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Implementing and Validating a Multi-platform, Standard-based Architecture to Integrate Electronic Health Records and mHealth Applications for Home Patients

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Summary

Background: Daily management of a patient at home is one of the most striking scenarios that call for the development of integrated health care systems for continuous assistance. Mobile personal health applications (mHealth apps) can enhance direct communication between patients and healthcare professionals. Moreover, patients' empowerment and caregiver education play a crucial role in daily management of home treatment.

Objectives: This study aims at implementing and validating both a proposed standard-based architecture and a new suggested template of clinical document generated by mHealth app.

Methods: We tested the architecture by an innovative integrated home monitoring system for tDCS (transcranial Direct Current Stimulation) daily treatment: the home-based and the professional environments exchange anonymous messages managed by a dedicated web server.

Results: Our results demonstrate that the system meets functional and non-functional requirements, and that it can be applied in real practice.

Conclusions: Validation tests reveal that the standard-based architecture can be implemented with multi-platform solutions, using a dedicated Clinical Document Architecture rel 2 (CDA-2) template named mHealth Personal Health Monitoring Record (mPHMR). In the future, this validated architecture can be implemented using new HL7 standards, such as Fast Healthcare Interoperability Resource (FHIR), developed to meet the needs of the web- and mobile- environments.

Keywords

mHealth Personal Healthcare Monitoring Report;

Electronic Health Record;

Health Level 7 (HL7);

mobile Health App;

Integrated Home Monitoring System;

transcranial Direct Current Stimulation (tDCS)

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1. Introduction

Health and social care systems are increasingly relying on technologies to control health and wellbeing of the patient at home, to monitor vital signs, and to give advice or care [1]. Mobile personal health applications (mHealth apps) run on personal devices and are part of everyday behavior of patients and citizens, thus making them more active, informed, and "empowered" [2]. According to the American Medical Association (AMA), a well-designed Electronic Health Record (EHR) system, integrated with mobile technologies, is essential for the coordination of team-based care, for the improvement of physicians' experience with technology, and for the reduction of administrative costs [3]. Also, AMA believes that finding mHealth app place in the overall health information technology (health IT) ecosystem is an important goal to be achieved as soon as possible.

Whereas international standards for exchanging healthcare information electronically also on web-based and mobile systems already exist (e.g., the HL7-FHIR, Health Level 7 - Fast Healthcare Interoperability Resources), they do not specifically address the scenario of bi-directional communication between healthcare professionals and patients at home. It is therefore necessary to investigate if the existing protocols suffice for the needs of the patients. In fact, for a home environment, data are generated by the patient through the personal mobile device, wearable devices or through a medical device connected to it, and the mobile connection is the communication channel. Hence, the need to design specific architectures able to include the patient as author of the medical data collected, and the mobile device/connection as communication channel. This new information is not included in the data exchange within and between hospitals, and should be taken into account when setting up a standard communication architecture. Then, the available standards, such as the FHIR, could be used to implement the defined architecture [4].

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1.1. State of the art

Literature presents some examples of integration between clinical web-based platforms and mobile technologies. Many examples come from low-income countries where mobile technologies are adopted to overcome the communication gap between cities and rural areas [9, 10, 11], e.g. using mobile phones to allow visit scheduling, reminder message generation, health status update from remote areas to a unique database of the national healthcare system. Other examples focus on architectural issues, where mobile devices are deployed to monitor remote patients in a soft real-time environment: temporary failures of the communication network (Wi-Fi, Bluetooth, 3G/4G) may require a proper efficient synchronization with the Electronic Health Record (EHR) system [12, 13] to recover data loss.

[14] describe the benefits of mHealth in the Onco-TreC project, a real time home monitoring system designed to improve the interaction between a cancer patient and a healthcare professional for the treatment adherence during oral therapies at home. The system is integrated into a local system (OncoSys) and it cannot be used in other technological environments.

[15] in "eCare/eCare Mobile" use healthcare communication standards for data transmission between a mHealth app and the health system. The project exchanges nursing care data among hospitals, nursing homes, and home healthcare services, but ignores patient-generated data. The system is based on the Health Information Exchange (HIE) guidelines and the standard Health Level 7 (HL7) CDA2 [16, 17]. In addition, the HL7 standard can be jointly used with ISO/IEEE 11073 to report observations on a medical device in a format readable by clinical applications.

[18] propose to use a generic HL7 v3 Refined Message Information Model (RMIM) that allows different output formats: HL7 CDA, HL7 PHMR (Personal Healthcare Monitoring Record), or web servers. The authors describe a new method for the migration of intensive care device data to a desired HL7 compliant output format. In their use case, the preferred output format is the CDA2 Personal Healthcare Monitoring Record (PHMR) document, which is an HL7 format to store and process monitoring data: the proposed solution is flexible, also allowing changes in the type of

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medical device. However, such a format has to comply with local/national requirements for the semantic interoperability between clinical systems. This need raises various issues [19] as, for instance, the management of a national list of object identifiers (OID, ISO/IEC Object Identifiers) for the identification of regional hospitals, registers or standards inside the PHMR, and the use of regional terminologies for the semantic definition of observations reported into the PHMR. Moreover, even though the PHMR template seems to be useful for exchanging patient (or device)-generated data, some major limitations exist: the validity and the soundness of measurements made by patients at home, as a standard PHMR does not specify how data are provisioned and in which context; the interpretation of the author field, when a document contains medical measurements taken at home; the insufficient information about devices, for the correct interpretation of measures valued by physicians.

At present, HL7 developed a new interoperability standard, the Fast Healthcare Interoperability Resource (FHIR), aimed to simplify the electronic exchange of data, especially in web-based and mobile systems [4]. FHIR, in fact, is based on XML and JSON structures that are exchanged using RESTful services and is mapped onto the HL7 reference information model (RIM). Despite being a powerful implementation resource, to address the problem of considering the patient as an active actor in healthcare data collection and the patient's house a preferred collection environment, there is the need to establish an architecture able to provide the right requirements and specifications to be then applied in FHIR-based systems.

A standard-based architecture framework for data exchange between EHR systems and personal mHealth apps was proposed by Marceglia and colleagues [20, 21]. The architecture defined a set of requirements for the correct exchange of information, and was based on the use of standard structured documents. The architecture was then applied in one single case study (home monitoring for congestive heart failure patients), using a specific technology (an open source longitudinal EHR system and iOS mHealth app) and with no patient validation. The authors

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partially adapted the available PHMR standard to allow the bi-directional exchange of information, but, they did not propose any new specific document template.

The first example of integration between home and professional environments, based on an innovative standard devoted to reports generated by the mHealth app used at home, was prototyped for monitoring patients under daily transcranial Direct Current Stimulation (tDCS) treatment [6]. In the prototype, a mHealth app collects monitoring data and supports patients and their caregivers for a personalized treatment at home: daily results of evaluation scales are stored inside the EHR system of the patient, so that the physician can evaluate in real time the effectiveness of patient empowerment and caregiver education, and, if necessary, prescribe new stimulation parameters and tDCS electrode placement montage. Moreover, the authors [6] propose a "mHealth Personal Health Monitoring Record" (mPHMR) template, adapting the PHMR CDA2 template [17] to fulfill the requirements of the mHealth App/EHR system data exchange.

1.2. Paper Outline

The structure of the paper is: Section 2 explain the objectives of this paper; Section 3 describes the methods used to analyze, design, and then deploy a prototype according to the proposed architecture; Section 4 describes the achieved results; Section 5 presents a discussion of the approach, highlights the results, and sketches out some possible future research directions.

2. Objectives

In this scattered scenario, the current study aims at implementing and validating both a previously proposed architecture [5] and a suggested template for clinical documents generated by mHealth apps [6, 7]. To do so, we developed and tested a new integrated care system dedicated to daily home monitoring of tDCS (transcranial Direct Current Stimulation) patients, using a proprietary EHR system and a dedicated mHealth app [6]. The system is based on the mPHMR

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(mHealth Personal Health Monitoring Record) Clinical Document Architecture rel 2 (CDA-2) template, that was previously proposed as possible standard architecture for the mHealth app-EHR bi-directional exchange [5]. The international standard HL7-CDA-2 solely focuses on electronic clinical documents, it does not support exchange of content not deemed to have clinical relevance [8]. The mPHMR avoids this limit without requiring equipping the EHR system with new Application Program Interface (API), unlike multipurpose standards as FHIR. We refined the template to: a) better consider every element of the clinical document generated by the mHealth app, with respect to a classical HL7 template; and b) validate the correct integration of data (coming from both EHR system and mHealth app) inside the same database.

