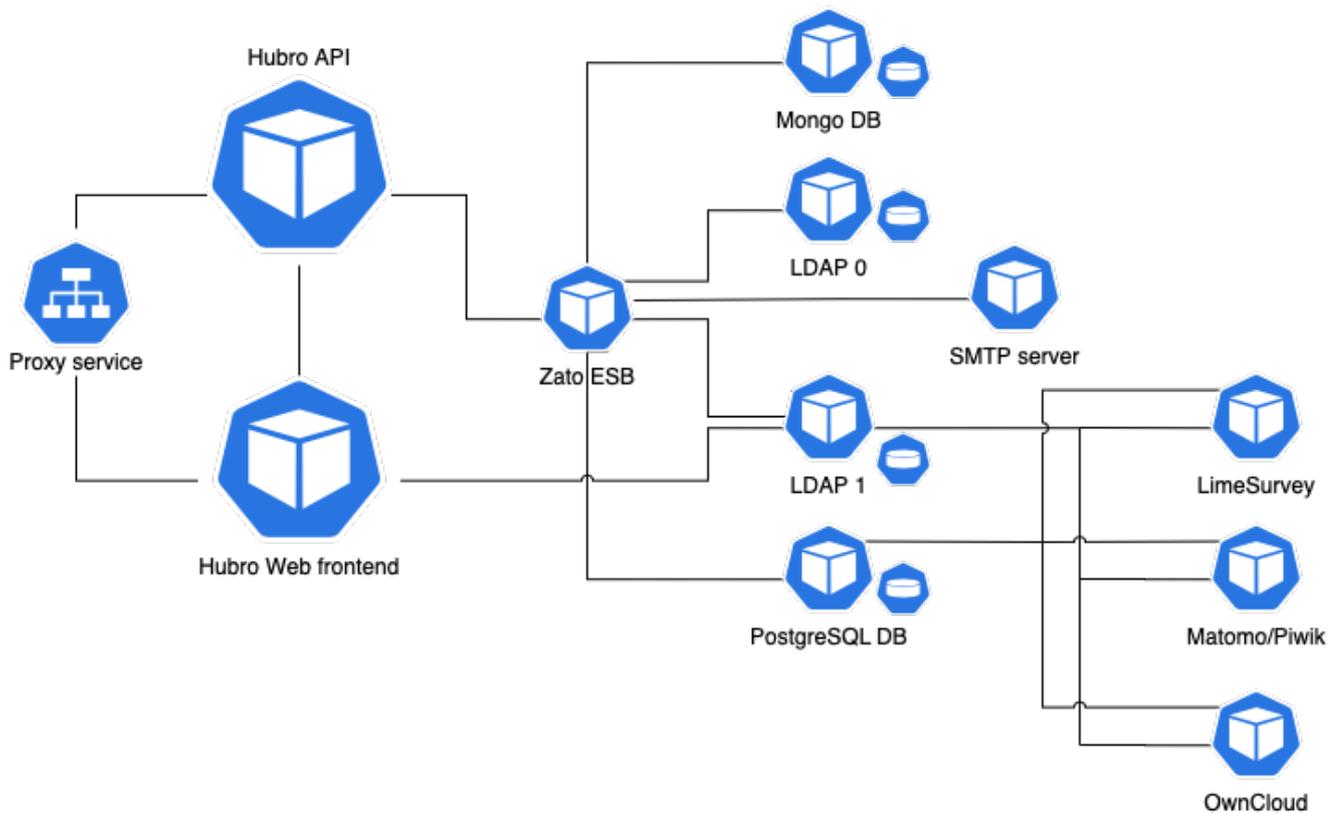


Figure 2 Kubernetes cluster diagram visualizing individual Docker containers that are sealing off services of Hubro.

