HIS-based support of follow-up documentation – concept and implementation for clinical studies

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Summary

Objective: Follow-up data must be collected according to the protocol of each clinical study, i.e. at certain time points. Missing follow-up information is a critical problem and may impede or bias the analysis of study data and result in delays. Moreover, additional patient recruitment may be necessary due to incomplete follow-up data. Current electronic data capture (EDC) systems in clinical studies are usually separated from hospital information systems (HIS) and therefore can provide limited functionality to support clinical workflow. In two case studies, we assessed the feasibility of HIS-based support of follow-up documentation.

Methods: We have developed a data model and a HIS-based workflow to provide follow-up forms according to clinical study protocols. If a follow-up form was due, a database procedure created a follow-up event which was translated by a communication server into an HL7 message and transferred to the import interface of the clinical information system (CIS). This procedure generated the required follow-up form and enqueued a link to it in a work list of the relating study nurses and study physicians, respectively.

Results: A HIS-based follow-up system automatically generated follow-up forms as defined by a clinical study protocol. These forms were scheduled into work lists of study nurses and study physicians. This system was integrated into the clinical workflow of two clinical studies. In a study from nuclear medicine, each scenario from the test concept according to the protocol of the single photon emission computer tomography/computer tomography (SPECT/CT) study was simulated and each scenario passed the test. For a study in psychiatry, 128 follow-up forms were automatically generated within 27 weeks, on average five forms per week (maximum 12, minimum 1 form per week).

Conclusion: HIS-based support of follow-up documentation in clinical studies is technically feasible and can support compliance with study protocols.

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1. Background

Clinical studies typically consist of several visits, and after an initial assessment, several follow-up visits need to be organized and documented. Therefore, follow-up data needs to be collected according to each study protocol at certain time points. According to Chan et al., "data completeness varied substantially across studies" [1] which may be caused by the huge documentation workload of physicians in routine care [2]. Forster et al. have reported that the median rate of loss to follow-up in a 15-country study was 8.5% [3]. Consequently, data completeness in studies is a critical and unsolved problem. There are different causes of patients being lost to follow-up. First, patients do not return to the physicians, and second, there are organizational issues in hospitals, for example regarding scheduling.

Commonly, electronic data capture (EDC) systems are used for research documentation which includes follow-up documents. El Emam et al. state that "Electronic data capture (EDC) tools provide automated support for data collection, reporting, query resolution, randomization, and validation, among other features, for clinical trials" [4]. Currently, there are separate systems for clinical documentation: EDC systems for clinical studies and hospital information systems (HIS) for routine medical documentation in electronic health records (EHRs). These systems are managed as a dual source concept [5]. ▶Figure 1 shows the architecture of these systems.

In a single source setting, routine and follow-up documentation takes place in the HIS. Research data are available for analysis after transfer from the HIS into the research database. ▶Figure 2 shows this concept. Data validity is monitored by the study data management team, a process that is supported by HIS tools. By avoiding multiple documentation, time and costs can be saved [6], transcription errors are removed and patient recruitment is facilitated [7].

In a single source system, routine clinical data are used for research purposes. High data quality is a prerequisite for clinical research. Unfortunately, there are limitations regarding data quality in the medical routine. Documentation in the clinical routine is often incomplete [8] and error-prone [6, 8]. Typical reasons for these shortcomings are: work done under time pressure [2], errors at data entry [9] and missing information. For instance, de Luisignan et al. state that "capturing data about death or reasons that patients stop attending a physician can be difficult…" [10]. In addition, follow-up documentation needs to be collected at certain time points; otherwise, these patients cannot be included into the final analysis of the study.

In this manuscript, we present a concept and an implementation of a HIS-based support for follow-up documentation in clinical research. We have developed a method and implemented it in two clinical settings (nuclear medicine and psychiatry).

A single source information system in nuclear medicine was developed in 2008-2009 for the first study. This system connected patient care and clinical research for studies on cardiovascular diseases according to the generic concept of ▶Figure 2. Medical history and findings of stress and rest injection data for myocardial scintigraphy on single photon emission computer tomography combined with two-slice computer tomography (SPECT/CT) were documented within the local clinical information system (CIS) and exported into a research database for analysis [11]. An extension of this documentation system to support patient follow-up was required. A study nurse needed to be informed at the correct time points according to the study protocol to contact the patient's cardiologist and to ask for the patient's general condition and cardiac events such as myocardial infarction or death. The patient's consent for this procedure was obtained during patient recruitment.

In the second study from the domain of psychiatry, there was a need to support follow-up documentation of patients with bipolar disorders. A specific depression score for inpatients was to be documented weekly. Automatically generated CIS-forms were tested to support documentation on time and to minimize missing data.

