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DICOM for Clinical Research: PACS-Integrated Electronic Data Capture in Multi-Center Trials

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Abstract Providing surrogate endpoints in clinical trials, medical imaging has become increasingly important in human-centered research. Nowadays, electronic data capture systems (EDCS) are used but binary image data is integrated insufficiently. There exists no structured way, neither to manage digital imaging and communications in medicine (DICOM) data in EDCS nor to interconnect EDCS with picture archiving and communication systems (PACS). Manual detours in the trial workflow yield errors, delays, and costs. In this paper, requirements for a DICOM-based system interconnection of EDCS and research PACS are analysed. Several workflow architectures are compared. Optimized for multi-center trials, we propose an entirely web-based solution integrating EDCS, PACS, and DICOM viewer, which has been implemented using the open source projects OpenClinica, DCM4CHEE, and Weasis, respectively. The EDCS forms the primary access point. EDCS to PACS interchange is integrated seamlessly on the data and the context levels. DICOM data is viewed directly from the electronic case report form (eCRF), while PACS-based management is hidden from the user. Data privacy is ensured by automatic de-identification and re-labelling with study identifiers. Our concept is evaluated on a variety of 13 DICOM modalities and transfer syntaxes. We have implemented the system in an ongoing investigator-initiated trial (IIT), where five centers have recruited 24 patients so far, performing decentralized computed tomography (CT) screening. Using our system, the chief radiologist is reading DICOM data directly from the eCRF. Errors and workflow processing time are reduced. Furthermore, an imaging database is built that may support future research.

Keywords Clinical trial · Systems integration · Workflow · Digital Imaging and Communications in Medicine (DICOM) · PACS · Open source

Introduction

Clinical trials are essential for developing novel drugs and devices. Particularly regarding biomarker-guided therapy in personalized medicine, biomarker validation is performed retrospectively and prospectively, where data from previously well-conducted randomized controlled trials (RCTs) is used or captured according to hybrid or adaptive trial protocols, respectively [1]. Hence, medical imaging is looming large today in clinical trials. Image-based surrogate endpoints provide eligibility, efficacy, and security evaluation by qualitative and quantitative disease finding in studies [2].

In all trial designs, subject data may be captured electronically, and the paper-based case report forms (CRFs) have been substituted by electronic data capture systems (EDCS), offering rich functionality for data storage and management in so-called electronic CRFs (eCRFs). Automatic evaluation of data during entry, specific views for various roles in a clinical trial (e.g., research nurse, principle investigator, monitor), multi-centered subject recruitment, and de-centralized data sharing improve quality of research and simplify secure access to the data.

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The American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) have established the Digital Imaging and Communications in Medicine (DICOM) protocol as the leading standard for storage and transfer of image data in medical applications [3]. In clinical routine for the patient's care as well as in clinical trials or cooperative research, DICOM is utilized in picture archiving and communication systems (PACS), decreasing turnaround time and increasing productivity [4].

However, today's architecture of EDCS is standalone. Integration of any binary information such as biosignals or image recordings is supported insufficiently. In particular, there is no structured way to capture DICOM data in EDCS. So far, storage or retrieval of DICOM-based data in the eCRF is impossible and interfaces for DICOM-based communication are unavailable. Image data is transferred and mapped manually between the systems in roundabout ways. Manual interaction of study personnel is required, decreasing data quality, increasing processing time, and magnifying costs in the EDC workflow.

In clinical research, there are some specific solutions for trial image management. The cancer Biomedical Informatics Grid (caBIG) of the National Cancer Institute (NCI) is a computational network for sharing binary large object (BLOB) data and analytical tools in cancer research [5]. Although caBIG has been retired in 2012,[1] it is utilized by ImagEDC,[2] an EDC tool for image data in trials. The Medical Imaging Resource Center (MIRC) of the Radiology Society of North America (RSNA) is a sharing platform for teaching files and clinical trial data [6]. An open source imaging platform for sharing, management, processing, and distribution of image and related study data is offered with the Extensible Neuroimaging Archive Toolkit (XNAT) of the Neuroinformatics Research Group (NRG) lab [7]. However, these solutions are rather specialized systems for certain diseases and disconnected from EDCS.

