Interconnecting Smartphone, Image Analysis Server, and Case Report Forms in Clinical Trials for Automatic Skin Lesion Tracking in Clinical trials

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ABSTRACT

Today, subject's medical data in controlled clinical trials is captured digitally in electronic case report forms (eCRFs). However, eCRFs only insufficiently support integration of subject's image data, although medical imaging is looming large in studies today. For bed-side image integration, we present a mobile application (App) that utilizes the smartphone-integrated camera. To ensure high image quality with this inexpensive consumer hardware, color reference cards are placed in the camera's field of view next to the lesion. The cards are used for automatic calibration of geometry, color, and contrast. In addition, a personalized code is read from the cards that allows subject identification. For data integration, the App is connected to an communication and image analysis server that also holds the code-study-subject relation. In a second system interconnection, web services are used to connect the smartphone with OpenClinica, an open-source, Food and Drug Administration (FDA)-approved electronic data capture (EDC) system in clinical trials. Once the photographs have been securely stored on the server, they are released automatically from the mobile device. The workflow of the system is demonstrated by an ongoing clinical trial, in which photographic documentation is frequently performed to measure the effect of wound incision management systems. All 205 images, which have been collected in the study so far, have been correctly identified and successfully integrated into the corresponding subject's eCRF. Using this system, manual steps for the study personnel are reduced, and, therefore, errors, latency and costs decreased. Our approach also increases data security and privacy.

Keywords: Mobile image management, Image analysis, Subject identification, Workflow optimization, System architecture

1. INTRODUCTION

Subject's data in clinical trials is captured today in electronic case report forms (eCRFs), which are provided by electronic data capture (EDC) systems [1,2]. In contrast to the traditional paper-based method, EDC reduces errors, latency and costs [3]. However, EDC systems lack in integration of image data, although medical imaging becomes increasingly important in trials [4]. Various approaches have extended EDC systems to overcome these drawbacks, for instance, by providing methods for integration of images directly into eCRFs via hypertext transfer protocol (HTTP) [5] or by interfacing via the digital imaging and communications in medicine (DICOM) standard [6].

Furthermore, a mobile health (mHealth) application (OC ToGo) has been developed, which allows research nurses to integrate subject's image data directly from bed site via smartphones into the popular EDC system OpenClinica (OC) [7]. Using inexpensive consumer hardware such as the smartphone-integrated camera, calibration of geometry, color, and contrast is based on standard color cards. The cards are placed in the camera's field of view next to the lesion. However, the research nurse has to manually map the photographic documentation to subjects in the EDC system. This is usually done using paper-based notes. Although OC ToGo directly transfers the images to the eCRF, the manual eCRF identification process is error-prone and may yield in subject-study-image sequence mismatches.

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In this work, a system architecture for automatic extraction of the subject identifier (ID) from the code-personalized color card is presented. Extending OC ToGo, the system architecture is enriched by an image analysis server (IAS), which is interconnected with the mobile device. Here, (i) the image is calibrated and (ii) the code is detected and mapped to the subject ID and study ID. After this, the EDC is connected, where (iii) based on these results, the photograph is automatically assigned to the corresponding study and the appropriate subject.

2. MATERIALS AND METHODS

2.1 Imaging equipment

A low-cost consumer color reference cards (CameraTrax, USA, Fig .1) with a size of 2 x 3 inches has been extended by the vendor with a unique code printed as barcode as well as optical character recognition (OCR)-readable text next to the color plates. During image capturing, the card is positioned next to the skin lesion within in the camera's field of view. The unique code is composed of 8 numerical digits in3 blocks, separated by hyphens. The barcode is generated using an ISO/IEC 16388:2007 encoding and includes a start and a stop sign. In our study, a smartphone-integrated 20,7 megapixel camera (Galaxy K Zoom, Samsung Electronics GmbH, Germany) with a ten-fold optical zoom lenses (Carl Zeiss, Germany) is used.

2.2 OpenClinica (OC)

OC is one of the world's most famous EDC systems [1,2]. The open source web application allows collecting, managing, and storing of data in controlled clinical trials. OC complies with industry standards and has been approved by the Food and Drug Administration (FDA). OC consists of a core package, providing the basic functionality for EDC, and, in addition, a web service package (OC-WS). OC-WS includes simple object access protocol (SOAP) and representational state transfer (REST) interfaces for data exchange.