In this context, we sought to develop a generic concept for HIS-based support of follow-up documentation and demonstrate its effectiveness using case study evidence.

2. Objectives

This manuscript assesses the feasibilty of a HIS-based follow-up system to support study documentation. This manuscript addresses the creation of follow-up forms on time and completeness according to study protocols.

3. Methods

3.1 Requirements
In general, a HIS-based follow-up system should satisfy the following requirements which are defined by each study protocol:
1. Consenting study patients are identified.
2. Relevant follow-up data items which are available in the CIS are identified.
3. The follow-up forms for each study patient are placed at the study nurse's/physician's disposal in a work list at the correct time point according to each study protocol.
4. Follow-up forms provide high data quality through plausibility and completeness checks.

3.2 Architecture and workflow
First, a data model to meet these requirements was developed. In this setting, ORBIS® from AGFA [12] as the clinical information system was used. The communication server e*gate from ORACLE [13] was used to transfer electronic data between departmental systems, CIS, laboratory information systems (LIMS) and the radiological information system/picture archiving and communication system (RIS/PACS) within the HIS by health level seven (HL7) messages.

A HIS-based follow-up system accounted for items of existing clinical documentation within the CIS and automatically created a follow-up form if the defined study-specific conditions were fulfilled. The architecture of the follow-up system is demonstrated in ▶Figure 3. The main procedure was started periodically by job control. It identified due records in a table which contained the follow-up schedule and started the related study-specific follow-up procedures. The corresponding study-specific queries were performed. The flow chart in ▶Figure 4 demonstrates the internal database processes of generating follow-up events for each study. Follow-up data had to be collected at different time points, as defined by each study protocol.

The queries were designed to reflect follow-up periods such as "follow-up six months after initial diagnosis ±1 week". For each resulting case ID per study, a corresponding follow-up event was created (see ▶Figure 3). In our implementation, a record which contained the required information for generating a form was inserted into a table. This table was fetched by the communication server. It translated the text string from a proprietary form into a standardized HL7 message. This message was transferred to the import interface of the CIS which generated the form.

3.3 Design of follow-up forms and data analysis
The follow-up forms were designed using the form designer of our CIS. To enable (semi-) automated re-use of data for research, highly structured forms were implemented with radio buttons, check boxes, lists, number fields and only few narrative text fields. To accelerate documentation, radio buttons and check boxes were preferred data entry elements. Real-time plausibility checks were implemented in order to improve data quality. Furthermore, several conditional items with related plausibility checks were implemented. These were only visible in the context of superordinate questions. For example: If vessel status of the left coronary artery (LCA) was selected, the degree of stenosis had to be filled in. Therefore, a number field had to be entered in the range of 1 to 100 (%) or the check box 'unknown' had to be ticked. Filling both fields was avoided by implementing conditions for entry. If vessel status of the LCA was not ticked, the relating items were invisible. Checks for correctness and completeness of documentation were applied. For instance, mandatory items needed to be completed before a form could be finalized, for example, 'myocardial infarction' and 'stroke' were mandatory items. An error message occurred if mandatory items were not completed. The protocol could be saved and closed at any time in a draft state which was a relevant feature for clinical acceptance. A work list contained links to uncompleted forms for physicians' review. Error messages were provided if data items were invalid or missing. Missing items

were highlighted in red. Checkboxes "unknown" were implemented to distinguish between missing data entry and clinically unavailable information.

The report generator of ORBIS® [12] was used to extract HIS-based follow-up data for research purposes. It enabled the generation of data queries by drag-and-drop of the relevant data items. These queries could be executed by authorized study physicians and generated csv-files which were compatible with statistics software such as Predictive Analytics Software (PASW) from SPSS [14]. Patient data privacy was protected by pseudonymized HIS reports using numeric IDs without patient names. Monitoring was performed by a data management team to verify data validity in the research database. This process was supported by specific HIS reports, for example a report of incomplete patient documentation.

3.4 Test scenarios

A simulation concept was designed to test HIS-based support of follow-up documentation in two settings. In the nuclear medicine setting, a systematic test of all possible 12 scenarios was conducted with a prototype system (▶Table 1). For each scenario, it was determined whether a follow-up form was required. Successively, all scenarios and follow-up periods were simulated while testing the system. In the psychiatry setting, a pilot test in clinical routine was conducted in addition to a simulation.

4. Results

The implementation of the follow-up system consisted of three components. The first component was a procedural language/structured query language (PL/SQL) procedure scheduled once a day by a unix crontab. It identified due study-specific follow-up procedures in a follow-up schedule table and started them.