In the commercial field of pharmaceutical trials, some EDCS solutions may support storing and viewing of DICOM data. Based on an Internet survey, we found candidates with Oracle Clinical and Oracle Remote Data Capture,[3] iMetNet EDC,[4] eCRFast,[5] Clinical Trials Solutions,[6] and DICOM Image Management.[7] Oracle Clinical and Oracle Remote Data Capture (Oracle Corporation, Redwood City, CA) are integrated applications for clinical data management (CDM) and remote data capture (RDC), respectively. Both systems apply the Oracle database, which supports storage of DICOM objects. However, it is not clear whether integration of DICOM objects into eCRFs is also supported. IMetNet EDC (MedNet Solutions Corporate, Minnetonka, MN) is an EDCS offering a DICOM imaging module. The EDCS eCRFFast (AST Clinical Solutions Inc, Quebec, Canada) provides rich functionality for clinical trial data and supports viewing of DICOM objects. Furthermore, Clinical-Trials Solutions (AG Mednet, Inc., Boston, MA) is a modular system for collecting of image data in clinical trials. Last but not least, DICOM Image Management (ClinicalStudio, Reno, NV) is a study management and EDCS, in which DICOM images can be attached to eCRFs. Particularly for investigator-initiated trials (IITs) and academic research, commercial approaches are inapplicable due to well-known barriers such as technical support, regulatory requirements, communication with users, timing of implementation, software installation, graphical user interface, availability of technology, and costs [8].

Hence, a first approach based on open source components has been presented by van Herk [9], who utilized OpenClinica and Conquest[8] as EDCS and PACS, respectively. In this architecture, DICOM content is queried from a Conquest instance, anonymized, and connected to the eCRF via web access to DICOM persistent objects (WADO) [10]. The patient's eCRF and image data is transferred to a research server. However, DICOM objects must be already available in Conquest. Advanced DICOM viewing functionality is not provided, limiting user interaction conducting the trial.

A similar architecture has been proposed by Skripcak et al. connecting OpenClinica and Conquest with Lua scripts [11]. DICOM data is integrated via a standalone client, which transfers the image data to the PACS and inserts references in the eCRF via web service envelopes. For viewing of subject data, the web-based DICOM viewers Weasis and DVW[9] are served by a middleware component via WADO. However, image data cannot be stored directly via the web. A special client has to be installed on all systems.

This work aims at seamlessly integrating DICOM data into EDCS with respect to the workflow in clinical trials. Based on a systematic requirement analysis, we add a PACS node for research, which is interconnected to the EDCS and feed from the eCRF. De-identification and re-labeling of DICOM data is done automatically, having the EDCS as the primary access point of the users. As proof of concept, we implement the system exclusively using open source components. Evaluation is performed on various DICOM modalities and transfer syntaxes, and by means of an ongoing

[1] http://cbiit.nci.nih.gov/ncip/about-ncip/
[2] https://code.google.com/p/imagedc/
[3] http://www.oracle.com/
[4] http://www.mednetstudy.com/technology/imednetedc/
[5] http://www.astclinical.com/solution.html
[6] http://www.agmednet.com/clinical-trials-solutions/
[7] http://www.clinicalstudio.com/features/dicom-image-management/

[8] http://ingenium.home.xs4all.nl/dicom.html
[9] http://ivmartel.github.io/dwv/

multi-center trial where subjects are screened with computed tomography (CT) to decide on their inclusion to the trial.

Material and Methods

Requirement Analysis

General (G) requirements are facing technical issues. Furthermore, needs regarding integration (I) as well as the retrieval (R) of DICOM data exist. All requirements are seen from the user's point of view, i.e., the study team (research nurse, investigator, radiologists), handling subject data including DICOM images.