3. Methods

This section focuses on the major requirements needed to integrate Electronic Health Record (EHR) systems with mobile personal health applications (mHealth apps), on the application domain of transcranial Direct Current Stimulation (tDCS), on the development environment we used to deploy a prototype, and on the testing methodology aimed at validating the proposed approach.

3.1. System Requirements for the Integration

In order to guarantee a secure and effective integration between the mHealth app and the EHR system, based on the architecture defined by [20, 21], we particularly focused on the following functional requirements:

R1. Document-centric. Clinical data have to be organized into "clinical documents" based on the standard document type HL7-PHMR. This should be an XML-based standard, intended to specify the encoding, the structure and the semantics of clinical documents produced by the mHealth app to exchange data with EHR system.

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R2. Secure data transmission. Internet is an unsecure environment. Clinical documents generated by mHealth apps should hence not include patient's personal identification information, but rather de-identified data. However, the patient has to be recognized and managed on the EHR system: on the web-based platform, clinical observation and patient number can be shared with mHealth apps, only. Moreover, no clinical/monitoring data should be stored on the mHealth app.

R3. Semantic interoperability. In the view of a standardization of health information exchange, it is necessary to use international codes and dictionaries, such as LOINC (Logical Observation Identifiers Names and Codes) or SNOMED (Systematized NOmenclature of MEDicine) [22]. Meaning of clinical observations and measurements should be unmistakable from different user's roles (patient, caregiver or physician) and in different care locations (home, hospital, clinic etc.).

R4. Technical interoperability. The architecture of the integrated care system should be based on standards, in order to overcome technological interoperability gaps due to the different environments for mHealth apps and EHR systems.

R5. Caregiver education and support. The caregiver is a central actor in most care processes. In particular, "informal" caregivers may be either family members or not, and people without specific skills on disease treatment. In this scenario, the direct connection between home and the professional environment is crucial in order to guarantee the correct and safe treatment of the patient at home. Moreover, it is necessary to pay specific attention to the stress level of the caregiver in case of degenerative pathologies [23].

R6. Patient monitoring. Extending clinical data collection to the home environment should improve patient's outcomes due to the increased amount of data available to the physician, who can evaluate the disease progression and treatment efficacy in real time [3].

R7. mHealth app content configurability. The content of the mHealth app used by the patient and the caregiver must be different according to the role of the user (patient or caregiver) and to

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the pathology or disease progression of the patient. The integrated system should allow the care team to change the content of the mHealth app according to the disease progression and the patient's state. For example, the care team can change the type and numbers of exercises, the evaluation scales and the operative instructions, in order to adapt the care process to the disease progression and caregiver's needs.

R8. Unique database. Data collected at home by the mHealth app should to be stored in the related EHR system. Using a unique and shared database avoids data replication and manual data entry and allows the care team to correctly access data [3] as well as to perform temporal queries on data to properly identify changes and trend changes of data [24].

R9. Data liquidity. The EHR system should automatically import data collected at home by mHealth app [3].

R10. Team-based care. Both the EHR system and the mHealth application should be manageable by users with different roles, in order to facilitate a team-based care of the patient at home [3].

R11. Traceability of the author of shared messages. The identification number of the author of the message generated by the mHealth app, together with the time stamp of the measurement(s), should be stored in the EHR system, so that the physician may retrieve full details about stored data (who, when, how etc.)

These requirements are fulfilled by implementing specific building blocks of the mHealth app [25, 6] as it follows:

B1. mPHMR. It is a new template (mHealth Personal Healthcare Monitoring Record) that implements a standardized clinical document devoted to mHealth app. mPHMR ensures the exchange of trusted information, a secure data transmission, a document-centric protocol and interoperability (both semantic and technical).

B2. mPHMR web service. It is the middle tier of a three-tier architecture, implemented via web services managing the connection between the personalized mHealth app and the

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corresponding EHR system of the patient. Together with mPHMR, this block guarantees technical interoperability between different mHealth apps and EHR systems.

B3. HDCapp. The mHealth app can exchange mPHMR templates with the EHR system and includes evaluation scales, exercises and operative instructions according to the customization suitable to the patient and authored by the physicians. This block fulfills the requirements of caregiver support and continuous patient's monitoring.

B4. Care pathway module. The EHR system side is devoted to the definition, monitoring, and update of the home treatment plan customized for every patient. These activities are carried out by the multidisciplinary care team members who can access the web-based platform through authentication (EHR system side). This module complies with the following requirements: team-based care, traceability of author of shared messages, and mHealth app content customizability.

Finally, the proposed system has to fulfill a set of non-functional requirements, with particular focus on quality and performance in order to validate multi-platform solutions.

P1. Flexibility. It is the capability of the architecture to support updates of mHealth app content according to the pathology and disease progression (based on the prescriptions inserted in the EHR system by the physician). So, both the mHealth app and the EHR system should be customizable for different pathologies and care processes.

P2. Reliability. It is the capability of the architecture to guarantee the correct user identification and data storage inside the corresponding EHR system. Change in operating systems (both on the mHealth app and the EHR system side) or connection availability should not affect the functionalities of the system, and the introduction of new data protection rule or new versions of health information exchange standards should impact only on the middle tier (web server) of the architecture.

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P3. Scalability. It is the capability of the architecture to manage a greater amount of data (in terms of several users, EHR systems, mHealth apps, clinical parameters or operative instructions) and to run on several types of mobile devices (having different processor type, memory size or display size and resolutions).

To design the new integrated care system that implements these requirements and building blocks, we first analyzed the architecture proposed by [20, 21]. Then we reviewed the available standards, guidelines, and literature: we focused on health information exchange between mHealth app and professional environments, in order to better define the mPHMR template and to validate it using the currently available and applicable technical solutions. The information sources were PubMed for journal papers, the International Organization for Standardization (ISO), the Food and Drug Administration (FDA), the Health Level 7 (HL7) initiative, the American Medical Association (AMA), the Cross Enterprise Document Sharing (XDS) profile, the Health Information Exchange (HIE), and the Integrating the Healthcare Enterprise (IHE) initiatives.

3.2. tDCS Case Study Process Modeling

We implemented a case study prototype in the home monitoring system for daily treatments with transcranial Direct Current Stimulation (tDCS). The entire care process, starting from the customization of stimulation parameters to the home monitoring, was designed according to the design methodology of [26]: the care process is already described in the literature by using UML (Unified Modelling Language) activity diagram [6] and can be executed by a Workflow Management System [27, 28]. The physician prescribes the patient's care plan inside the EHR system, including stimulation parameters, electrode montage, and operative instructions to the caregiver for safe home treatment and monitoring activities. The prescription is sent to the mHealth app that schedules tDCS treatments. The mHealth app provides the patient and/or the caregiver with operative instructions about correct electrode hydration and placement, additional rehabilitation

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exercises, and evaluation scales before and after every treatment. Each time the evaluation scale is filled in, the app creates a report and automatically sends it to the EHR system for the professional healthcare team to review. The entire process is graphically depicted by Figure 1.

