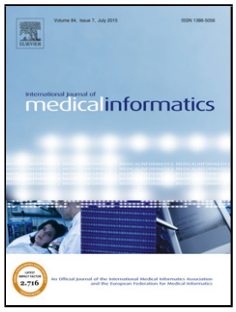

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# Connecting Healthcare and Clinical Research: Workflow optimizations through seamless integration of EHR, pseudonymization services and EDC systems

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# Highlights

- Integration of healthcare and research systems is feasible
- Such a connection leads to significant time reduction and avoids transfer errors
- An architecture for connecting healthcare, research and pseudonymization systems
- Direct pseudonymization for research from the EHR system has significant benefits
- Clinicians can recognize study patients as such directly within the EHR system

## Abstract

**Objective**: In the last years, several projects promote the secondary use of routine healthcare data based on electronic health record (EHR) data. In multicenter studies, dedicated pseudonymization services are applied for unified pseudonym handling. Healthcare, clinical research and pseudonymization systems are generally disconnected. Hence, the aim of this research work is to integrate these applications and to evaluate the workflow of clinical research.

**Methods:** We analyzed and identified technical solutions for legislation compliant automatic pseudonym generation and for the integration into EHR as well as electronic data capture (EDC) systems. The Mainzelliste was used as pseudonymization service, which is available as open source solution and compliant with the data privacy concept in Germany. Subject of the integration was the local EHR and an in-house developed EDC system. A time and motion study was conducted to evaluate the effects on the workflow.

**Results**: Integration of EHR, pseudonymization service and EDC systems is technically feasible and leads to a less fragmented usage of all applications. Generated pseudonyms are obtained from the service hosted at a trusted third party and can now be used in the EDC as well as in the EHR system for direct access and re-identification. The evaluation of 90 registration iterations shows that the

time for documentation has been significantly reduced in average by 39.6 seconds (56.3%) from 71±8 sec. to 31±5 sec. per registered study patient.

**Conclusions**: By incorporating EHR, EDC and pseudonymization systems, it is now feasible to support multicenter studies and registers out of an integrated system landscape within a hospital. Optimizing the workflow of patient registration for clinical research allows reduction of double data entry and transcription errors as well as a seamless transition from clinical routine to research data collection.

**Keywords:**

Data management; Electronic Data Capture; Health Information Systems; Pseudonymization; Workflow Optimization

# 1. Introduction

Adoption rates of electronic documentation systems, in particular electronic health records (EHR) and electronic data capture (EDC) systems, are steadily increasing in the recent years [1]. Several advantages such as availability of information, better communication, higher readability, support in different tasks, decrease of documentation errors, etc. are reported to accompany with the use of such systems [2,3]. Studies have shown however, that manually transferred information from one system to another contains a large source of errors [4]. Electronic documentation, reusing of those and sharing of data between stakeholders in healthcare has even been deemed so important by politics that legislations such as the Health Information Technology for Economic and Clinical Health Act (HITECH) in the United States in 2009 [5] or the eHealth-law in Germany [6] were decided.

Introduction of new applications harbors the potential risk of workflow interruptions frequent task switching causing stress and dissatisfaction [7,8]. In addition to that, clinicians and general practitioners spend 25-50% of their daily work for EHR-related tasks such as documentation or administrative issues and the time for research documentation comes on top of the daily routine work [9–11].

In this regard, the re-use of routinely collected medical data, e.g. for research or quality assurance purposes, offers several incentives, for instance the reduction of redundant documentation or increase of data quality [12]. Clinical trials usually consist of several stages in which routinely collected data is eligible to support e.g. trial feasibility, patient recruitment or the execution of trial documentation. Recent research has shown that data elements required for clinical trials overlap with available ones in the EHR [13–17]. Therefore, different projects have developed technical infrastructures that address single and multicenter approaches for a broad legislation compliant, syntactical and semantical interoperable solution to accompany the heterogeneous landscape of EHR

systems and organizational burdens [18–20]. In Münster, we developed the x4T-architecture (exchange for Trials) that allows the automatic pre-population of study eCRFs (electronic Case Report Forms designed to capture all of the protocol required information to be reported to the sponsor on each study subject) with validated routine data of the EHR [21]. Technical limitations of common EHR systems resulted in a middleware component called “Clinical Interface” that handles the secure pre-population data transfer with EDC systems.