G1. *Open Source*: All used components should be licensed as open source projects to support low-budget research (IITs).
G2. *Integration Level*: All processes should be performed in the background, completely hidden from the user. This requirement yields all integration levels, such as data, context, function, and visual integration.
I1. *Storage*: DICOM data should be storable from inside the center's IT system (e.g., via DICOM workstation) as well as from outside (e.g., via the eCRF).
I2. *Formats*: All types of DICOM data formats should be supported (including DICOM-convertible data) to avoid manual conversion steps before integration.
I3. *De-identification*: The subject's personal data should be removed automatically from DICOM objects and substituted with the appropriate trial identifiers when entered into the research database.
I4. *Record Linkage*: The data context (e.g., patient, study, event identifier) should be considered during integration and linked between the EDCS and PACS.
I5. *Reliability*: The transfer of DICOM data via the Internet should be stable, robust, and secure to ensure successful completion of all transactions.
R1. *Data Access*: All integrated DICOM objects should be directly retrievable from the trial-specific eCRF. This requires web-based DICOM viewers rather than software that needs installation on client systems.
R2. *Transfer Syntax*: All types of DICOM modalities and transfer syntaxes should be viewable to broadly support medical imaging.
R3. *Data Visualization*: Rich functionality for 2D/3D image interaction (e.g., measurement tools) should be provided during viewing of DICOM objects.
R4. *Data Enhancement*: Image annotation and DICOM structured reporting (DICOM-SR) results should be stored back within the research PACS.
R5. *Future Research*: Collected DICOM data should be centrally and study-independently accessible for further research purposes.

System Architecture

Various levels for combining EDCS and PACS via integrated and separated storage and viewing components have been discussed in our previous work [12]. Basically, these strategies differ in storing, retrieving, and handling of images on the trial center's site as well as the central site for image reading (Fig. 1). Several options and protocols exist.

- *External Storage*: Captured image data is kept separately from the subject's medical data in the clinical PACS.
- *Internal Storage*: If the EDCS provides functionality for integration of BLOB data, captured image data can be directly stored within the eCRF together with other patients' data.
- *Integrated Storage*: The image data is transferred into a research PACS that is integrated with the EDCS. The transfer is done either via the eCRF or directly using a DICOM-conformant workstation. A reference identifier linking PACS and EDCS is deposed in the eCRF.
- *Separated Retrieval*: A DICOM viewer for standalone platforms (e.g., Windows, Linux, and Mac) is installed on each client system, and DICOM objects are

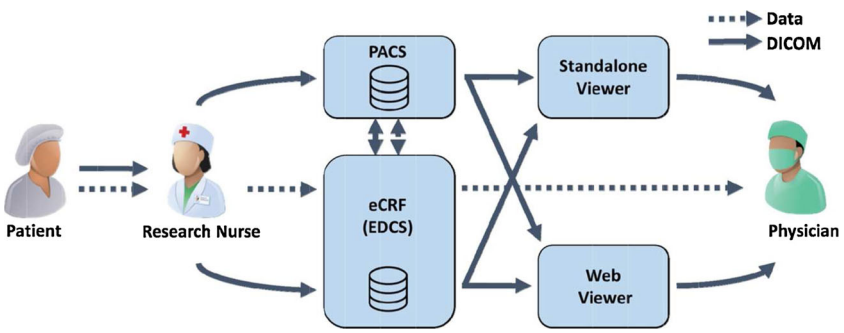

Fig. 1 Various strategies for integration of DICOM image data into EDCS [12]

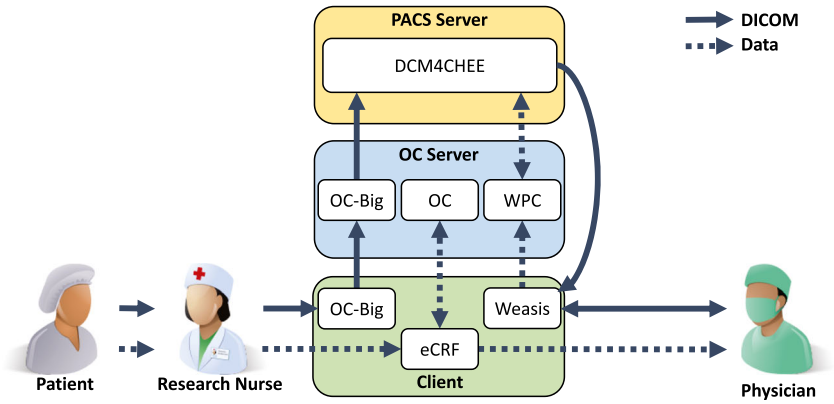

Fig. 2 Proposed architecture for connecting EDCS and PACS

separately retrieved via DICOM transfer functionality (e.g., C-FIND).