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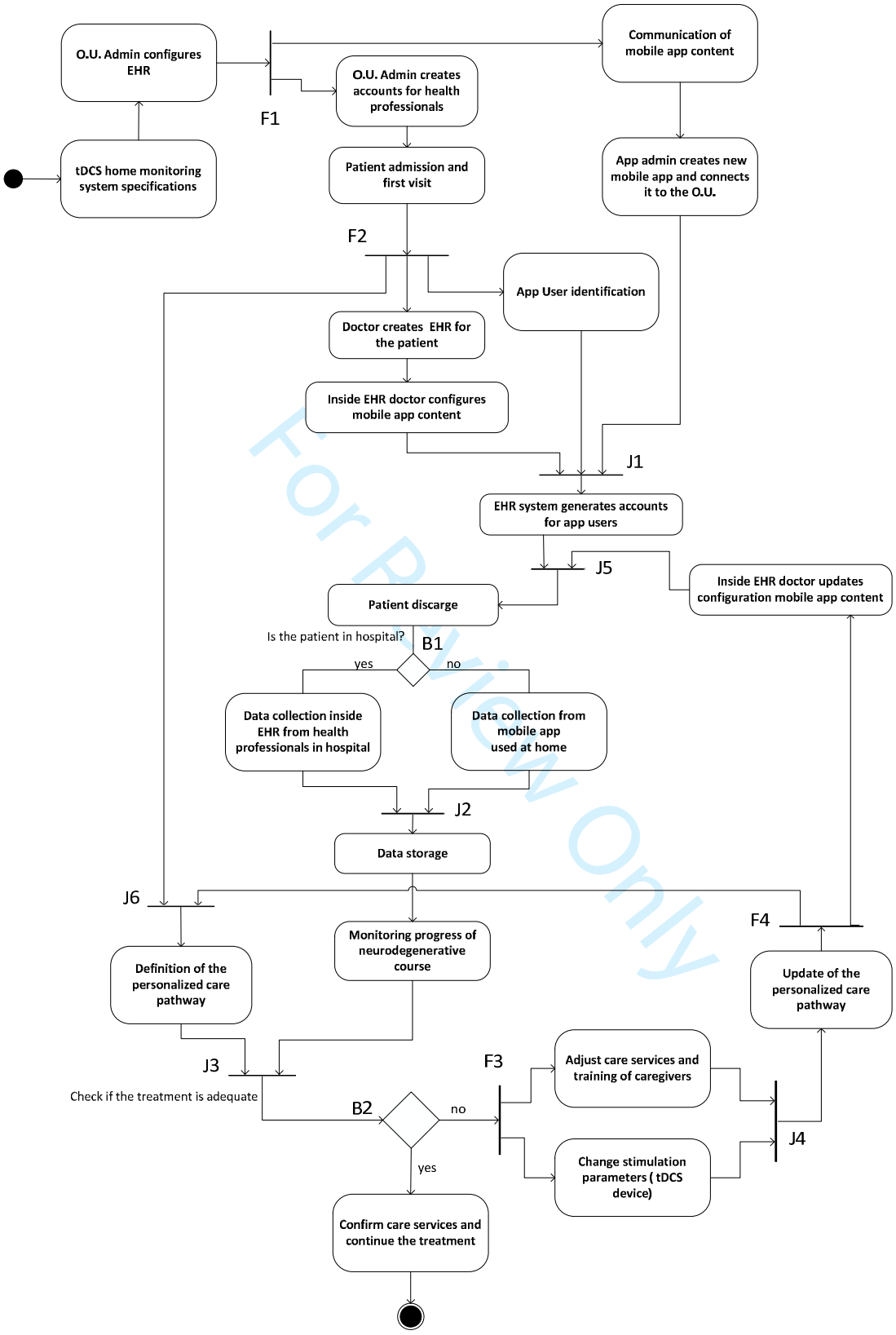

Figure 1: UML (Unified Modelling Language) activity diagram of the integrated tDCS care process. F1, F2, F3, F4 are AND splits; B1, B2 are XOR splits; J1, J3, J4 are AND joins; J2, J5, J6 are OR joins.

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To implement the integrated system, we adopted the customizable WebBioBank system [29] as EHR system and Windows Phone as patient's personal device. WebBioBank allows the physician to directly create and manage EHR templates (i.e., clinical forms), working with de-identified patient's demographics, thus allowing multi-center or multi-operative unit collaboration. By WebBioBank, the physician can customize the content of the mHealth app dedicated to the patient, and create proper user accounts. At home, the patient and the caregiver can log in the mHealth and access the main menu whose entries depend on user's role and app customization. At the end of every patient's evaluation at home, the mHealth app automatically generates the report (mPHMR) and sends it to the EHR system for storage.

In the current use case (tDCS), we considered two pathologies, namely chronic pain and depression, and defined one mPHMR template for the Hamilton Rating Scale for depression [30] and three mPHMR templates for the sections of the McGill Pain Questionnaire [31].

A unique shared database is accessible from the EHR system and from the mPHMR web server devoted to data exchange with the mHealth app. Every time the user at home logs in and accesses the mHealth app, the web server retrieves the last app customization and the pre-customized XML templates.

The app customizes its menu according to the prescription received and the related XML templates, and summarizes the different types of activities that can be included into the care pathway of the patient. To perform an evaluation scale, the user selects the corresponding page: at the end of the activity, the page retrieves the related XML template, inserts the results and the identification number of the user, and finally sends the resulting mPHMR to the EHR system.

3.3. mPHMR

The clinical documents shared between home and hospital environments must comply with a new format of monitoring report based on international standards and adapted to mHealth applications, allowing one to store into a unique shared database data acquired from the two

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environments (hospital and home). For the definition of all the elements and attributes inside these new reports, we first analyzed the Personal Healthcare Monitoring Report (PHMR), a standard issued by HL7 [17], and the suggested adaptation for the mHealth app [6, 7]. We selected PHMR as reference standard because the report includes personal healthcare monitoring information and it is automatically produced by Personal Healthcare Monitoring devices. Moreover, this international HL7 standard data format was already used to encode measurements made by devices at home [19].

The new template, named "mHealth Personal Healthcare Monitoring Report, mPHMR", differs from the PHMR in terms of author of the clinical document and of device that generates monitoring reports. In our integrated care system, the mPHMR author is the patient or the caregiver who uses a mHealth application at home. In addition, mPHMR allows the exchange of anonymized (de-identified) clinical documents between mHealth app and EHR system [7]. To ensure comprehensive high-quality clinical content in health records, the mPHMR includes terminologies' mapping with SNOMED CT [22]. Figure 2 summarizes the main features of the new mPHMR template.

In the current scenario of "tDCS Integrating home monitoring system" two actors exchange mPHMR templates: the mHealth application and the EHR system. Both are consumer and source, because during the app customization the EHR system generates pre-customized mPHMR, and sends it to the mHealth app; meanwhile during the evaluation of the patient at home, the mHealth app fills in the mPHMR and sends it back to the EHR system. In this use case, data can be viewed only by authorized physicians inside the EHR system of the patient: thus, there is no need to also share a style sheet file for the rendering of mPHMR.

In the mPHMR Header (Figure 2) patient's personal information is not included: nullFlavor is MSK (masked), as information is available, but it has not been provided by the sender due to security, privacy or other reasons.

```
<ClinicalDocument xmlns="urn:hl7-org:v3"
```


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```
    xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
<realmCode code="IT/>
<typeId root="2.16.840.1.113883.1.3"
   extension="POCD_HD000040"/>
<templateId root="2.16.840.1.113883.10.XX.YY"/>
<setId root="wbb.381" extension="2015-08-
   11T175157+02:00"/>
<versionNumber value="1"/>
<id root="wbb.381" extension="2015-08-
   11T175157+02:00"/>
<code code="53576-5"
   codeSystem="2.16.840.1.113883.6.1"/>
<title>Mobile Document: tDCS home
   monitoring</title>
<effectiveTime value="2015-08-11T175155+02:00"/>
<confidentialityCode code="L"
   codeSystems="2.16.840.1.113883.5.25"/>
<languageCode code="en-US"/>
<recordTarget>
   <patientRole classCode="PAT"/>
      <id root="wbb_pID" extension="153"
         assigningAuthorityName="WebBioBank"/>
      <addr nullFlavor="MSK"/>
      <telecom nullFlavor="MSK"/>
      <patient>
         <name nullFlavor="MSK"/>
         <administrativeGenderCode
            nullFlavor="MSK"/>
         <birthTime nullFlavor="MSK"/>
      </patient>
   </patientRole>
</recordTarget>
<author>
   <time value"2015-08-11T175155+02:00"/>
   <assignedAuthor>
      <id root="wbb_uID" extension="153_p"
          assigningAuthorityName="WebBioBank"/>
      <telecom use="WP" value="tel:+391234567890"/>
   </assignedAuthor>
```

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```
        </author>
```

Figure 2: XML snippet with the Header of mPHMR: the elements patientRole and author (boldfaced in Figure) are anonymized according to the app customization from the EHR system. Author identification depends on the user actually logged into the mHealth app. During the app customization, the element ClinicalDocument/id is set to the identification number of the Electronic Health Record of the patient where data collected at home have to be archived. ClinicalDocument/custodian is set to the Operative Unit (OU) where the patients' electronic record is stored in the WebBioBank. Date and time are coded according to the HL7 adoption of ISO8601 and include the time zone.