In clinical research, de-identification of subjects i.e. study patients plays an essential role preserving and respecting patient’s privacy. Pseudonymization services provide secure and legislation compliant solutions to ensure (1) that subjects can be identified only by the person in charge of identifying data and (2) that patients who appear in multiple institutions obtain the same pseudonym and are not handled as two different persons. Aamot et al. analyzed and compared different methods and applications for pseudonymization services [22]. In all pseudonymization methodologies a trusted third party (TTP) is placed to trustworthy handle pseudonyms. Examples for pseudonymization services are the generic Pseudonym Administration Service (gPAS) [23] and the “Mainzelliste” [24]. Both services offer web services for managing and obtaining pseudonyms.

A direct integration of pseudonymization services into EDC systems can be found in a few research data capture solutions. In addition to that, Schrimpf et al. reported about the linkage of a randomization service into the open-source EDC system OpenClinica [25]. In terms of patient safety and regulatory requirements, it is essential to be aware of whether a patient participates in a clinical trial to report current conditions as serious adverse events. Nevertheless, to our knowledge the seamless and overarching integration of a pseudonymization service into the direct context of EHR and EDC systems has not been performed so far.

Since EHR, EDC and pseudonymization applications are generally disconnected the aim of this research is to design, implement and evaluate an IT architecture that allows the direct pseudonymization of patient within the EHR by integrating the systems and workflows of EHR, pseudonymization and EDC system.

## 2. Material and Methods

System integrations require a careful analysis of the clinical workflow in which they are introduced. Agfa ORBIS is used as main EHR system at the University Hospital Münster (UKM). Based on experiences and interviews with study nurses, we analyzed the workflow of patient pseudonymization, adding of subjects within the EDC system and the manual data transfer process. Technical capabilities of the EHR ORBIS, the pseudonymization service "Mainzelliste" and the x4T-EDC system [26] were examined to propose an integrated IT architecture.

Since we already gained experiences with the Mainzelliste, we chose this solution for our implementation. The Mainzelliste is a web-based pseudonymization service offering a user interface and a also RESTful services to allow secure creation of pseudonyms and the interaction with other applications. It is in line with the German data protection legislation for research projects. Per default, patient administrative data such as name*, surname*, date of birth*, birth name, zip code and city (*= mandatory) are used as identifying parameters to generate a pseudonym. Additional arbitrary parameters can be configured for the de-identification procedure in the Mainzelliste. An integrated customizable algorithm discovers unsure cases of similar entries to prevent spelling errors.

Currently, x4T's "Clinical Interface" tackles the communication between the EHR system and EDC solutions based on web services and international standards such as CDISCs Operational Data Model (ODM) [27]. Depending on available EHR interfaces, customary communication servers can also be integrated. The Clinical Interface requests routine medical data from the EHR system, converts it into ODM and transfers it to the EDC system.

To propose a generalizable and reusable infrastructure we reviewed available interfaces of all IT components and analyzed possibilities to extract data from and store information in the EHR. x4T's "Clinical Interface" was enhanced to handle the secure connection with external web service-based applications, namely the interface towards the Mainzelliste and a single sign-on mechanism towards the EDC system. Furthermore, the interface was also capable of receiving pre-population data from a

primary source to pre-fill study documentation forms with clinical values including provenance data. We developed an EHR form that allows two registration options straight from the EHR system: 1) enter a pseudonym manually or 2) generate a pseudonym using a pseudonymization service.

Transferring and handling of medical data always requires respecting data privacy and protection regulations. Therefore, a formal description (procedure directory) of involved IT systems and processes was jointly developed with and approved by the local data protection officer.

## 2.1. Workflow evaluation

Context of the evaluation was a multi-center cross-sectoral registry for patients with traumatic brain injury (TBI), which was funded by the Ministry of Health, Equalities, Care and Ageing. Partners from acute care, early rehabilitation, long-term rehabilitation and coordinators of follow-up care participated in this project.

The evaluation was performed before and after implementation of the pseudonymization service into the EHR system and interconnecting all systems. Due to the circumstances that physicians usually perform the task of patient registration and documentation infrequently spread over the workday, we chose a laboratory evaluation setting. Three independent observers were instructed in the workflow and time measurement. Three study nurses, who were used to the old workflow since they worked with the systems, were observed. All study nurses were trained after introduction of the new system infrastructure. Evaluation of the new workflow took place four months later. For both observations we obtained 30 eligible patient names from the study's principal investigator to be included in the TBI register. These names and date of births were included in an Excel-spreadsheet for the evaluation.