– *Integrated Retrieval*: The DICOM viewer is installed on a server and shared through the web. The functionality for retrieval of DICOM objects is accessible through modern web browsers on client systems.

Each approach defines different requirements to suitable DICOM viewing software with respect to licensing, technical platforms, interfaces, 2D and 3D functionality, as well as support. Integrated storage and retrieval is preferable over separated designs. It is seen as the most advantageous solution when implemented as a web-based solution [13].

Open Source Implementation

A variety of web-based and open source tools is available for each of the components EDCS, PACS, and DICOM viewer. The proposed architecture (Fig. 2) is composed of OpenClinica (OC) with OC-Big [14], DCM4CHEE as PACS, and Weasis as web-based DICOM viewer, connected via the Weasis PACS Connector (WPC).

OpenClinica as EDCS

OpenClinica (OC) is an EDCS and CDM system. The Community Edition (Version 3.4) is open source and designed as a web-based application. OC offers rich functionality for storage and management of subject data in multi-center trials. Following industrial standards, it has been approved by regulatory authorities such as the Food and Drug Administration (FDA). Therefore, OC is one of the most popular EDCS and, due to its open source license, especially attractive for low-budgeted research [15, 16]. Furthermore, OC is supported by a large user community, which continuously improves the EDCS by development of new extensions, such as OC-Big.[10]

OC-Big (Version 1.1.0) is an add-on for OC. The open source tool allows context-based integration of BLOB data (e.g., medical image data) into eCRFs [14]. The plug-in is embedded into the eCRF substituting OC's native file upload component. To reduce transfer time, data is compressed instantaneously.

DCM4CHEE as PACS

DCM4CHEE[11] (Version 2.17.2) [17] is part of DCM4CHE, a community-driven collection of open source utilities for the healthcare enterprise. It is designed modularly and provides several interfacing protocols including DICOM and Health Level Seven (HL7). DCM4CHEE comes with a web-based user interface. It supports WADO to serve DICOM data via the web.

Weasis as DICOM Viewer

Focussing on the integrated retrieval strategy, it is of particular importance that the viewer is web- or Java-based, supporting invocation from a web-based context, e.g., via the Java network launch protocol (JNLP). Furthermore, interfaces for receipt of DICOM objects (e.g., via WADO) and context information (e.g., via parameter transfer) are important. In our previous work [18], a catalogue of 29 requirements has been composed, which have to be met for the integrated strategies, and 27 DICOM viewers have been evaluated. The open source viewer Weasis[12] achieved the highest rank supporting the data workflow in multi-center trials.

Weasis (Version 2.0.2) is an open source web-based viewer for DICOM objects. The tool is developed in Java and provides a wide range of image functionality (e.g., windowing, information overlay, pseudo-coloring, measurements, and annotations). Weasis supports interfacing with Integrating the Healthcare Enterprise (IHE) systems and PACS via cross-

[10] http://idmteam.github.io/oc-big/

[11] http://www.dcm4che.org/confluence/display/ee2/Home

[12] http://www.dcm4che.org/confluence/display/WEA/Home

Table 1 Cleared and linked DICOM header elements

Cleared elements			
Identifier	Description	Identifier	Description
0008,0090	ReferringPhysicianName	0010,1000	OtherPatientIDs
0008,1010	StationName	0010,1001	OtherPatientNames
0008,1030	StudyDescription	0010,1005	PatientBirthName
0008,1050	PerformingPhysicianName	0010,1010	PatientAge
0008,1052	PerformingPhysicianIDSequence	0010,1040	PatientAddress
0008,1060	NameOfPhysicianReadingStudy	0010,1060	PatientMotherBirthName
0008,1070	OperatorsName	0010,21B0	AdditionalPatientHistory
0010,0010	PatientName	0010,2154	PatientTelephoneNumbers
0010,0030	PatientBirthDate	0010,2160	EthnicGroup
0010,0032	PatientBirthTime	0010,2180	Occupation
0010,0040	PatientSex	0010,4000	PatientComments
Linked elements			
Identifier	Description	Identifier	Description
0010,0020	PatientID	0012,0040	ClinicalTrialSubjectID
0012,0030	ClinicalTrialSiteID		

enterprise document sharing for imaging (XDS-I) and WADO, respectively. Its add-on, the Weasis PACS Connector (Version 4.0), supports invocation of the Java application via JNLP.