4.1 Follow-up system in the nuclear medicine setting

In the nuclear medicine setting, the protocol of the SPECT/CT study was defined to collect follow-up data from one up to ten years after a patient's first SPECT/CT examination. The processes of generating a follow-up event for the study in nuclear medicine were implemented according to the flow chart in ▶Figure 5. To deliver the actual case IDs, retrospective queries were performed on a yearly basis for up to ten years from the creation date of the medical history form. For each case ID, only the first medical history form was considered and only patients with available informed consent were selected. As a next step, survival and loss of follow-up status (status of participation in the study) of the patient were checked according to previous follow-up forms, if they existed. Subsequently, a follow-up event in a proprietary form was enqueued into a table which was fetched by the communication server e*gate [13] – the second component of this follow-up system. This event was translated from a proprietary form into a standardized HL7 message and transferred to the import interface of ORBIS® [12] for interpretation. The interface generated the follow-up form, assigned the medical date, initialized data fields and enqueued the form to the nurse's/physician's work list. The medical date is the follow-up time point defined in the study protocol. In the case of delayed documentation, the medical date differed from the documentation date. However, in most cases, the medical date corresponded to the documentation date. ▶Figure 6 presents an example of two enqueued follow-up forms in this work list.

The third component of this follow-up system was the HIS-based follow-up form. The form designer of our CIS was applied. ▶Figure 7 presents a screenshot of the follow-up form of the SPECT/CT study with predominantly structured data like radio buttons, check boxes, lists and number fields as well as few additional text fields. Plausibility and completeness checks for data quality were implemented as described in the methods section.

The number of attributes in the follow-up documentation amounted to 105 whereas 103 (98%) were required under certain conditions. Therefore, data entry efforts were reduced. For instance, lost to follow-up patients could be documented as demonstrated in ▶Figure 8 when the patient's address was unknown.

4.2 Simulation of test cases of the SPECT/CT study

The PL/SQL-scripts were enhanced for simulation purposes with an optional date parameter. This enabled the user to pass any future date parameter to the procedure. By using dates of certain time points according to the study protocol each scenario from ▶Table 1 was tested. The results of the test concept for creating a follow-up form were compared with the actually generated forms. Medical history and follow-up forms with an up-to-date timestamp were created in order to simulate inclusion and exclusion criteria to generate follow-up forms according to each scenario of the test concept. To verify the correct functionality of the HIS-based follow-up system, we applied the optional date parameter of the PL/SQL procedure. During the simulation phase, future dates (from one to ten years) were passed to the procedure. When a follow-up form was due, this simulated date was inserted in the HL7 message in order to be interpreted as a medical date by the import interface of ORBIS®. Thus, follow-up forms with future medical dates (reference date + 1 year, reference date + 2 years, …, reference date + 10 years) were created in a simulation phase and accordingly scheduled in EHRs. Each scenario from the test concept was simulated and each test scenario passed the test. Consequently, a HIS-based follow-up system is technically feasible.

4.3 Follow-up system in the psychiatry setting

An analogous follow-up system was integrated into the clinical workflow in the department of psychiatry. For certain inpatients the attending physician created a depression score form. This form acted as a trigger to activate the follow-up system. Using SQL queries the follow-up system identified all manually and automatically created depression score forms which were created exactly one week previously and determined the related case IDs (▶Figure 9). For each distinct case ID, a follow-up form was generated if the patient was not yet discharged. ▶Figure 10 shows the number of forms generated by the follow-up system per calendar week. In the period from February 1st, 2010 to August 15th, 2010, 128 follow-up forms for 23 distinct patients were automatically generated (on average 5 forms per week with a maximum of 12 and a minimum of 1 form per week); 14 forms were canceled due to additional manual creation of a depression score form by mistake in the introduction phase. The remaining 114 follow-up forms were finalized by electronic signature. Thus, they were completely documented and the HIS-based follow-up system was integrated into the clinical workflow.

5. Discussion

Timely and complete follow-up documentation is a significant issue in clinical studies. This task is supported by the HIS-based follow-up system. Recruitment of suitable patients and complete documentation are key issues in clinical trials. In 2006, a meta-analysis of more than 100 trials showed that "less than a third (31%) of the trials achieved their original recruitment target and half (53%) were awarded an extension" [15]. Computerized recruiting for clinical trials in real-time improves study investigator notification [16]. Recruitment rates were increased significantly by the use of an EHR-based clinical trial alert system [17]. However, standard EDC systems are not integrated into the routine clinical workflow of the HIS.