To keep track of the identification information, the value of the attribute "extension" in the element "PatientRole/id" is set by the EHR system and it corresponds to the patient's identification number (MPI). Also, to include the caregiver as potential author, the identifier can be set to "MPI_p" (patient) or "MPI_c" (caregiver). In particular, during the user's authentication on the mHealth application, the system contacts the web server, that in turn retrieves the IDBAC (i.e., the patient identification number MPI in the WebBioBank system [29]) of the corresponding patient, and creates a userID set to "IDBAC_p" or to "IDBAC_c" according to the user's profile. All these data are saved on a storage location separate from the application: these data are then automatically erased as session ends. The element "telecom" is the phone number of the mobile device where the mHealth app is installed for use at home: such a phone number is mandatory for the traceability of the source of the clinical documents (mPHMRs).

```
    <component>
       <observation classCode="OBS" moodCode="EVN">
       <templateID root="2.16.840.1.113883.10.20.1.21"/>
          <! CCD: 20.1.31 numeric observation-->
       <templateID root="2.16.840.1.113883.10.20.9.8"/>
          <! CCD: 20.9.8  numeric observation-->
       <id root="273593001-q-01" name="question1"/>
          <!--id question 1-->
       <code code="273593001"
          codeSystem="2.16.840.1.113883.6.96"
          codeSystemName="SNOMED CT"
          displayName="Hamilton rating scale for
             depression"></code>
       <statusCode code="completed"/>
```


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```
        <effectiveTime value="20080501123333-0500"/>
        <value xsi:type="PQ" value="5" unit="points"/>
        </observation>

        <entryRelationship typeCode="COMP">
           <observation classCode="OBS" moodCode="EVN">
           <id root="273593001-q-02" name="question2"/>
              <!--id question 2-->
           <code code="273593001"
              codeSystem="2.16.840.1.113883.6.96"
              codeSystemName="SNOMED CT"
              displayName="Hamilton rating scale for
                 depression"></code>
           <value xsi:type="PQ" value="1" unit="points"/>
           </observation>
        </entryRelationship>

        <entryRelationship typeCode="COMP">
           <observation classCode="OBS" moodCode="EVN">
           <id root="273593001-q-03" name="question3"/>
              <!--id question 3-->
           <code code="273593001"
              codeSystem="2.16.840.1.113883.6.96"
              codeSystemName="SNOMED CT"
              displayName="Hamilton rating scale for
              depression"></code>
           <value xsi:type="PQ" value="1" unit="points"/>
           </observation>
        </entryRelationship>
     </component>
```

Figure 3: a)

```
     <entryRelationship typeCode="COMP">
        <observation classCode="OBS" moodCode="EVN">
        <id root="273503001-q-Mcondition"
           name="measurement condition"/>
        <code  code="255234002"
           codeSystem="2.16.840.1.113883.6.96"
```


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```
            codeSystemName="SNOMED CT"
            displayName="After"/>
            <value type="string" value="After
               stimulation"/>
         </observation>
      </entryRelationship>
```

Figure 3: b)

```
      <entryRelationship typeCode="COMP">
         <observation classCode="OBS" moodCode="EVN">
            <id root="273503001-q-tester" name="tester"/>
            <code  code="133932002"
               codeSystem="2.16.840.1.113883.6.96"
               codeSystemName="SNOMED CT"
               displayName="Caregiver"/>
            <value type="string" value="Caregiver"/>
         </observation>
      </entryRelationship>
```

Figure 3: c)

```
      <participant typeCode="SBJ">
         <participantRole classCode="MANU">
            <templateId
               root="2.16.840.1.113883.10.20.1.52"/>
            <templateId
               root="2.16.840.1.113883.10.20.9.9"/>
            <id
               root="1.2.840.10004.1.1.1.0.0.1.0.0.1.2680"
               assigningAuthorityName="EUI-64"
               extension="gB1rXIhXK8bIXorMWvrPal1wmes="/>
            <code nullFlavor="OTH">
               <originalText>Unregulated
                  Device</originalText>
            </code>
            <playingDevice>
               <code code="469022007"
                  codeSystem="2.16.840.1.113883.6.96"
```