De-identification and Record Linkage

DICOM data captured for clinical trials is usually not neatly de-identified in all DICOM header tags. Images have to be integrated anonymously to the research PACS. For de-identification, we determined a set of DICOM elements that hold patient-related information (Table 1, top). The recordings are linked with the subject's eCRF using specific context information (e.g., study, site, patient identifiers), which is extracted from OC and inserted into corresponding header elements (Table 1, bottom).

Evaluation

To demonstrate general applicability, public-available data is used. We used a variety of data types from different imaging modalities and transfer syntaxes. So far, 12 DICOM data sets have been collected including

Table 2 Characteristics of public and VitaVasK study DICOM data for evaluation

No.	Name	Size	Modality	Transfer syntax	Source
1	CT0001	53	CT	Explicit VR Little Endian	ftp://medical.nema.org/
2	CT-MONO2-16-chest	1	CT	JPEG Lossless (Process 14 - 1)	http://www.barre.nom.fr/
3	XA-MONO2-8-12x-catheter	12	XA	JPEG Lossless (Process 14 - 1)	http://www.barre.nom.fr/
4	MR-MONO2-12-shoulder	1	MR	JPEG Lossless (Process 14)	http://www.barre.nom.fr/
5	Assurancetourix \PET-WB\	227	PET	JPEG 2000	http://www.osirix-viewer.com/
6	Cetautomatix\cine_retro_aortic	25	MR	JPEG 2000	http://www.osirix-viewer.com/
7	CR-MONO1-10-chest	1	CR	Implicit VR Little Endian	http://www.barre.nom.fr/
8	ABDFATDY	112	MR	Explicit VR Little Endian	ftp://medical.nema.org/
9	MammoTomoUPMC\20080408	1	MG	Explicit VR Little Endian	http://www.dclunie.com/
10	GRUSELAMBIX	75	XA	JPEG 2000	http://www.osirix-viewer.com/
11	DICOM Samples "CT"	361	CT	JPEG 2000	http://www.dicomlibrary.com/
12	I_000036.dcm	70	US	JPEG Baseline (Process 1)	http://www.triltech.com/
13	VitaVasK CT	192	CT	Explicit VR Little Endian	–

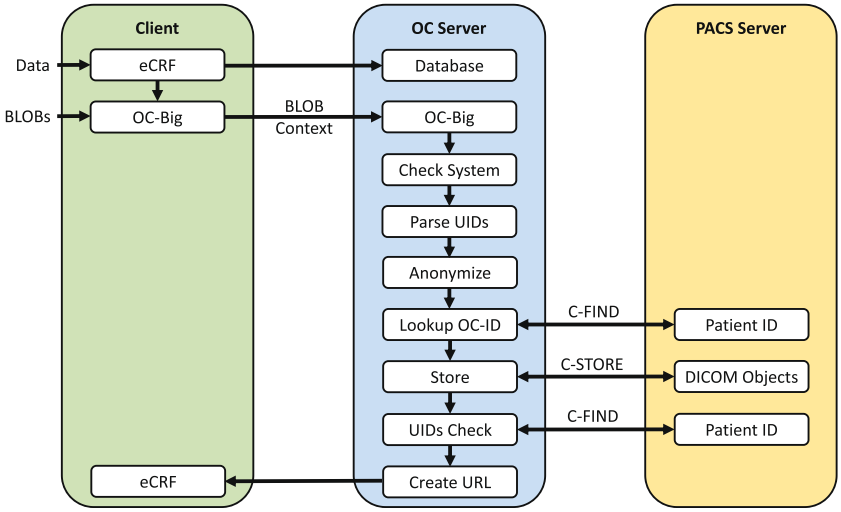

Fig. 3 Storage of DICOM objects in the EDCS

CT, X-ray angiography (XA), magnetic resonance (MR), positron emission tomography (PET), computed radiography (CR), mammography (MG), and ultrasound (US) (Table 2).

We demonstrate the workflow by means of the clinical trial VitaVasK (ClinicalTrials.gov: NCT01742273), in which the effect of vitamin K_1 on the human body is investigated. In this controlled clinical trial, vitamin K_1 is administered to hemodialysis patients to slow down the vascular calcification, and CT data is captured de-centralized in the trial sites, collected centrally in the eCRF, and evaluated reproducibly by the same expert. Based on the CT readings, the subject is enrolled to the trial or excluded as screening failure.