EDC systems can support follow-up documentation. Welker states that "The central storage of data and ubiquitous user access allows the inclusion of intelligence that can remind individual users to perform required tasks; i.e. remind the investigator site when an enrolled patient is due for a follow-up visit…" [18]. Usually, this occurs upon the patient's return to the hospital for follow-up, but sometimes only specific information such as survival status is required for research purposes (like in the SPECT/CT study), where a follow-up visit is not necessary. In such cases, it is critical to inform the study nurse at the correct time when follow-up data are due.

In a single source information system, queries can be performed on routine data in order to create follow-up forms for research. Using this approach, redundant data entry is avoided [2, 6, 19] and documentation on EHR and eCRF is synchronized [20]. Unfortunately, at present, a single source information system depends on each individual HIS product which generates additional

efforts in multicentric studies. There are two requirements for integration with other HIS which are currently not yet fulfilled: first, standards for (e)CRF are necessary. There is ongoing research on standardized data element definitions for the use in applications across different studies. These definitions are integrated into a globally accessible electronic library called CDISC SHARE developed by the non-profit organization Clinical Data Interchange Standards Consortium (CDISC) [21]. Second, import and export of standardized (e)CRF-schemes from HIS has to be enabled. Therefore, HIS functionality must be enhanced. In addition, HIS-based study documentation systems need to be validated according to Good Clinical Practice (GCP).

The design and implementation of this HIS-based follow-up system show that, currently, it is technically feasible within commercial HIS environments. It extends the existing EHR. Furthermore, the system queries already entered data across several electronic forms in order to react in a previously defined way. Further research is needed to quantify the effect of our method on completeness and timeliness of follow-up documentation.

If the local CIS was capable of generating follow-up forms independently, the architecture of the follow-up system would be simpler than in our approach as the configuration of the communication server would be dispensed. However the communication server approach increases flexibility, as for every form type, an import interface command must be defined. In the approach described in this manuscript, only one call must be defined, and the logic for running the related procedure for each form type is deposited in a table of the follow-up database package using PL/SQL. An important advantage of this approach is that we are able to pre-populate several items in the forms which are created by HL7 import. For several studies, it may be relevant to provide different follow-up forms after the expiration of different follow-up periods. In general, the follow-up system using the communication server provides a higher flexibility with regard to job control and initializing items than a follow-up system only based on the CIS as a stand-alone system.

In addition, our approach to automatically generate follow-up forms could be implemented in other HIS environments. This concept is successful in academic home-grown HIS as well as commercial standard CIS which generally are complex and restrictive with regard to further design and development as well as data access. The opportunity of wide use is a prerequisite for further dissemination of this concept. A form designer tool is needed in order to design follow-up forms. Furthermore, the CIS must provide the possibility to mark study patients. In addition, a work list is needed. A further requirement for the implementation of this concept is an interface to a communication server and the ability to implement new interfaces.

To our knowledge, the literature regarding HIS-integrated follow-up documentation in clinical research is limited. There is some related work in the clinical care setting. Since 1967, the Health Evaluation Through Logical Processing (HELP) system has been implemented and successively expanded [22]. It allows clinical care and computerized decision-support. Mosen et al. analyzed the effect of a computerized reminder system on the prevention of postoperative venous thromoembolism [23]. An increase of the prophylaxis rate from 89.9% to 95.0% was reported. Both studies referred to home-grown CIS. Barnett et al. published their results of a study on a computer-based monitoring system for follow-up of elevated blood pressure [24]. They reported that computer-generated reminders which were sent to the patient's primary physician improved follow-up of a newly discovered elevation in diastolic blood pressure. Both Barnett's and our system resulted in the increased care of collection of follow-up data on schedule. According to Staes et al., computerized alerts improved outpatient laboratory monitoring of transplant patients [25]. Nurses were informed if a transplant patient had overdue laboratory results. Completeness of laboratory result reporting increased from 66% to 99%.

The use of commercial CIS is predominant in America and in Germany. However, comprehensive use of EHRs in the U.S. is quite rare [26]. In Germany, almost all hospitals use commercial CIS which are generally restricted in terms of further design and development as well as data access. A unique feature of our approach is that it can be applied in a commercial HIS setting.

In the future, HIS-based support of follow-up documentation will be an important component in clinical studies as clinical routine and research data is expected to be increasingly inter-connected in order to improve the efficiency of medical documentation.

6. Conclusion

In this study, we have shown that automatic generation of follow-up forms in clinical studies based on HIS data is technically feasible. It can support protocol-conforming high-quality documentation through highly structured data entry and real-time plausibility checks, and it can be integrated into the clinical workflow of standard HIS environments.