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```
                codeSystemName="SNOMED CT"
                displayName="Entry phone"/>
             <manufacturerModelName>Manufacturer:
                Microsoft; Model: RM-1072_1013;
                Phone ID: gB1rXIhXK8bIXorMWvrPal1wmes=;
                mobile App Name: tDCS_home_WP;
                mobile App revision:
                   1.0.0.0</manufacturerModelName>
          </playingDevice>
          <scopingEntity>
            s <desc>Microsoft</desc>
          </scopingEntity>
       </participantRole>
    </participant>
```

Figure 3: d)

Figure 3: XML snippets from the Body of mPHMR app: a) the coded answers refers to questions concerning the Hamilton rating scale for depression; b) the code refers to measurement conditions ("After the tDCS stimulation"); c) the code refers to Id data of the tester ("Caregiver"); d) the code refers to the description of the mobile phone used for the mPHMR.

The Body part of the mPHMR (Figure 3) features an XML content, and it is organized by sections identified by LOINC coding. In mPHMR, the sections Results and Medical Equipment are mandatory: other sections, such as Purpose, Medications and Vital signs, are optional.

In the mPHMR generated at the end of an evaluation scale, all the subsequent questions of the questionnaire refer to the first question of the evaluation scale (primary clinical act statement of the mandatory section, namely Result): every answer is coded within the corresponding observation that appears directly under the entryRelationship statement (Figure 3.a). Also, the measurement condition (the time when the questionnaire is filled in, Figure 3.b) and the tester (the user who filled in the form, Figure 3.c) are all related to the first question of the questionnaire.

The second mandatory section in the mPHMR Body, namely Medical Equipment (Figure 3.d), includes details about the mobile device that generates the monitoring records and the version of the mHealth app used in the integrated care system. The "extension" attribute of the element "id" is a valid EUI-64 device ID. the IMEI (International Mobile Equipment Identity), the MEID

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(Mobile Equipment Identifier) or the MAC address assigned by the manufacturer of a network interface controller (NIC). Such information depends on the used mobile device and is automatically inserted into the mPHMR by the mHealth app. The element "manufacturer-ModelName" contains data from the Continua data model (plain text with no constraint on formatting): Model, Unspecified, SerialNumber, PartNumber, HardwareRevision, SoftwareRevision. Finally, the element "scopingEntity/desc" contains manufacturer's name of the mobile device.

3.4. Development Environment: WebBioBank, HDCapp

According to the above specifications defined by the UML models, using different development environments and technologies we developed a prototype system to validate the proposed standard mPHMR [7] and the overall system architecture [5]. The integrated care system for tDCS daily home treatment was developed using an EHR system, namely WebBioBank, and a mHealth app, namely "HDCapp".

WebBioBank is a web-based platform based on a proprietary customizable framework [29] for the EHR management, which also includes specific functionalities such as the de-identification of patients' data and the anonymization of data, to support multicenter clinical studies. The WebBioBank also manages and shares advanced algorithms for signal processing, which can be combined in analysis chains, ensuring that data processing and analysis are the same in all the centers involved in the research study. The WebBioBank actors include: the administrator of the Operative Unit (OU, equivalent to a ward inside the hospital); the data manager; and a single operative user (physician, researcher or administrator of the operative unit). WebBioBank was already used for the anonymous data collection and processing during multicenter studies regarding Deep Brain Stimulation [21], Parkinson's Disease [29] and nutrigenomic research [32, 33].

In the current study, the mHealth app was developed by using Visual Studio IDE. In order to create a cross-platform application, Xamarin Framework was used for simultaneously targeting not

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only iOS and Android, but also Windows Phone devices. Indeed, despite being an obsolete technology, in our reference ambient this last platform remains the most used. The mHealth app, named “HDCapp”, integrates web services to store and retrieve data in the EHR system. The web service “ws_mobile” is devoted to mPHMR compliant message exchange between these two environments.

3.5. Testing Methodology

The validation test of the integrated care system consists of two different experiments: the first one aims at checking the correctness of the app customization and of the data storage; the second one aims at checking if the mHealth app runs well on different mobile devices and fulfills all the quality requirements. Possible errors are detected when the test result is different from the expected result. Further app code examination or database checks are necessary to identify the cause of an unexpected behavior of the system and to fix the corresponding code. Every action and the related debugging are repeated until the expected result is achieved.

The first experiment is performed using the Visual Studio App Center (VSAPC), in order to automate GUI testing on multiple devices with different operating systems and screen resolutions.

Once the correct app customization and the data storage are verified, the second experiment aims at verifying the quality of the mHealth app on a physical mobile device. The device deployed for the final validation of the integrated system is a Microsoft Lumia 640 RM-1072, with a storage of 8GB and a LCD display of 5" (1280x720). The app responsiveness (the time between every user touch interaction and the corresponding displayed response) to pass this testing phase must be under 950 ms to satisfy the average user expectation [34].

A final experiment considers the maximum amount of memory used by the mHealth app. This test is carried out performing the same operation both on the cloud emulator (VSAPC) and on the deployed smartphone. During the debugging of the mHealth app the amount of used memory (average and maximum) and the performance parameters (i.e. startup time, total amount of

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uploaded data, total amount of downloaded data) was monitored. The maximum memory acceptable was 180 MB due to the Windows Phone 8 low memory device limitations [35].

The nonfunctional requirements are tested during the two above experiments, simulating potential situations to identify which building block could be affected by the malfunctioning. The capability of the architecture to support content customization of both the EHR systems and the mHealth app (Flexibility, P1) according to different pathologies is verified during the first and second actions of Experiment 1 (see Table 1). The capability of the architecture to guarantee the correct app user identification and data storage inside the corresponding EHR system (P1) are tested during the second part of Experiment 1. Reliability (P2) of the integrated system is also investigated considering three possible situations: the update of the OS on the mobile device side or on the EHR system side, the disconnection of the mobile device, and the publication of new HL7 standards. The last nonfunctional requirement (Scalability, P3) is verified by debugging the mHealth app with the help of emulators over different operating system, display sizes or customizations, and carrying on Experiment 2. Also, Experiment 1 is considered for the evaluation of the scalability of the architecture, because during the test the system managed simultaneously a total of six app users (two patients, one physician, two data manager with also administrator privileges, and one caregiver accounts were emulated and logged simultaneously) and two pathologies (two different EHR contents and a total of four different mPHMR templates).

3.6. Ethical considerations

No approval from the ethical committee was needed as no patients or animals were investigated in this study.

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4. Results

This section describes our prototype aimed at validating the proposed architecture for the entire systems: the mobile app connects to an EHR system managing data from patients treated by tDCS.

4.1. The Healthcare Professional Side: the Electronic Health Record (EHR) Devoted to tDCS Patients