Results

Workflow for Storage

When initiated from the eCRF, the subject, site, and trial context have been already selected. Using OC-Big, DICOM data is passed as BLOBs via the EDCS to the research PACS (Fig. 3). The BLOB data is transferred either directly in DICOM format or as DICOM convertible. Metadata containing context information (study, site, subject identifier) is extracted from the eCRF and passed along the DICOM data. The data is de-compressed and stored on the server's file system. A unique identifier (OC-ID) is generated based on the extracted context information.

As kind of middleware, OC-Big's server component invokes a Linux shell (bash) script on the same system, which first validates the system's environment (e.g., PACS connection available, DICOM converter present). The transferred files are parsed and processed successively. All non-DICOM objects are converted. Then, all objects are de-identified and linked accordingly as described. The Study Instance UID values, which uniquely identify a study in DICOM, are extracted from the DICOM headers. The PACS is queried via C-FIND for the patient with the OC-ID identifier, and all objects are stored under this patient ID via C-STORE. This mapping is validated to ensure that the parsed Study Instance UIDs have the same value as the DICOM objects, which are returned on querying the PACS via C-FIND. A Weasis URL including the OC-ID value is generated and stored into the eCRF by OC-Big.

Workflow for Retrieval

Retrieval of DICOM objects is triggered by a click on the Weasis URL embedded in the eCRF, which invokes the Weasis PACS connector on the OC server (Fig. 4). The