2.3 OC ToGo

OC ToGo is a mobile application that integrates images taken with the mobile device-integrated camera into OC's eCRFs [7]. After image capturing, existing subjects, studies, and events are queried via SOAP web services from an OC instance. After this, the correct values are selected by the user to identify the properly eCRF of the subject. The image data is transferred and integrated into the eCRF via the secure file transfer protocol (SFTP) and a SOAP envelope, respectively.

2.4 Image Analysis Server (IAS)

The IAS is embedded within a clinical trial management system (CTMS) as web-based application [5]. It is developed with the Google Web Toolkit (GWT). It integrates black-box image analysis algorithms based on Java or Matlab

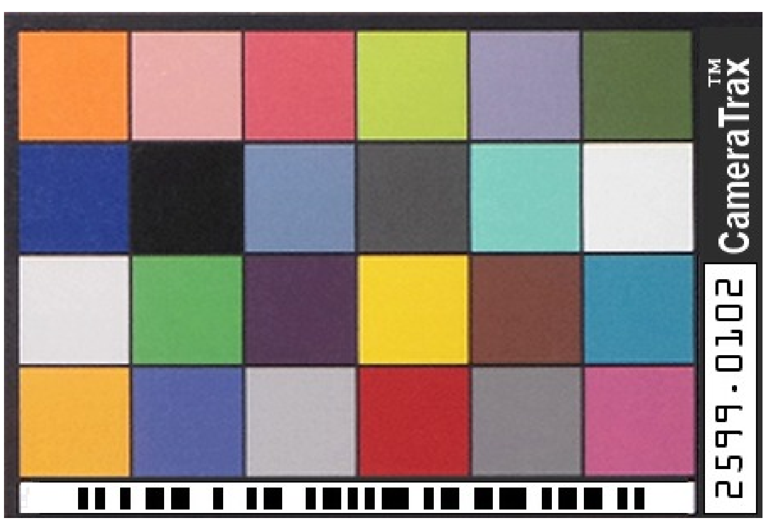

Figure 1: Color card with bar and OCR code containing subject identification.

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Table 1: Card codes are mapped dependently from the date to a study and a subject ID on the image analysis server.

Card Code	Study ID	Subject ID	Expire Date
03 - 15 - 0003	S_IMS	SS_0001001	01.03.2016
03 - 15 - 0013	S_IMS	SS_0001002	01.03.2016
07 - 15 - 0005	S_IMS	SS_0002001	30.06.2016
07 - 15 - 0003	S_VITAV	SS_0001001	30.06.2016
07 - 15 - 0003	S_EVIE	SS_0001001	31.12.2020

programming language. The server component allows other (mobile) systems to send image data and optional parameters as well as to trigger the analysis step (remote procedure call). Via a client component, the resulting images and data of the analysis process are sent back to the requesting system.

Implemented on the image analysis server, we apply the algorithm described by Jose et al. [9] for geometric and color registration. The image processing pipeline is using the lattice detection algorithm by Park et al., which is based on a mean-shift belief propagation in a Markov random field to locate the color card in any location and perspective projection within the image. Based on the card geometry, which is known a-priori, the character-printed ID field is extracted and parsed by the ocr-method of Matlab. Based on a look-up table that is stored on the server (Tab. 1), the code is mapped to the corresponding study and subject IDs. An expiration date allows multiple use of cars within and between different trials.

2.5 System interaction

In the workflow of the extended OC ToGo application (App), the systems interact as follows (Fig. 2):

- Step 1: After image capture, the original image is transferred via SFTP to the IAS, where the image calibration and OCR algorithm are performed. The image calibration results in an additional transformed image. Based on the result of the OCR, the subject and study ID are queried from the look-up table that is hosted on the server.
- Step 2: The original image, the transformed image, processing parameters, and the looked-up IDs are transferred back to OC ToGo App via SFTP and web services, respectively. The subject and study identification is confirmed by the user.
- Step 3: The events that correspond to the subject and study IDs are queried from the OC instance via web services.
- Step 4: The original and transformed images are transferred via SFTP to the OC server and references of their location on the file system are integrated into the eCRF via web services.