The "Care Pathway" module is implemented using the proprietary system WebBioBank [29, see Section 3] to support the activities of definition, monitoring, and updating of the home treatment plan customized for every patient. The multidisciplinary care team is set up by physicians, nurses, physiotherapists, speech therapists and psychologists, who can access the web-based platform and, after authentication, access the list of patients.

The system is configured to support different user's roles: administrator of EHR system, administrator of mHealth app, physician, data manager, caregiver and patient. After authentication, the physician accesses the patients' list and every patient's electronic record. We recall that the web-based platform stores no personal data. Patient's personal identification information (name, surname, birthdate, SSN) are replaced by a patient code (IDBAC) and a EHR code (IDEHR) inside the specific Operational Unit. According to the General Data Protection Regulation (GDPR), this pseudonymization is irreversible outside the boundaries of the local operative unit but, in order to address the needs of physicians, on client-side a mechanism to visualize the data-set related with the data subject is provided. The physician could maintain a local registry, which is an XML file, with personal data under his/her responsibility and use it to fill in the empty fields on the system (no data will be sent to the server, data will be managed just on client-side). Without such a local file, the user can only see the creation date of the patient's electronic record, the name of the operative unit where the electronic record is stored, and the seril number of the stimulator assigned to the patient.

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The EHR systems includes the following sections:

- "Pre tDCS Evaluation Scales": it includes the administrative modules rating the scales to assess patients before the tDCS treatment starts (baseline evaluation). The Hamilton Rating Scale for depression and the McGill Pain Questionnaire for chronic pain rating are chosen for the case study, since their respective SNOMED coding is available to the mPHMR;
- "tDCS treatment": it includes the modules for treatment prescription of tDCS, both in terms of stimulation parameters and electrode montage, and for the mHealth app customization. The novelty is the module "mHealth app customization" which allows the user (required role: "physician") to customize the contents of the app according to the pathology, the disease progression and the caregiver's level of education. The system generates the accounts for the users with roles "patient" and "caregiver", who will use the mHealth app at home;
- "Post tDCS Evaluation Scales": it displays patient's monitoring at home after every tDCS treatment. These data are both used for effects' evaluation and for prescription updating. Data collected at home can be accessed in real time by the physician within the EHR system by the proposed system architecture, featuring a unique shared database where data exchange between the mHealth app and the EHR system is managed by suitable web services.

4.2. The Patient Side: mHealth App for mobile devices

The "HDCapp" is developed as a multi-platform mHealth application (Figure 4) devoted to tDCS patients and their caregivers, to support and monitor therapy administration.

After authentication, the user can access the mHealth app customized according to the latest prescription defined by the physician through WebBiobank. Entries/activities are customized according to the user's role (patient or caregiver). When the scales are filled in, the "Save" button updates the XML template with current measurements, sends the anonymized mPHMR to the EHR system (via the web server), and immediately deletes data from the local storage of the mHealth application. The mHealth app includes both a "Before tDCS" and "After tDCS" evaluation scales,

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which are identified by the SNOMED coding (e.g., the code "255234002" corresponds to the measurement condition "after the stimulation").

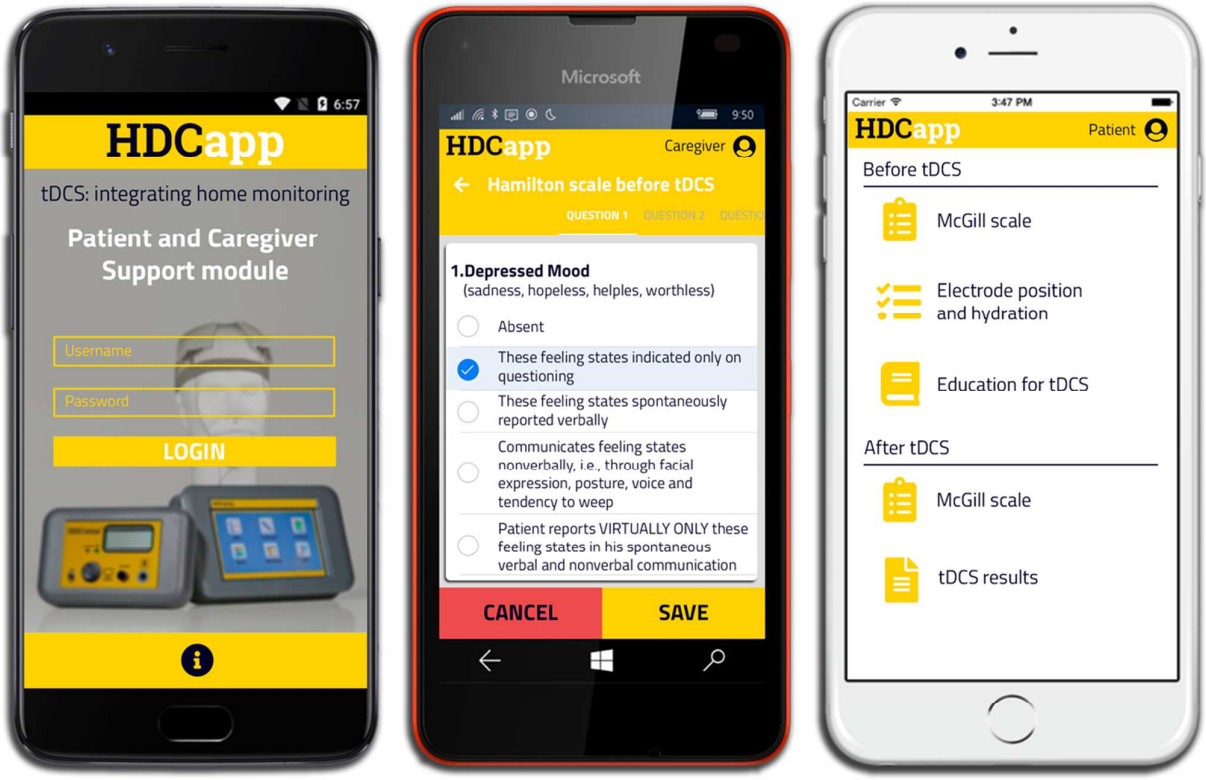

Figure 4: mHealth app on Android, Windows and iOS mobiles. Different devices show different pages (from left to right): landing page, evaluation scale page, menu page.

4.3. Integration between the mHealth App and the EHR System

The integration between the EHR system and the mHealth app takes place by the middle tier of the system architecture (Figure 5). The web server can both access the database and manage the mPHMRs. The web server sends the customized content and the pre-customized XML templates to the mHealth app: as the web server receives back the report from the mHealth app, the web server interprets the mPMHR and stores the results into the corresponding EHR system.

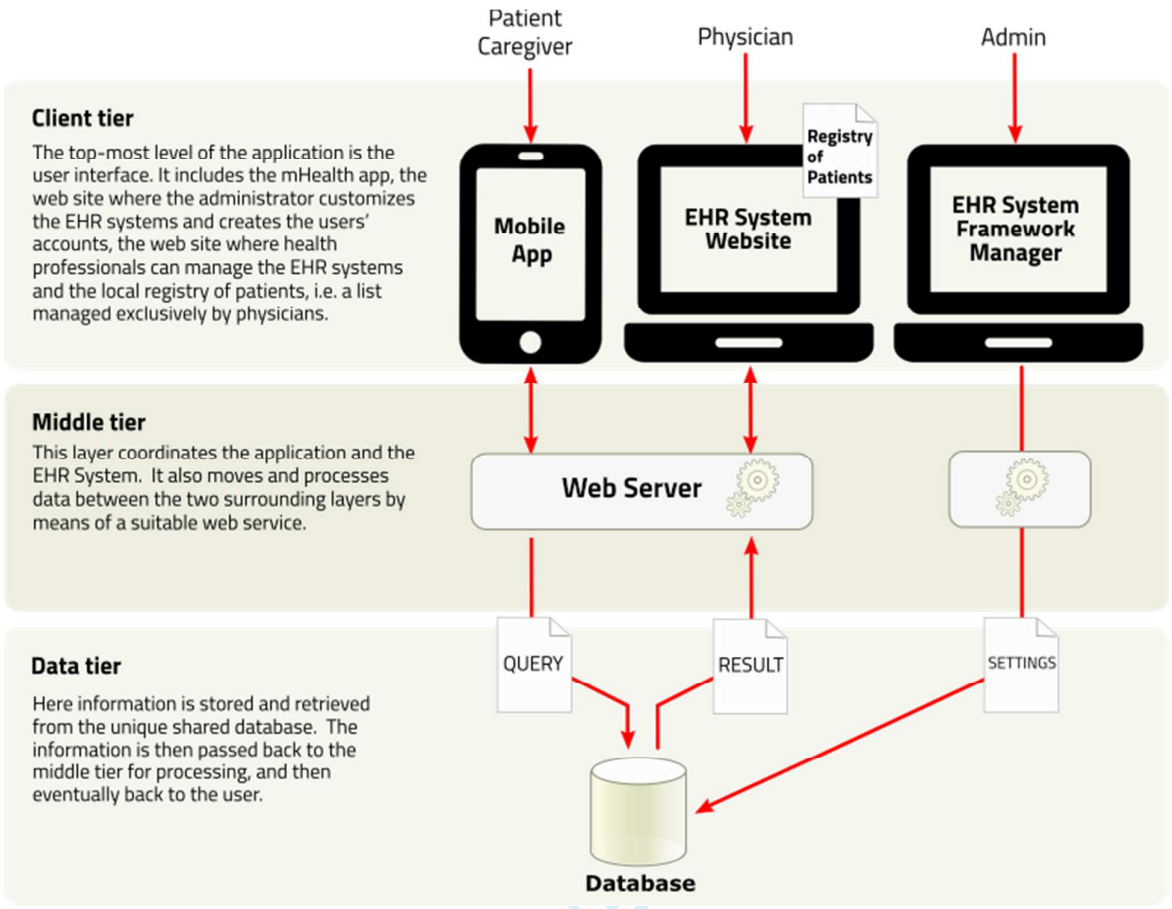

Figure 5: Three-tier architecture model of the integrated home care system.

All in all, the integration between the care team support module "EHR System" and the patient/caregiver support module "mHealth app" (Figure 6) is performed during the following two phases:

- User authentication in the mHealth app: while customizing the app on the WebBioBank, the system creates two users, namely patient and caregiver. As the user at home logs in the mHealth app, the web service "ws_mobile" looks for an app customization assigned to the user (method "GetUserApp"), who can then access the app.
- Loading app content in the EHR System: when customizing the app on WebBioBank, the physician can select the contents of the mHealth application according to the patient's pathology. As the user at home logs in the mHealth application, the system runs the web method "GetXmlTemplate". The client of the service receives the templates for the XML files, which

are pre-customized for the corresponding patient, and saves them into the local storage of the mHealth application.

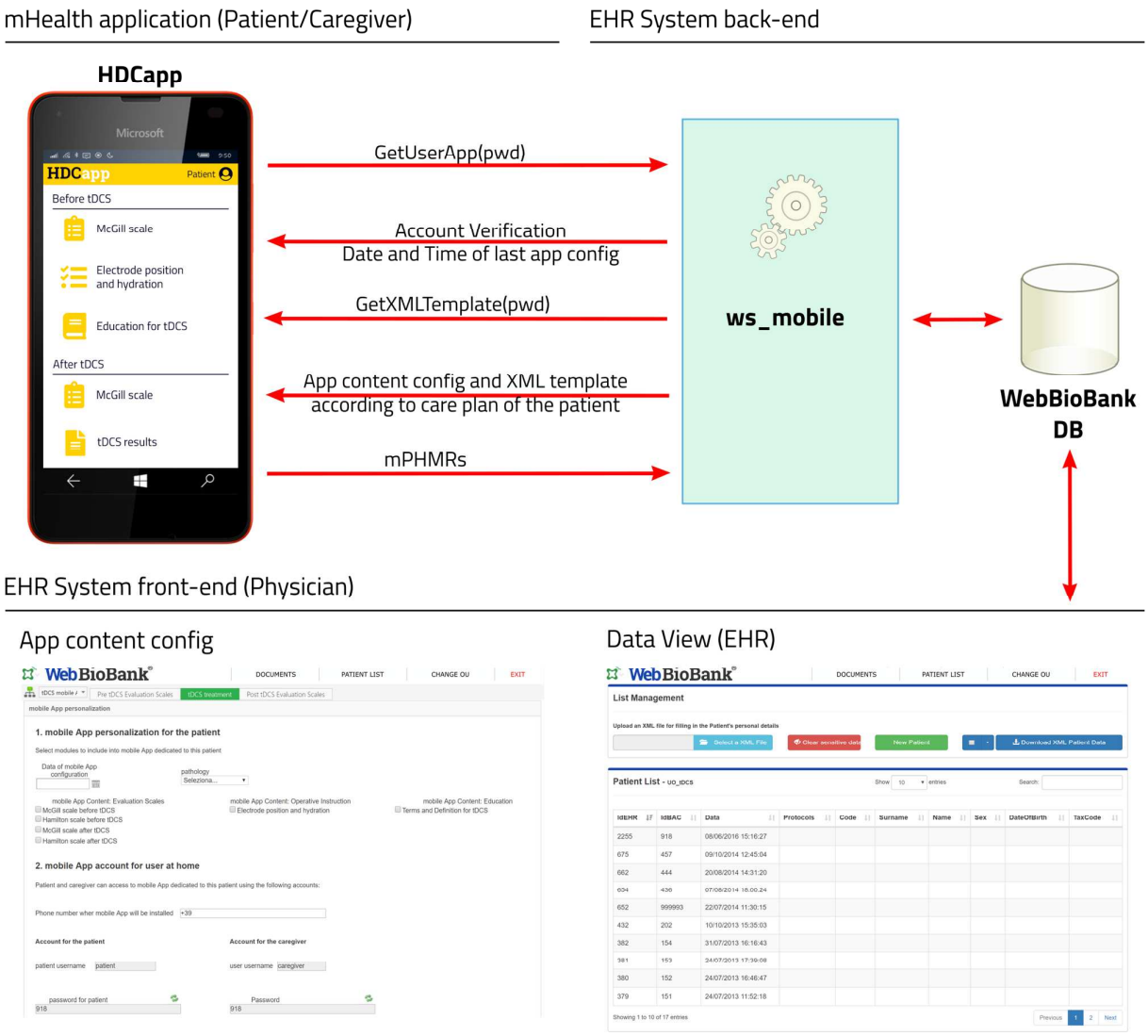

Figure 6: tDCS integrated home monitoring. The HDCapp is a mHealth application used at home by the patient and his/her caregiver; the EHR System is a web-based platform for the EHR management (namely, WebBioBank) and a web service (namely, ws_mobile) for anonymous data exchange with the HDCapp. Both the EHR System and the ws_mobile run on the same server. The ws_mobile manages user authentication on the mHealth app, customization of the app according to the latest prescription of the care plan of the patient; ws_mobile also pre-customizes the templates of the mPHMR according to the identification number of the patient and of the Operative Unit where the patient's electronic record is stored in WebBioBank. When the mHealth app receives the files, it locally archives them: next the Save button of mHealth app does not locally save data, but updates one of the received templates, generates a real mPHMR, and immediately sends it to the ws_mobile for its subsequent storage within the WebBioBank database.

The menu on the app depends on the type and the number of XML templates received, which depend on the pathology of the patient. E.g., for depression, one mPHMR template

("Hamilton.xml") is received, only, and the menu of the app includes the buttons "Hamilton scale before tDCS" and "Hamilton scale after tDCS"; for chronic pain, the client of the ws_mobile service receives three mPHMR templates, corresponding to the three sections of McGill Pain Questionnaire (i.e., "McGill_s1.xml", "McGill_s2.xml" and "McGill_s3.xml"). In this latter case, the menu of the app includes two entries: "McGill scale before tDCS" and "McGill scale after tDCS" with the corresponding sections.

All the templates of mPHMR, locally stored by the mHealth application, include the identification number of the EHR (IDEHR) and the Operative Unit where the EHR is managed on WebBioBank (Header elements: Custodian, InformationRecipient and DocumentOf). At the end of every evaluation, as the user clicks on the Save button, the mHealth application generates the mPHMR report and sends it to the web server for archival into the WebBioBank database.

4.4. Validation

Approach and prototype validation is performed by two separate experiments. The first experiment (Table 1) validates a correct customization of the app and data exchange between the mHealth app and the EHR system. The mHealth app content complies with the customization, as prescribed by the physician and generated by the mPHMR for a correct data storage into the EHR system. This experiment proves that the proposed architecture fulfills both flexibility and reliability (P1 and P2 nonfunctional requirements). As shown in Table 1, the first experiment proves the correct implementation of the integrated system, and all the expected results are achieved.

Table 1: results of experiment 1 for system validation. The first column depicts the actions that the tester has to do; the second column depicts the expected result for every action; the third column depicts the observed result of the test.