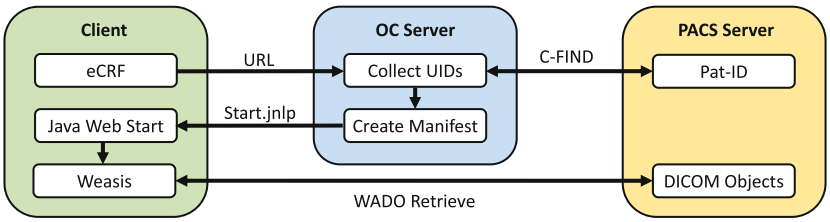

Fig. 4 Retrieval of DICOM objects from the EDCS

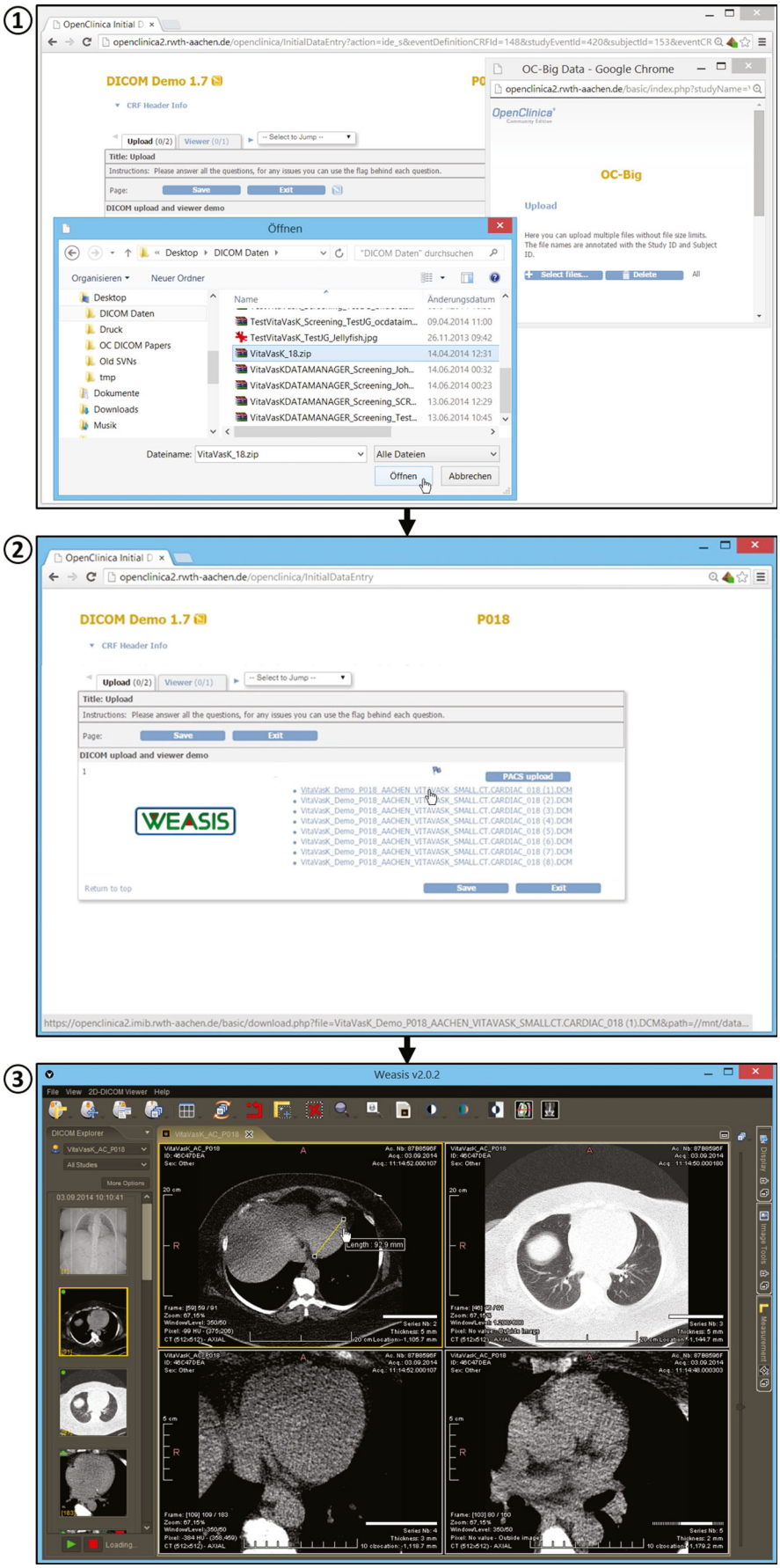

Fig. 5 Resulting workflow in the VitaVasK study for storage and retrieval of DICOM data

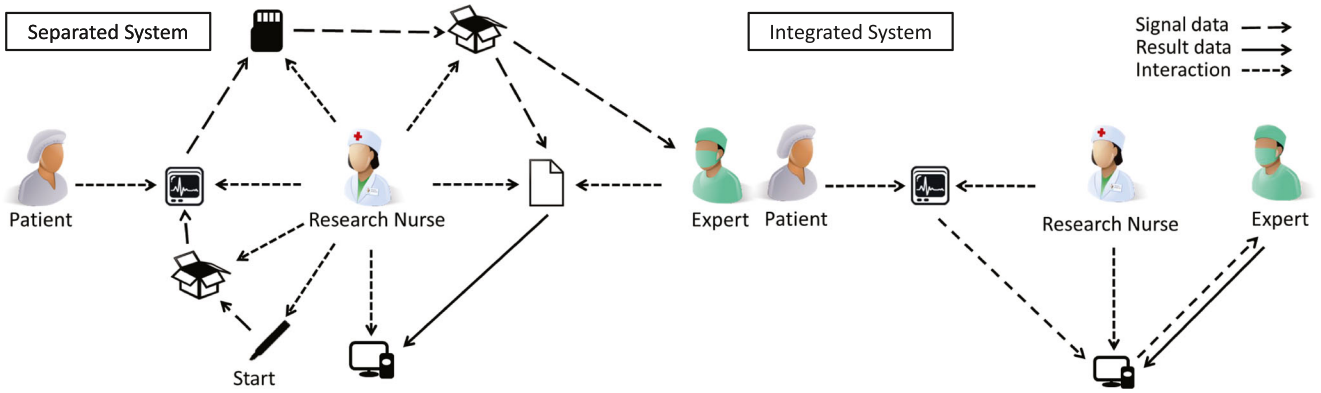

Fig. 6 Workflow of clinical trials EDC with (*left*) and without (*right*) image integration (adopted from [14])

connector parses the URL and fetches all IDs of DICOM objects from the PACS, which are mapped to the OC-ID identifier via C-FIND. These IDs are written into an extensible markup language (XML)-based manifest encapsulated in a JNLP file, which is sent back to the OC client. With the execution of the JNLP file via Java Web Start, the invocation of the Weasis web viewer is started. Using the encapsulated IDs, Weasis now iteratively gathers all DICOM objects from the PACS via WADO and visualizes the image data in the Java application.