One of the primary goals was to avoid an exhausting time dedication to study management as the number of participants increases. Therefore, we designed the user interface in a way, that the researcher can discover actions which may require his attention with a glance, using logical color coding (red, yellow and green). We introduced an informational column for each participant, that summarizes the following information:

- date and time when the app installed on a participant's phone checked for new messages

- indication, whether there are any unfilled questionnaires
- date and time when the participant was enrolled in the study
- date and time when the data was uploaded to the Hubro server

A general overview of participants' statuses is depicted in Figure 3.

Project group: Group 1 - Control

Group's questionnaires

A. Spørreskjemapakke ved oppstart av studien
B. Spørreskjemapakke etter 3 måneder - Gruppe 1

Group's file areas

No file areas in project group

Group's members

Name	Consent form: 0. Informert samtykke (Participant admin)	Questionnaire: A. Spørreskjemapakke ved oppstart av studien (Participant admin) (Invite remaining)	Questionnaire: B. Spørreskjemapakke etter 3 måneder - Gruppe 1 (Participant admin) (Invite remaining)		
anon-53852 ▶ Added 26. mars 2017 20:49	Completed - 27. mars 2017 12:30 View response	Completed - 27. mars 2017 22:38 View response	Not participating	Add user	Actions ▼
anon-45795 ▶ Added 26. mars 2017 19:46	Completed - 26. mars 2017 21:01 View response	Not completed - Last reminder sent: 29. mars 2017 18:23 Send reminder	Not participating	Add user	Actions ▼
anon-28253 ▶ Added 24. mars 2017 12:22	Completed - 25. mars 2017 10:42 View response	Completed - 25. mars 2017 12:53 View response	Not participating	Add user	Actions ▼
anon-42634 ▶ Added 23. mars 2017 10:18	Completed - 23. mars 2017 11:32 View response	Completed - 24. mars 2017 08:26 View response	Not participating	Add user	Actions ▼

Figure 3 Treatment group management as viewed by study manager in the Hubro Web front-end.

One of the aims was to provide an easy-to-use administration interface, eventually usable also from a smartphone, on-the-go if needed. Based on these requirements, we have chosen a web application as a user interface for the Hubro.

The user interface of the web application is responsive, i.e. it scales nicely on small device screen sizes. This way, the study manager can interact with the system dynamically through the smartphone or tablet at every place with internet access. This way, the researcher can operate the system on-the-go e.g. randomize users or send messages.

Messages in the Hubro system can be distributed through various channels. So far, the Hubro system supports distribution of information via an ordinary e-mail, 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.

3.2 Results of the Hubro platform practical implementation

We were able to design a full functioning system that fulfilled most required tasks for a clinical trial, as presented in Figure 1. We received all the necessary acknowledgments from the national data protection

authority DPA, the regional ethical authority REK, and the local security and privacy team at the University Hospital of North Norway (UNN) to run two clinical trials.

The first trial in which Hubro was used included 50 patient participants and the second included 8 participants. In each study, participants were asked to test new functions of mHealth tools, especially the Diabetes Diary self-management application.

The first study [14] lasted for 12 months, where the study manager estimated 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 were estimated to triple these times. In total, 30-minutes per user. The second study [15] was conducted for a 6 months period, and time usage for this study is currently being estimated in an ongoing follow-up study [16].

3.3 Results of evaluation Research-users' experiences using Hubro

The questionnaire about research-users' experiences was distributed to three researchers who had directly worked with the Hubro system, throughout the two studies.

- 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 the two studies, while the system developer has provided technical support (service availability assurance and data extraction support).