Outcome measure of the evaluation was the time between opening a patient's electronic medical record within the EHR as a starting point for transferring research data and the successfully registered patient within the EDC system. In-between the x4T-EDC was accessed, the Mainzelliste used for pseudonym generation and the spreadsheet managed to insert the corresponding

pseudonym. We measured the execution time before and after the implementation on six days including a block of five patients each day. Each participant paused for half an hour time between before and after the observation. The task order was switched every day to prevent bias in terms of being familiar with already known patient names from the prior round. Each study nurse got an own instance of the Excel-spreadsheet to compare the manually generated pseudonyms afterwards in the previous workflow. Automatically generated pseudonyms in the new workflow were compared with the human created ones of the old workflow to examine whether the integrated infrastructure operates correct. In order to discover typing errors, generated pseudonyms were compared among each study nurse.

IBM SPSS version 25 was used for descriptive statistic and independent t-test calculations.

## 3. Results

### 3.1. Workflow optimization through system integration

Figure 1a depicts the previous workflow of patient registration. The process starts with accessing the EHR system (1) and looking up eligible patients (2) based on the separate Excel-spreadsheet. Research documentation begins with opening the patient's electronic medical record (3). Clinicians log-in the x4T-EDC system (4a) to create new subjects (5a).

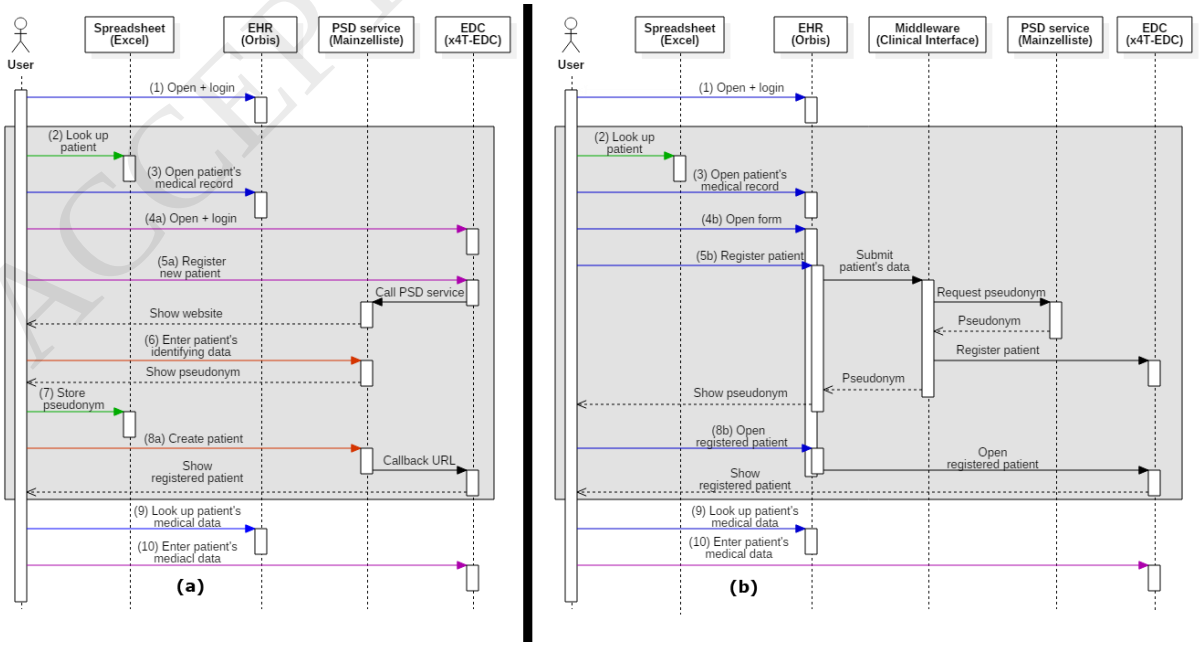

Figure 1: Sequence diagram of the (a) old workflow and the (b) new one. The colors of message arrows starting by the user highlight different target systems. The integration resulted in less active interactions and frequent application changes.