Evaluation

The implementation has been evaluated on the collected DICOM data sets. All DICOM objects have been integrated into the eCRF, retrieved, and appropriately provided for viewing, independently from modality or transfer syntax. All DICOM objects have been mapped to the correct patient in the PACS, and context information has been integrated successfully into the DICOM header. In two cases, the de-identification missed some patient-related information, which was hidden in header elements such as SeriesDescription (0008,103E).

Application

Figure 5 depicts the workflow of the VitaVasK trial. CT data is stored during clinical data entry in the eCRF invoking OC-Big by a simple button click. In OC-Big, the research nurse selects a DICOM archive of (multiple) CT series from the local file system and starts the transfer (step 1). References to the patient's DICOM objects are stored in the eCRF (step 2). The physician clicks on the link to make the subject's DICOM data available for viewing and annotation (e.g., distance measurements) (step 3). So far in this ongoing trial, 24 out of 348 planned subjects have been enrolled in five centers and 16 CT series have been integrated. De-identification and record linking always performed appropriately.

Discussion

Focussing on EDC in multi-center trials, we have composed a web-based system, where user interaction is performed completely in the eCRF. DICOM data is stored in a research PACS that is linked to the EDCS. Analyzing the defined requirements, our solution is almost perfect.

All components are open source and affordable for IITs (G1). System communication for storage and retrieval is hidden from the user. Data and context integration is obtained between system components. Visual and function integration is achieved using appropriate DICOM data viewer (Weasis) (G2).

Focussing on the research nurse's workflow, the subject's DICOM data is integrated with the eCRF (I1). DICOM archives are automatically uncompressed and DICOM-convertible data is converted appropriately. Manual steps of data conversion are avoided (I2). ECRF's image data is automatically de-identified and context-linked, which ensures data security and consistency, respectively (I3 and I4). However, some cases were insufficiently de-identified. This finding is along with Onken et al. reporting on the "big challenge" of anonymizing DICOM objects [19]. Transfer of BLOB data may be affected by Internet connectivity. OC-Big minimizes transfer errors by dividing data into small parts before transfer (I5).

The patient's images in the eCRF are retrieved and viewed directly via Weasis (R1), supporting a broad range of DICOM modalities and transfer syntaxes (R2). Weasis provides rich functionality for image reading and annotation (R3) [18]. Although the evaluation data is too small to cover all DICOM occurrences, trial personnel must not care about specific DICOM types. Images are served via WADO, which currently excludes any methods to pass image annotations back to the PACS (R4), e.g., using DICOM-SR. All data passed through our system is anonymized, stored, and available for further research (R5).

Implicitly, a research database is built collecting valuable data for the future. Direct storage via DICOM-compliant

workstations is possible, but currently bypassing our middleware component. Hence, data submitted directly via DICOM interfaces is not linked with any eCRF. However, a more general use of trial data is in line with Parkinson, who claims that clinical trial data shall be stored centrally in an electronic health record [20]. This benefit also has been seen by van Herk and Skripcak et al. interconnecting a research PACS in the EDC workflow. Including our system, all three solutions aim at appropriately managing clinical data, which enhances the speed of drug development and commercialization, as Lu and Su already have reported in 2010 [21]. In van Herk's solution, DICOM data is stored in the PACS first, and in the system of Skripcak et al., DICOM objects are integrated using a standalone tool. Contrarily, our approach sets the EDCS as the primary access point into the center of communication, which optimally supports different workflows in clinical trials. Comparing EDC workflows with and without instantaneous image integration (Fig. 6), detours are avoided and distances between trial sites become insignificant.

Conclusion

Simplifying the workflow in clinical trials reduces errors, latency, and costs [14]. In this work, an EDCS is connected with a research PACS managing DICOM data in clinical trials. For instance, a remote decision on the subject's trial inclusion can be made immediately after the data is entered into the EDCS and the physician has been notified. The workflow can be further improved by including DICOM communication in the feedback loop for storage of reading results. Advanced DICOM modules for EDCS will be investigated in future.

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