Clinical Relevance Statement
Incompleteness in study documentation is a critical problem across clinical research studies. A HIS-based follow-up system can improve completeness in a single source information system.

Conflict of Interest
The authors declare that they have no conflicts of interest in the research.

Human Subject Research
The study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained in all cases.

Abbreviations
HIS: hospital information system; CIS: clinical information system; EHR: electronic health record; CRF: case report form; LIMS: laboratory information systems; RIS/PACS: radiological information system/picture archiving and communication system; HL7: health level seven; SPECT/CT: single photon emission computer tomography combined with two-slice computer tomography; ECG: electrocardiogram; PL/SQL: procedural language/structured query language; LCA: left coronary artery; PASW: Predictive Analytics Software; GCP: Good Clinical Practice
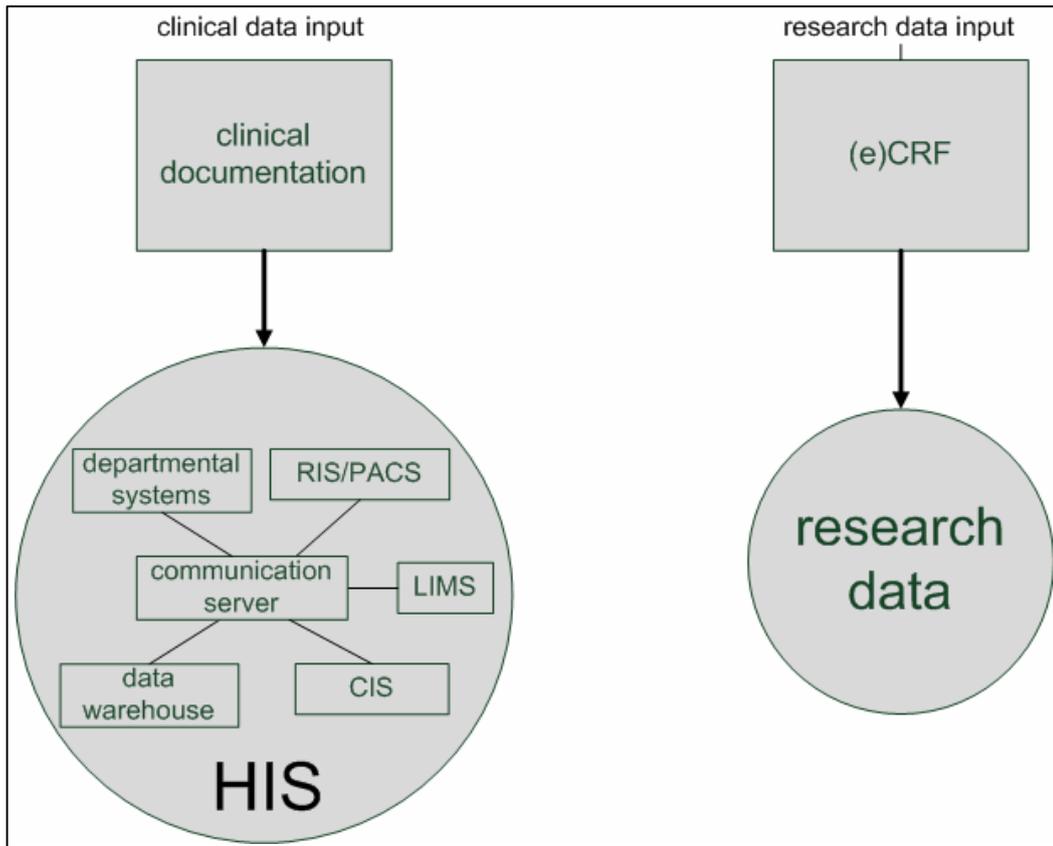
Fig. 1 Architecture of dual source information systems: HIS and research databases are separated systems. Case report forms (CRFs) are entered into the research database and are not available in the hospital information system (HIS) [5]; CIS: clinical information system; LIMS: laboratory information systems; RIS/PACS: radiological information system/picture archiving and communication system.
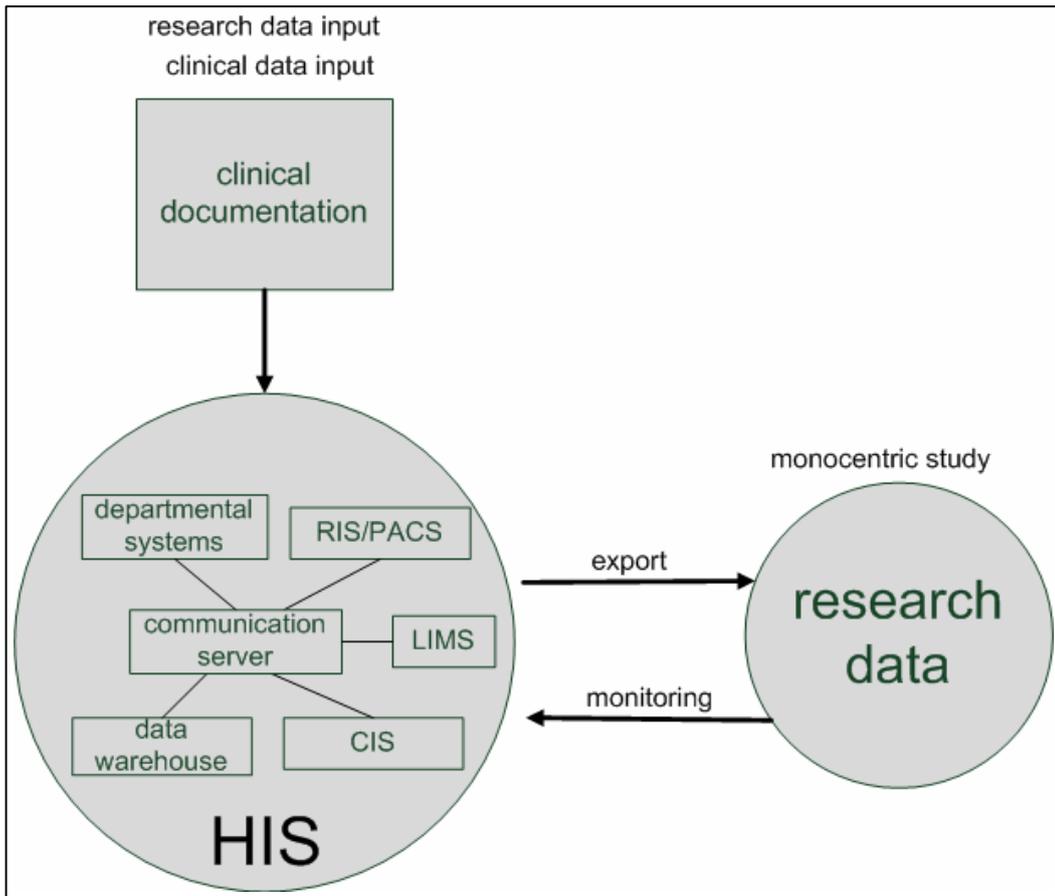
Fig. 2 Architecture of single source information systems: Routine and research data are collected within HIS. Research data are exported into the research database. Monitoring takes care of incomplete or incorrect data elements [5].
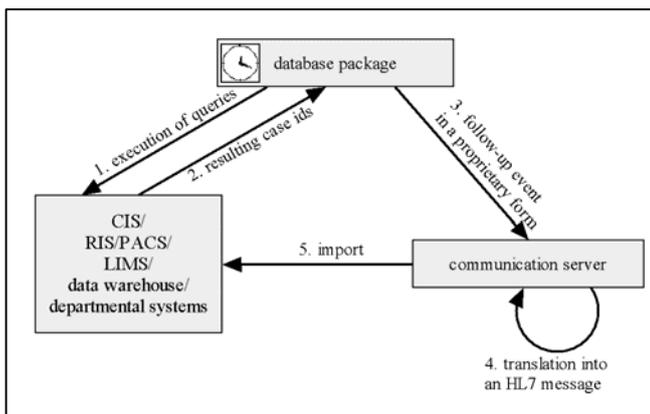
Fig. 3 Architecture of automatic generation of follow-up forms: A scheduled database procedure executes defined queries on existing documentation. For related case IDs, a follow-up event is created and transferred by the communication server to the import interface of the CIS, RIS/PACS, LIMS, data warehouse or a departmental system respectively generating the follow-up form.