2.6 Evaluation study

The incision management system (IMS) study (ClinicalTrials.gov #NCT02395159) investigates the healing process ad reduction of groin wound infections after a vascular surgery by negative pressure. In this controlled clinical trial, a wound is recorded photographically at baseline (after surgery) and during follow-up at week 1, 2, 5 and 7. In total, 5 subsequent images are captured from any study subject. So far, 41 subjects have been included in the ongoing trial, and 205 images are available.

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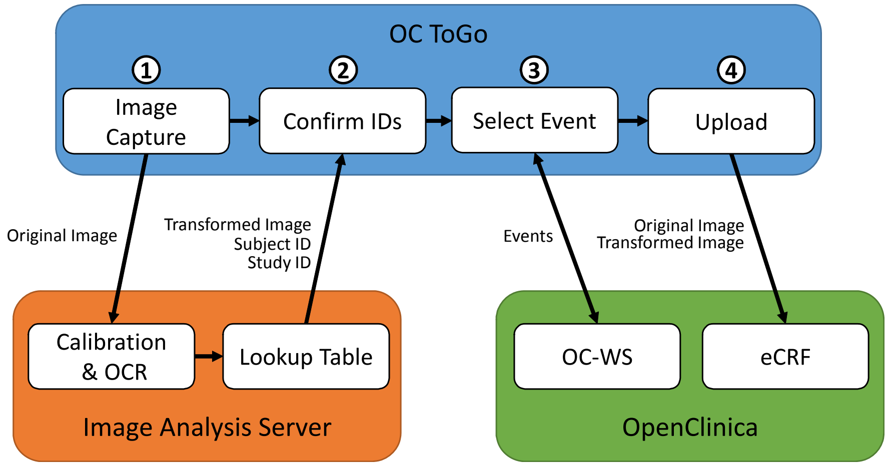

Figure 2: System architecture and workflow of OC ToGo with ID detection.

3. RESULTS

The workflow for smartphone-based documentation of skin lesions is summarized in Figure 2: The research nurse captures images using the smartphone-integrated camera while placing a personalized calibration card next to the skin lesion (Fig. 2, Step 1). The system suggests the ID of the subject (Fig. 2, Step 2). After confirmation, the research nurse selects the actual event according to the study protocol (Fig. 2, Step 3), and the image data is transferred to OC (Fig. 2, Step 4).

After successful transfer, the original and the calibrated image are integrated into the eCRF, which corresponds to the subject and event of the study. If the ID is not recognized, the user can manually select from existing studies and subjects of the OC instance. If no internet connection is available, the images are securely stored on the device and are mapped to the eCRF as soon as an internet connection is established.

Until now, 205 images of wounds have been captured in the IMS study. For all images, the subject identification has been successfully performed and the photographic documentation has been embedded into the correct eCRF.

4. DISCUSSION

The identification of subjects for mobile, photographic documentation in controlled clinical trials is automatized completely. Based on a color reference card, which is already used for geometric calibration, too, OCR-based subject identification is applied allowing the automatic transfer of captured images into the eCRF. The system architecture consists of an App running on the mobile camera device (smartphone), an image analysis server embedding Java and Matlab codes, and the EDC system OpenClinica.

Avoiding any manual steps performed by the study personal, the error-prone mapping of image, study, and subject is performed seamlessly in the workflow and automatically in the system communication. Code labelling of medical material already has simplified medical processes such as the identification of blood transfusion recipients [11]. In general, all kinds of subject identifiers such as quick response (QR)-codes are applicable. However, a reliable image quality still has to be ensured by appropriate standard operation procedures (SOPs). To improve the robustness of the detection, the barcode will be analyzed in future, too, and both codes compared in a double check.

Furthermore, the App ensures that the captured images are securely released from the devices, after they are successfully integrated into the eCRF. If internet connection is temporarily not available, the images are directly transferred as soon as an internet connection is re-established. Meanwhile, the image data is securely stored in the internal memory of the App. However, image encryption has to be added in future, to avoid access by other Apps on rooted devices.