EXPERIMENT 1		
Action	**Expected result**	**Result**
The physician creates a new EHR in WebBioBank and fills in the module to	Inside every EHR, the module for the customization of the app is filled in. The	The database table has two rows, storing data for the app customization, identification

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customize the app contents according to the pathology of the patient. Next, the physician creates a second EHR for another patient, and customizes the app for a different pathology.	entries include the customization of the app menu and two user accounts, namely patient and caregiver.	number IDEHR, user account. The app accounts must differ in the two rows because the physician inserted two separate prescriptions into two EHRs.
Log in the mHealth app with patient and caregiver's account.	The user can access the application and the menu complies with the pathology of the patient and the role of user.	Evaluation scales depend on patient's pathology and user's role: McGill questionnaire for chronic pain (patient role) and Hamilton for depression (requires the caregiver role).
The patient fills in the McGill questionnaire in the mHealth app and clicks the "Save" button.	The mHealth app sends the web server the mPHMR.	The database stores data into the proper tables. If the physician logs in the web-based platform, he/she can access the McGill scale inside the EHR for the selected patient. The physician can also access details such as author, date of data collection inside the EHR.
The caregiver fills in the Hamilton scale in the mHealth app and clicks the "Save" button.	The mHealth app sends the web server the mPHMR.	The database stores data by proper tables. By the web-based platform, the physician can access the results of the Hamilton scale inside the EHR for the selected patient. The physician can also access details (author, data collection date) inside the EHR.

The second experiment proves that using either devices with different performance configurations, on the cloud emulator, or a real memory-constrained Windows smartphone does not affect the performance. In Table 2, only results regarding the physical mobile device are reported; no significant differences about performance and usability were detected for the several devices tested on the cloud environment: the startup time (the longest interaction detected) was always below the 950ms limit [34] and the maximum memory usage was always below 180 MB [35], in average we recorded a latency interaction of 100ms and a memory usage of 40.5MB. This experiment demonstrates that the architecture meets the scalability requirement (P3). The analysis reveals a good quality level of the app according to the reports generated by the Visual Studio App

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Center. Certification requirements regarding app launch time, responsiveness, and maximum memory usage by the app are fulfilled.

In order to verify the reliability (P2 nonfunctional requirement) of the integrated system three possible situations were considered: an update of the OS (operating system) on the mobile device or EHR systems side; the absence of an internet connection; and the adoption of new HL7 standards. In the case OS updates, both the applications (server side and client side) can run because they are designed as standalone software: the mHealth app uses a local storage, and data are deleted as the user logs off. On the other hand, the EHR system uses standard software (e.g., SQL Server, IIS), which remain available on the server also after OS updates.

Without internet connection, the mHealth app Controller either retrieves the application configuration and XML Templates from the local data synchronized during the last session and stores in a temporary local file the evaluation scales filled-in from the View. When the internet connection is re-established, the Controller synchronizes local data with the ones in the remote EHR System and clears any temporary local files from the mobile device.

The adoption of a new HL7 standard will affect only the mPHMR templates that should be re-defined, stored inside the database, and used by the "GetXmlTemplate" method. It is mandatory not to alter, inside the revised mPHMR template, the elements for the identification of the app's user and the EHR, which are specific for the solution, so that no update is required to the code of the mHealth app and of the web server.

Table 2: results of experiment 2 for system validation running the application on a physical mobile device. The first column depicts the action to be performed; the second column depicts the observed result of the test.

EXPERIMENT 2	
Action	**Result**
Log in the mHealth app. Select and fill in the Hamilton scale.	Startup time: 0,76 sec Max memory used: 82,22 MB Average memory used: 41,53 MB
Log in the mHealth app. Select the McGill	Startup time: 0,70 sec

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questionnaire and fill the first session.	Max memory used: 59,78 MB Average memory used: 39,80 MB
The mHealth app generates a report where the section Medical Equipment includes technical details about the device used	Manufacturer: Microsoft Model: RM-1072_1013 Phone ID: 'gB1rXIhXK8bIXorMWvrPal1wmes=' mHealth app name: tDCS_home_WP MHealth app revision: 1.0.0.0 (see Figure 3.d)

5. Discussion

mHealth (mobile Health) apps enable healthcare delivery and patient's monitoring anytime and anywhere, overcoming geographical, temporal, educational and organizational barriers: their integration and interoperability with institutional health information systems is necessary to make them effective. In this work, we validated the integrated architecture proposed by [20, 21] and a new report template for a mHealth app [6, 7] as part of a new system allowing bi-directional exchange between EHR systems and mHealth apps.

Such information exchange between mHealth apps and information systems has to face the limits imposed by EHR (Electronic Health Record) vendors. EHR systems currently available on the market are formatted in such a way that modification or customization for the specific hospital, ward or physician, are quite difficult. In 2009, Mandl et al. [36] proposed a EHR-like platform with a selection of modular applications (apps) characterized by a functional separation between the core system and substitutable apps, called SMART Platform [37]. The project, funded by the Office of the National Coordinator for Health Information Technology as a part of the Strategic Health IT Advanced Research Projects (SHARP) Program [38], was based on the definition of SMART APIs providing read-only views of the patient record. Hence, SMART API can be used in several EHR apps developed by another team, thus partly overcoming the lack of interoperability in health ITs.

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In most cases, the application creates a direct connection between a patient and the health professional with the aim to allow the patient to view his/her own personal medical report. To the best of our knowledge, in one study only [14] the patient at home can insert data into a mHealth application connected to a devoted web-based platform (electronic Oncological Patient Record system, OncoSys) integrated to the local health system. Many other examples of such integration can be found in the literature, but all of them differ from the prototype described in the present work, because they are all developed for the hospital environment and for the use by healthcare professionals or researchers [39, 40, 41, 42].

Comparing with previous studies, our architecture improves the flexibility of the integrate care system [5], introducing the possibility of customizing the mHealth app contents according to a care pathway specific for the pathology and the progression of the disease. Also, it improves security in integrating care systems based on wireless network, introducing the possibility of exchanging anonymous messages between the mHealth app and the EHR system, and managing de-identified data inside the EHR system using different user's roles. Finally, it improves scalability of the integrated care system, introducing a middle tier inside the architecture: a web server that can manage the mPHMR (mHealth Personal Health Monitoring Record) and it can be invoked both by EHR systems and mHealth apps.