- 2) Based on the feedback from the researchers, the following new functionalities and system updates would be appreciated: integration of reminders to the researchers; integration with more advanced recruitment capabilities other than those currently implemented; recruitment scheduling and monitoring; notifications; more secure implementation of the messaging function.
- 3) The previously mentioned connection between the systems' 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 the third-party tools – the app usage analytics platform (Piwik/Matomo) and the 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 the following optimizations to minimize manual efforts and frequent check-ups in the following ways - a better process of keeping track of the recruited patients, i.e. placing them into groups; more understandable user-interface; easier distribution of questionnaires and tools (applications); more streamlined process of questionnaire completion checks, and a user interface to interact directly with the LDAP servers (e.g. removing participants).
- 5) From the researcher's point of view, it was suggested to implement a two-way messaging function, which would mitigate the necessity to use an ordinary e-mail as a primary communication channel from patients to researchers. Also, the user interface for user's look-up based on their e-mail addresses was perceived as a candidate for improvement, as it required a manual effort in terms of e-mail 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. Re-submitting the un-finished questionnaire (i.e. an edit function) should thus be implemented.
- 6) PI/project manager was able to use the Hubro functions to recruit and randomize study participants through the smartphone, e.g. 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 the user-friendliness of Hubro's user interface. All agreed that it was a complex and steep learning curve for both

main third-party components, the Piwik/Matomo and LimeSurvey. The complexity of these tools was discussed in question 3.

Researchers stated that no negative feedback has been reported about Hubro from the study participants.

In addition, we present a summary of identified missing functions, functions that need improvement and problems with the Hubro system in Table 2.

Response categories	Summarized responses
Appreciated functions	<ul style="list-style-type: none"> • Reliability • Cost-effectivity • Convenience of participant management
Functions that should be implemented in a more user-friendly way	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • User's look-up (deanonymization) based on their e-mail addresses requires much manual effort • Should allow editing and re-submission of questionnaires

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

As mentioned, most of the functionalities were implemented and used. However, data analysis was only performed to a limited degree using Hubro. Data extraction, organization and analysis was performed manually through a collaboration between a researcher and a developer. This took several months (not effective time, but to coordinate) and data needed to be shared via a separate secure research platform. The secure data-sharing platform required additional and un-planned set-up of the files and granting access. The bulk of the un-planned work included the researcher learning three different formats of anonymous data as well as how to reformat, translate and analyse them using a more well-known program such as Microsoft Excel. This reinforced the challenges as well as opportunities of developing the Hubro system further, to support also more of the last parts of clinical trials, analysis and conclusions.

4 DISCUSSION

Considering the nature of health data, rolling the Hubro system out as a service to end-users might be troublesome, due to compliance matters. Also, a naïve, on-premise distribution might be complicated because of many onboarded components resulting in a significant workload on IT system operators. The way for seamless delivery and

operation could be a use of self-sealed container-based architecture orchestration through the management system like Kubernetes, bringing in the best of both worlds – an easily manageable and configurable system running on hardware located within the premises of the institution, or within a cloud computing environment.

The concept of a user ID and anonymous ID 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 in a more user-friendly manner.

It is also important to note, that Hubro, currently, neither collects nor generates documents formally required by regulatory authorities or compliance protocols i.e. Trial Master File (TMF) or its electronic equivalent (eTMF), that must be maintained alongside the electronic study management system separately in a dedicated repository. Similarly, the Hubro keeps a very limited audit trail of specific actions, that require access to the link table, or the implemented link function respectively (deanonymization).

5 CONCLUSION

The motivation behind the need to move to new study management methods is driven by the fact that traditional methods for clinical interventions may provide outdated results, given the fast pace of technological advances. Therefore, it is necessary to react on current trends 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 used clinical trial study management systems are too scattered and time-consuming, to provide results in a reasonable time as they are not systematically addressing the identified challenges.

The system we designed proved to improve areas of recruitment, enrollment, engagement, and retention of participants into an RCT and a clinical trial. Use of the system objectively improved the time spent managing individual patients in the study. Also, the primary investigator (PI) stated the feedback from audience was overly positive when presenting the system to other researchers at conferences, workshops, and other occasion. 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, because of clinical trials' disrupted nature, may result in a delay of development of optimal treatment practice, and/or an additional financial burden.

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