The process of patient pseudonymization was already optimized since the Mainzelliste was integrated in x4T-EDC. Pseudonymization services are sometimes stand-alone and need to be accessed separately. Patient credentials (surname, forename, date of birth) are entered on the Mainzelliste webpage to generate the pseudonym (6). Subsequently, the pseudonym is displayed with patient information to ensure correct data entry. A PDF of this information can be printed but more important the pseudonym is stored in the Excel-spreadsheet (7) to allow inference to the patient. After that the study subject is created automatically in the EDC system (8a) and clinicians can begin the research documentation; (9) and (10).

The new workflow (compare Fig. 1b) starts and ends similar to the previous one with clinician's log in (1), patient loop up (2) and opening the medical record (3) as well as looking up patient's medical data (9) and entering it (10). After that, the entire registration management is performed by the EHR form (indicated by blue arrows) in the background. Therefore, they use the implemented EHR form, which obtains pseudonyms and registers patients as subjects in the EDC system. Therefore, the registration is triggered within the study patient registration form in ORBIS (Fig. 2 upper left corner). With the aid of the internal right and role management, clinicians are assigned to certain studies they are permitted to access.

Clinicians choose the desired study and start the automatic pseudonymization service-based registration process. After selecting the "registration" (Fig. 2 (1)), a study ID, patient ID, the user and identifying data (patient name, surname, and date of birth) are sent to the middleware component (Clinical Interface). Access to the Mainzelliste is granted through a handshaking mechanism with API keys for specific functions such as "addPatient". This handshaking is performed by the Mainzelliste (2). Based on secured transactions, the Clinical Interface sends the patients' identifying data to the Mainzelliste (2) and receives a pseudonym (3), sending it to x4T-EDC (4a) triggering the creation of a

new subject. Simultaneously, the pseudonym is inserted into a separate table of ORBIS (4b) linked with the patient ID.

As depicted in Fig. 1 the login into the EDC system (4a) is replaced by opening the EHR registration form (4b) and the manual steps of entering patient credentials and storing the generated pseudonym (7) disappear.

In our new integrated scenario shown in Fig. 2, the following systems are interacting: due to missing standard communication interfaces of the EHR system and the fact that data from the EHR is accessed, the Clinical Interface is placed as a central middleware component within the hospital environment. Pseudonymization service and EDC system can be placed at any TTP organization.