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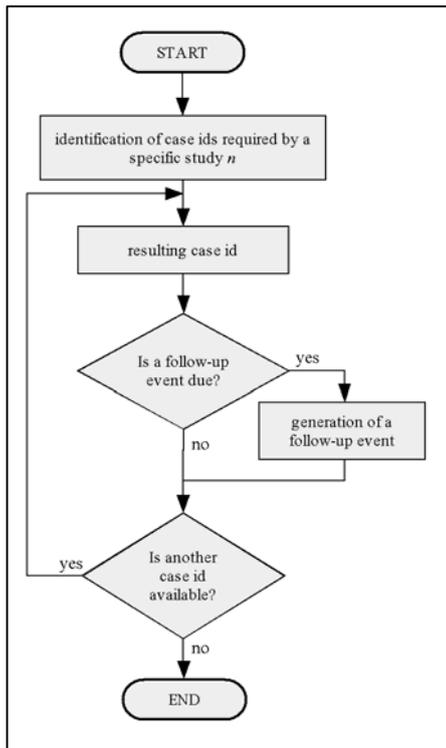
Fig. 4 **Flow chart to generate follow-up events:** Periodic queries identify due follow-up forms for n studies where $n \in \{1, \ldots, n\}$. The system was implemented using procedural language/structured query language (PL/SQL).
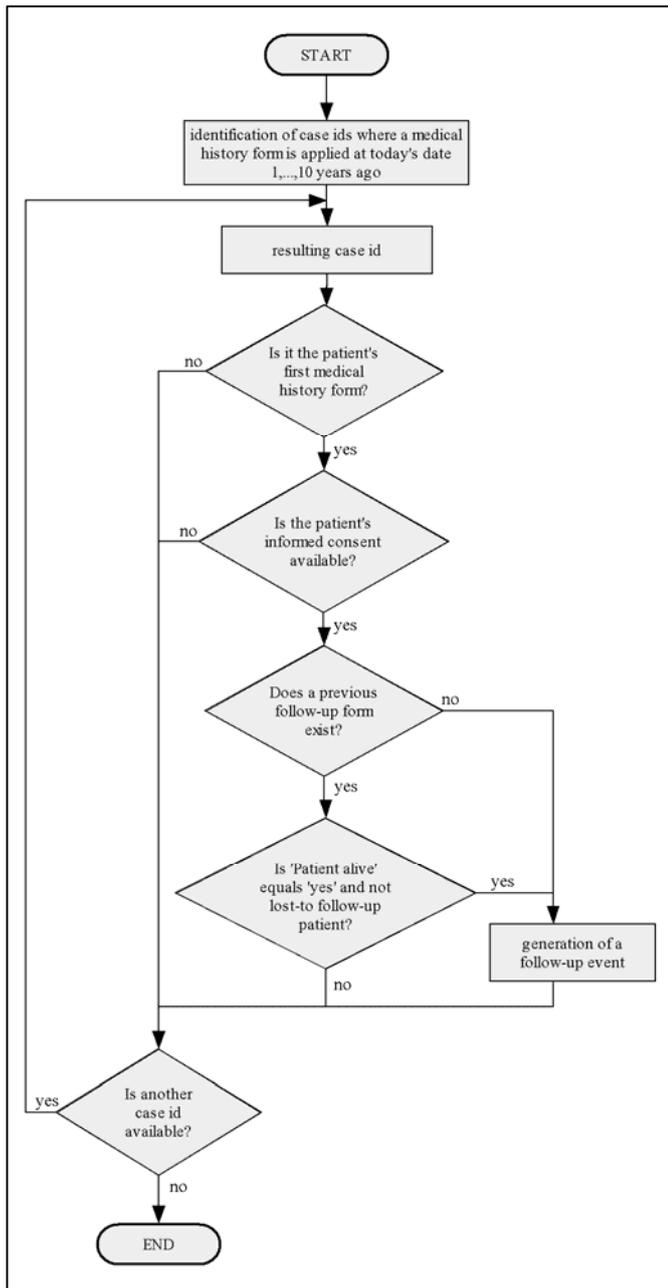
Fig. 5 Flow chart of the implementation to generate follow-up events for the SPECT/CT study: Study-specific periodic queries identify due follow-up forms.