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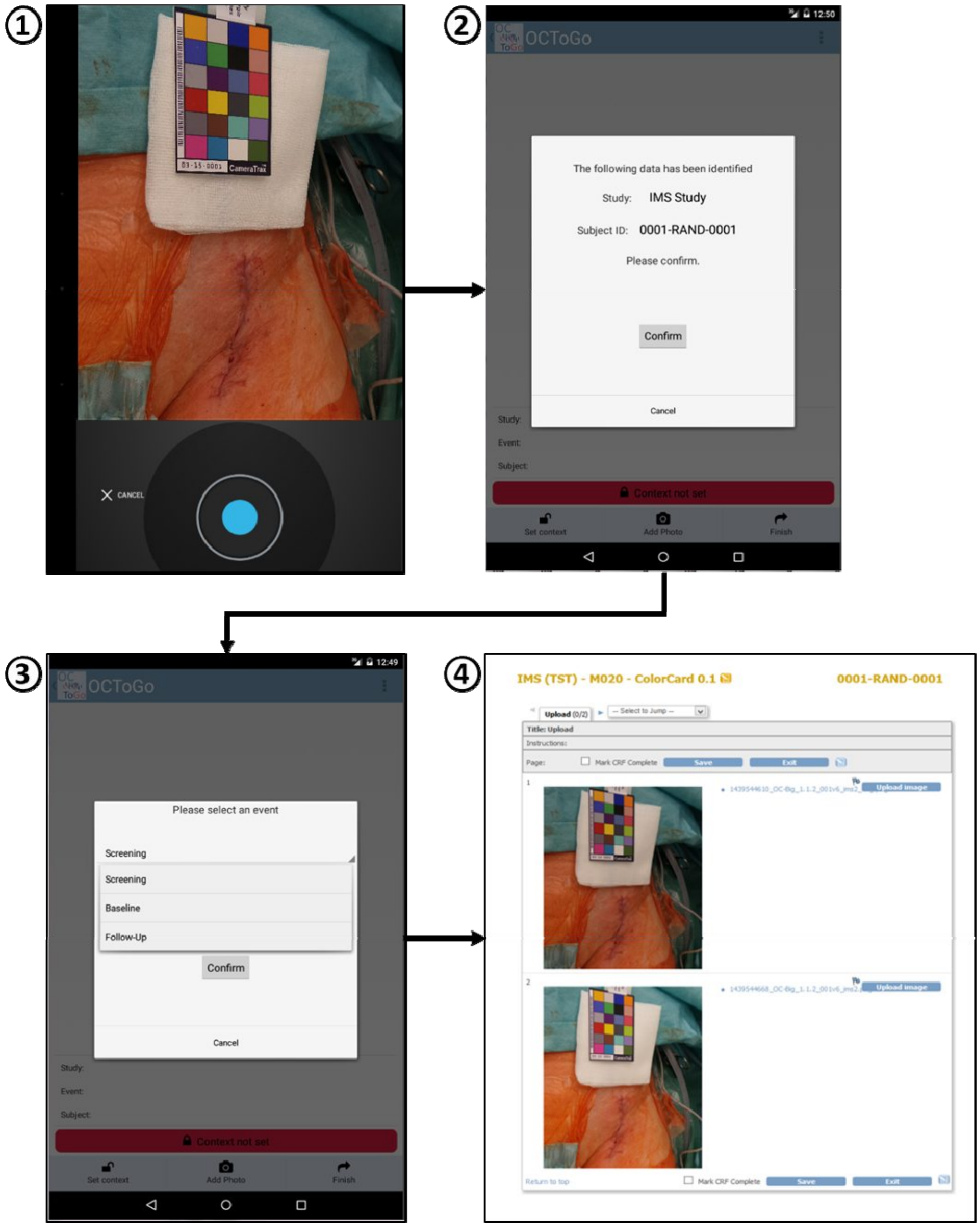

Figure 2: Final workflow of OC ToGo with subject ID detection.

5. CONCLUSIONS

This work has demonstrated that the workflow in clinical trials can be simplified easily, and that human errors are prevented instantaneously applying personalized codes to standard calibration cards during photographic documentation of skin lesions. At the bed site of trial subjects, image data is captured and transferred directly to remote servers and services for automatic subject identification, surrogate endpoint computation, and eCRF integration, which avoids error-prone manual data handling.

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