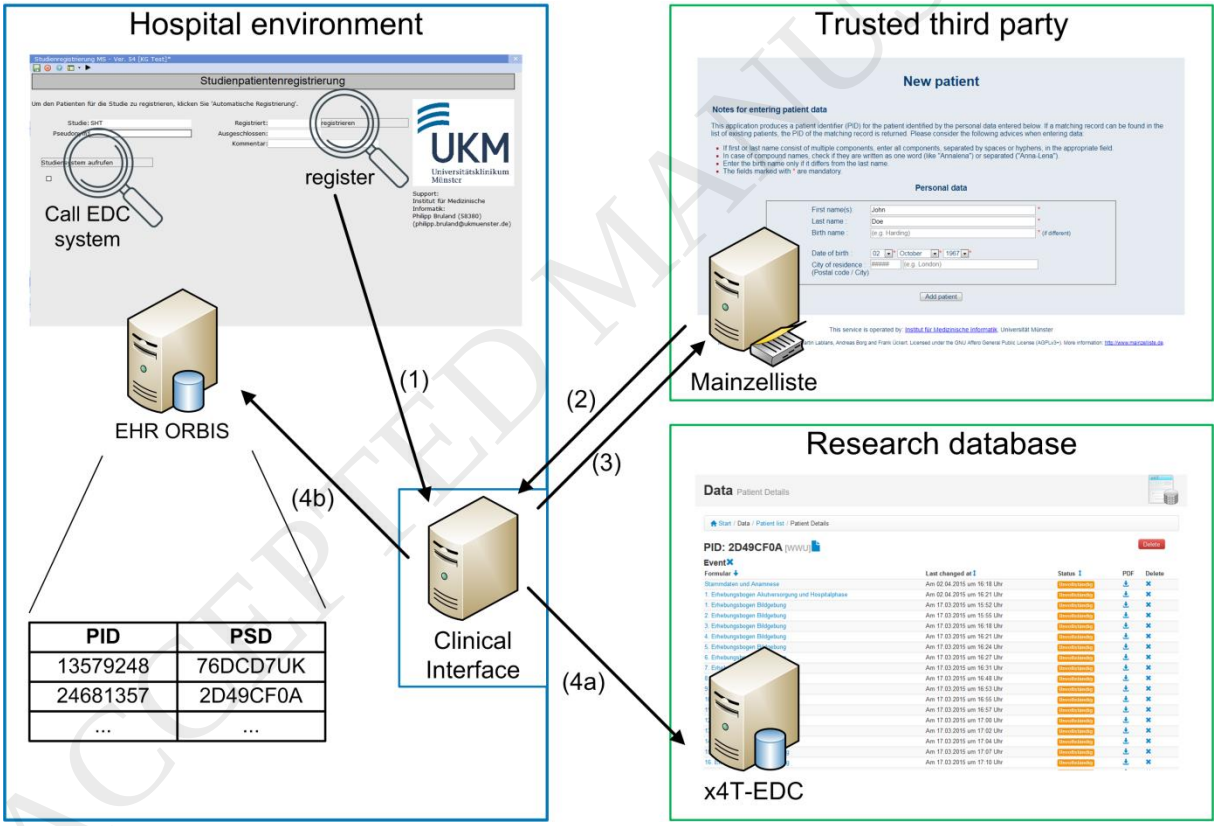


Figure 2: Overall architecture of the system's interaction. The hospital environment consists of the EHR system and the Clinical Interface as middleware component. The research database contains the EDC system and a trusted third party operates the Mainzelliste.

As depicted in the upper left corner (Fig. 2), the “call EDC system” button opens a single sign-on link with the study ID, user credentials and the respective pseudonym. Thereby the user is forwarded automatically to the study subject’s overview page within x4T-EDC and can directly start data capturing, without having to log in again to this second system. Data already documented in ORBIS can be transferred to x4T-EDC and only the additional study relevant information need to be captured.

In our setting, treating physicians and study nurses are the same person, which is a common situation at university hospitals. Therefore, the physician is allowed to access the clinical information and the study data including the pseudonym, both stored in ORBIS. Since x4T-EDC is a research database, patient identifying information such as name and date of birth is not stored. The Mainzelliste is hosted at a TTP, located at the Center of Information Processing (ZIV) of the University of Münster. To comply with privacy regulations, a contract and standard operating procedures with the ZIV were implemented to specify *who* can access *what information* under *what condition*. In general, the ethics committee of the university has to approve if any patient data from the pseudonymization service shall be disclosed.

### 3.2. Evaluation Results

In the TBI registry 127 patients have been registered and documented using the new integrated workflow between Dec. 2015 and Dec. 2016. Study nurses and physicians reported to be highly satisfied with the new workflow. Information is no longer needed to be redundantly entered and a list of study participants can easily be looked up in the EHR.

Observing the typical workflow of patient registration in a research context resulted in a faster execution after orchestrating EHR, EDC and pseudonymization service. The previous task of registering patients as study subjects and switching between patient list, EHR, EDC, and pseudonymization service resulted in an average time of 71±8 sec. per processed patient. After seamless integration of all systems, participants spent in average 31±5 sec. for this task. Per patient it

resulted in a significant ($p<0.001$) average reduction of 39.6 seconds (56.3%). In the previous workflow one subject got a wrong pseudonym which was discovered during the comparison of registered pseudonyms in the subject mapping table in which all participants entered the created pseudonym. All automatically generated pseudonyms in the new workflow corresponded to the ones in the manual workflow.

## 4. Discussion

Our proposed integrated system infrastructure is technically feasible and reduces the number of actively used systems as well as the overall research documentation time significantly. Such integration promotes the satisfaction of clinicians who are in charge of a double function but also of study nurses that are frequently confronted with research documentation workflows. Being aware of whether a patient participates in a clinical trial, patient safety and regulatory reporting obligations can be accomplished. This implies that clinicians from a different department know that a medical condition may be subject of a possible serious adverse event, which has to be reported to prevent punishments. Unless EHR systems are rarely capable to offer interfaces beyond typical HL7 messages to exchange medical data and integrate external applications, we implemented a “Clinical Interface” for these purposes. Customary communication servers can also be integrated with x4Ts “Clinical Interface” gaining a more general system architecture. We have learned from different projects such as one about patient recruitment systems across Germany [28] that most EHR systems allow in-house developments to a certain extent. Thus, to our knowledge it is very likely feasible to integrate this infrastructure in different EHR solutions.