Fig. 6 Screenshot of the nurse's/physician's work list: Tasks from the clinical routine are presented in these lists; therefore, nurses and physicians regularly review the list items. Automatically generated follow-up protocols are enqueued in this list.

Fig. 7 Screenshot of a follow-up form in nuclear medicine: Radio buttons and check boxes are preferred data elements in order to speed up documentation. Data entry efforts are minimized by the use of many conditional items.

Fig. 8 Screenshot of a follow-up form in nuclear medicine with regard to loss of follow-up status: The follow-up form allows documentation of loss of follow-up patients.
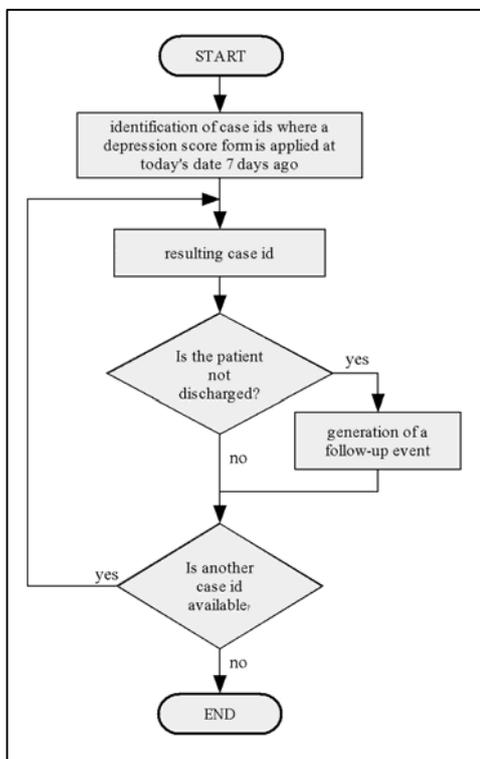