In a typical hospital hundreds of clinical subsystems are in place. Most of them act stand-alone or are inter-connected via a communication server to e.g. send/receive orders and results or share patient admissions [29]. Available EHR interfaces would dramatically promote the integration of systems and therefore, allow creating complete workflows to support clinical research. However, research and routine documentation are still separated areas, although many projects are currently working on data integration aspects to enable re-use of data for secondary use purposes [30–32].

In addition, the use of multiple systems oftentimes leads to a disruption of the workflow [33]. To minimize workflow disruption, functionalities of existing systems already known to users were used to support registration of patients for studies directly within the EHR. With a directly integrated external pseudonymization service multicenter studies can be supported. Our implementation has shown that the integration of EHR and EDC in combination with an external pseudonymization service is technically feasible and reduces working time and transcription error. Initial feedback about the new functionality by clinicians is throughout positive because of the “streamlined” documentation workflow. This is also emphasized by the evaluation, which yielded a significant time reduction for the patient registration process. The integration of the pseudonymization service into the clinical research workflow has led to a reduction of frequent task switching as well as active switching between several applications. Patient information does not need to be entered several times, which is a possible source of transcription errors. Walther et al. have identified that most transcription errors occur in free text and date fields [34]. Since pseudonymization is gained through the name, surname and date of birth of the patient, those three fields contain the highest potential for errors during the pseudonym generation process.

Integration of routine and research documentation systems is a focus of several recent IT research projects. Already more than 10 years ago the CDISC electronic Source Data Interchange (eSDI) Group released a document that proposes different single-source scenarios (“Leveraging the CDISC standards to facilitate the use of electronic source data within clinical trials” [35]). In comparison to our approach, those scenarios did neither use nor integrate an external pseudonymization service to enable multicenter studies. Several single source approaches exist to reduce the time needed for documentation work in multiple systems [17,21,36]. Ganslandt et al. have reported about integrating the TMF pseudonymization service in the process of mass pseudonymization source data on the way into a research database [37]. In contrast to these systems, our approach goes beyond data exports and provides an integrated workflow between EHR, EDC and pseudonymization systems, which to our knowledge has not been implemented before.

Limitations of this study were that we had to disable the sureness functionality of the Mainzelliste that allows detecting similarly spelled patient parameters, since ORBIS is only capable to send requests but not to directly receive responds or interact with the user. However, usually the patient identification data is automatically transferred into the EHR system by the health insurance card reducing the potential for typewriting errors. For this study name, surname and date of birth were the only parameters used for pseudonym generation. Nevertheless, additional mandatory parameters can be configured in the Mainzelliste to be used for the generation algorithm.

### 4.1. Further research

Our integrated infrastructure is implemented in a single hospital setting and we aim to adopt this approach in hospitals with different technical infrastructure such as EHR or EDC systems. Concerning EDC systems, commercial but also freely available EDC solutions such as REDCap or OpenClinica provide APIs [38] for secure communication. Further research would be to generalize the current approach towards a broader scope of EHR and EDC systems.

Due to infrequent system usage, the evaluation was performed under laboratory conditions. We would expect similar results but a broader evaluation with clinicians using different EHR solutions is intended. An in deep focus on transcription errors would also be relevant to determine whether this approach results in fewer patients with incorrect pseudonyms.

## 5. Conclusion

In hospitals usually several systems are used which are often disconnected and an integrated workflow over system borders is often not supported. Frequent system changes, different authentications and error-prone transfer of relevant data are the consequence. We proposed a concept for seamless integration of a pseudonymization workflow into the domains of routine care and clinical research. Therefore, interfaces were established between EHR and EDC system with direct integration of a pseudonymization service. This integration facilitates the automatic

registration of patients from the EHR and led to a significant reduction of execution time and elimination of transcription errors.

## Summary table

What was already known on the topic:

- Integration of IT systems can lead to a more fluid and less fragmented workflow.
- Pseudonymization services support multicenter research and prevent double registration of same patients visiting different institutions.

What this study added to our knowledge:

- Direct patient registration with automatized pseudonymization from the EHR is feasible and applicable.
- Integrating routine and research IT systems results in a significant reduction of documentation time and avoids transcription errors.

## Authors' contributions

PB, JD, MS and MD developed the concept. PB, JD and MS implemented the interfaces. TB, PB and MS conducted the evaluation. PB and JD wrote the manuscript. All authors have read and approved the final manuscript.

## Competing interests

The authors declare they have no competing interests.

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Conflict of interest

No conflict of interest was reported by the authors.

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