Fig. 9 Flow chart of the implementation to generate follow-up events for the depression study: Periodic queries identify due follow-up forms.
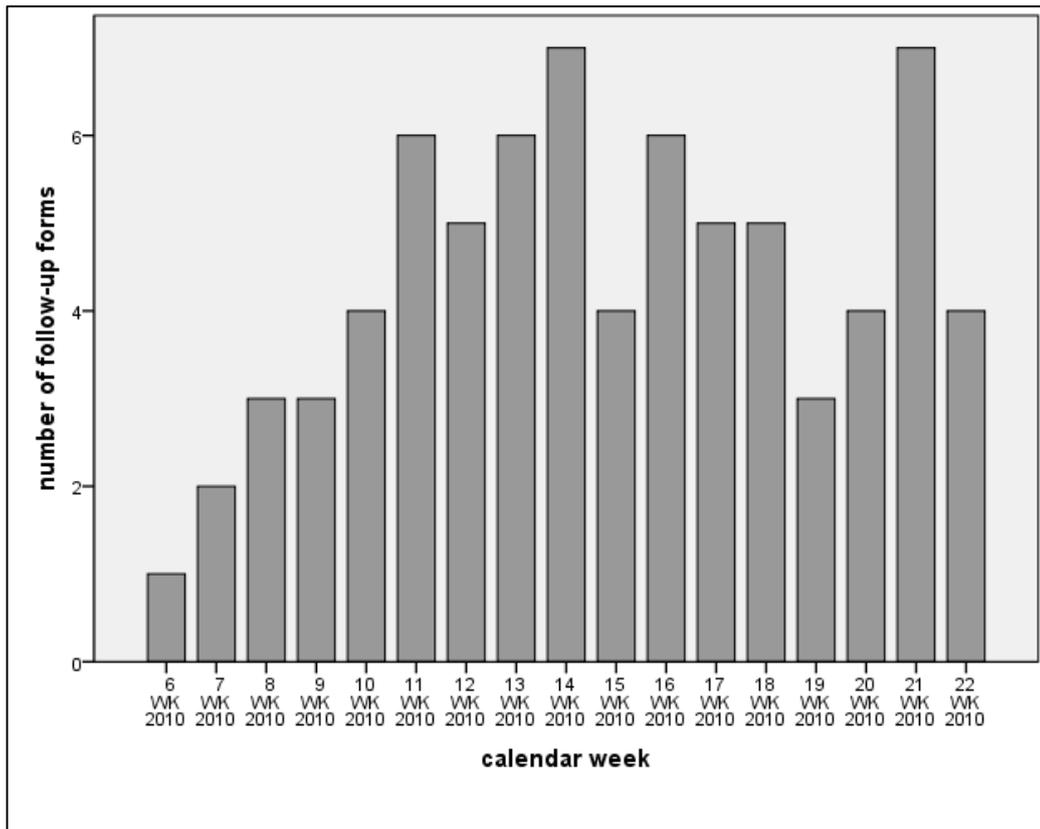
Fig. 10 **Bar diagram of automatically generated follow-up forms per calendar week:** Bar diagram of automatically generated follow-up forms per calendar week. Within 27 weeks, 128 forms were generated, on average five per week (WK: week).

Table 1 **List of possible scenarios of the SPECT/CT study:** The last column shows that only the first and third scenario require to generate a follow-up form.

Scenarios	First medical history form of the patient after study start?				Is a previous follow-up form available?			Follow-up form required?
	yes		no		yes		no	
	Is the patient's informed consent available?		Is the patient's informed consent available?		Patient status "alive" and "no loss of follow-up patient"?			
	yes	no	yes	no	yes	no		
1	X				X			yes
2	X					X		no
3	X						X	yes
4		X			X			no
5		X				X		no
6		X					X	no
7			X		X			no
8			X			X		no
9			X				X	no
10				X	X			no
11				X		X		no
12				X			X	no

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