In order to validate the system architecture proposed by [20, 21], we used a proprietary EHR system, a different mobile platform, and we considered the daily monitoring of patient treated with tDCS at home as use case. In addition, we improved such architecture introducing a middle tier, in order to guarantee scalability of the system and reliability in case of new standard publication. The integrated care developed in this study is flexible, because it allows the physician to customize mHealth app contents according to the care pathway and according to patient's pathology and disease progression. In this use case, real time data collection from home environment to the EHR system, using a unique shared database, allows the care team to optimize the treatment and adjust the stimulation parameters according to the disease progression. Previous studies [6, 7] suggested

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that a dedicated standard for reports generated by a mHealth app is necessary whenever a mobile device is used at home during integrated home care services. Our results demonstrate that the proposed mPHMR template includes all the necessary information for the correct data storage inside the EHR systems of the patient even if it is anonymous.

The proposed web-service approach ensured that information can be exchanged following this architecture even with different EHR systems and/or app environments. In the future, the same architecture could be implemented using the FHIR standard, which is as well based on HL7 RIM (mapped onto the mPHMR template) and based on web-services, to allow full interoperability and applicability to any healthcare system.

6. Conclusion

In conclusion, sharing data between mHealth apps (mobile health applications) and EHR (Electronic Health Record) systems will always generate issues in terms of regulations and interoperability. The management of de-identified data from the professional side (EHR systems in hospitals) and of anonymized messages from the non-professional side (mHealth apps used at home) represents an important technological challenge. The present work validates both the standard-based architecture and the suggested clinical document, mPHMR (mobile Personal Health Record System), devoted to mHealth apps. Our results demonstrate that the integration and bi-directional exchange is possible if based on standards, and it is applicable to different environments thus producing benefits for various kinds for patients requiring home-based intervention and monitoring.

In this context, where specific standards dedicated to mHealth apps are lacking [43; 44; 45] and low usability of EHR systems [3] obstructs electronically health information exchange, it is imperative to focus the attention on how mobile tools can favorite the integration between healthcare enterprises. mHealth apps are so widely spread in daily activities that they can really

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accelerate the realization of the "health IT ecosystem" vision suggested by HIE [46] (Health Information Exchange)). This work can guide the decision to confirm or to adjust the current HL7 (Health Level 7) protocol, to include cases where the patient is involved into the integrated health care process through a mHealth application, taking into consideration not only the technical view but also issues regarding access to health personal records.

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References

[1] Valdez Rupa S, Holden Richard J, Novak Laurie L, Veinot Tiffany C. Transforming Consumer Health Informatics through a Patient Work Framework Connecting Patients to Context. J Am Med Inform Assoc JAMIA 2014; 22 (1): 2-10.

[2] Bell Douglas S, Cretin Shan, Marken Richard S, Landman Adam B. A conceptual framework for evaluating outpatient electronic prescribing systems based on their functional capabilities. J Am Med Inform Assoc JAMIA 2004; 11 (1):60-70.

[3] American Medical Association (AMA). Improving Care: Priorities to Improve Electronic Health Record Usability. Chicago, IL: American Medical Association; 2014.

[4] Health Level Seven International "FHIR overview". Available at https://www.hl7.org/implement/standards/fhir/overview.html (last accessed 5 April 2018).

[5] XXX

[6] XXX

[7] XXX

[8] Health Level Seven International "Comparison between FHIR R3 and CDA R2". Available at https://www.hl7.org/fhir/comparison-cda.html (last accessed 5 April 2018).

For Review Only

[9] Combi C, Pozzani G, Pozzi G. Telemedicine for Developing Countries. A Survey and Some Design Issues. Applied Clinical Informatics 2016; 7 (4): 1025-1050.

[10] Abaza H, Marschollek M. mHealth Application Areas and Technology Combinations. Methods Inf Med 2017; 56.

[11] Coppock D, Zambo D, Moyo D, Tanthuma G, Chapman J, Lo Re III V, et al. Development and Usability of a Smartphone Application for Tracking Antiretroviral Medication Refill Data for Human Immunodeficiency Virus. Methods of information in medicine 2017; 56 (05):351-359.

[12] Lomotey R K, Nilson J, Mulder K, Wittmeier K, Schachter C, Deters R. Mobile medical data synchronization on cloud-powered middleware platform. IEEE Transactions on Services Computing 2016; 9 (5):757-770.

[13] Lomotey R K, Jamal S, Deters R. SOPHRA: A Mobile Web Services Hosting Infrastructure in mHealth. 1st IEE International Conference on Mobile Services; 2012. p. 88-95.

[14] Galligioni E, Piras E M, Galvagni M, Eccher C, Caramatti S, Zanolli D, et al. Integrating mHealth in Oncology: Experience in the Province of Trento. J Med Internet Res 2015; 17(5).

[15] Mayr H, Franz B, Mayr M. IHE-compliant mobile application for integrated home healthcare of elderly people. 6th International Conference on Information Technology; 2010. p. 798-803.

[16] Health Level Seven International "Introduction to HL7 Standards". Available at http://www.hl7.org/implement/standards/ (last accessed 11 June 2018).

[17] Health Level Seven International "HL7 CDA® R2 Implementation Guide: Personal Healthcare Monitoring Report, Release 1". Available at http://www.hl7.org/implement/standards/product_brief.cfm?product_id=33 (last accessed 11 June 2018).

For Review Only

[18] Ingenerf J, Kock A K, Poelker M, Seidl K, Zeplin G, Mersmann S, Handels H. Standardizing intensive care device data to enable secondary usages. Studies in health technology and informatics 2012; 180:619-623.

[19] Christensen H B. Localizing the HL7 Personal Health Monitoring Record for Danish Telemedicine. Stud Health Technol Inform; 2014. p. 251-255.

[20] Marceglia S, Fontelo P, Ackerman M J. Transforming consumer health informatics: connecting CHI applications to the health-IT ecosystem. JAMIA 2015; 22(e1):e210-e212.

[21] Marceglia S, Rossi E, Rosa M, Cogiamanian F, Rossi L, Bertolasi L, Vogrig A, Pinciroli F, Barbieri S, Priori A. Web-based Telemonitoring and Delivery of Caregiver Support for Patients with Parkinson Disease after Deep Brain Stimulation: protocol. JMIR Res Protoc. 2015; 4(1):e30.

[22] IHTSDO "SNOMED CT Starter Guide". Available at https://confluence.ihtsdotools.org/display/DOCSTART/SNOMED+CT+Starter+Guide (last accessed 11 June 2018).

[23] Yıkılkan H, Aypak C, Görpelioğlu S. Depression, anxiety and quality of life in caregivers of long-term home care patients. Archives of psychiatric nursing 2014; 28 (3):193-196.

[24] Combi C, Pozzi G, Rossato R. Querying Temporal Clinical Databases on Granular Trends. Journal of Biomedical Informatics 2012; 45 (2):272-291.

[25] Rossi E, Pozzi G, Rossi L, Priori A, Marceglia S. Integrating home monitoring for transcranial direct current stimulation (tDCS) therapy to professional care environment. Stud Health Technol Inform. 2015; 210:970-1.

[26] Ferrante S, Bonacina S, Pozzi G, Pinciroli F, Marceglia S. A Design Methodology for Medical Processes. Applied Clinical Informatics 2016; 7(1): 191-210.

[27] Combi C, Pozzi G. Towards temporal information in workflow system. 2nd Int. Conf. on Evolution and Change in Data Management; 2002. p. 13-26.

For Review Only

[28] Combi C, Pozzi G. Architectures for a Temporal Workflow Management System. 19th Symposium on Applied Computing; 2004. p. 659-666.

[29] Rossi E, Rosa M, Rossi L, Priori A, Marceglia S. WebBioBank: a new platform for integrating clinical forms and shared neurosignal analyses to support multi-centre studies in Parkinson's Disease. J Biomed Inform. 2014; 52:92-104.

[30] Hamilton M. A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 1960; 23:56-62.

[31] Hawker G A, Mian S, Kendzerska T, French M. Measures of adult pain: Visual analog scale for pain (vas pain), numeric rating scale for pain (nrs pain), mcgill pain questionnaire (mpq), short□form mcgill pain questionnaire (sf□mpq), chronic pain grade scale (cpgs), short form□36 bodily pain scale (sf□36 bps), and measure of intermittent and constant osteoarthritis pain (icoap). Arthritis care & research; 2011:63(S11).

[32] Conti C, Rossi E, Marceglia S, Tauro V, Rizzi F, Lazzaroni M, Barlassina C, Soldati L, Cusi D. An integrated Diet Monitoring Solution for nutrigenomic research. Stud Health Technol Inform. 2015; 210:632-6.

[33] Conti C, Rossi E, Marceglia S, Tauro V, Rizzi F, Lazzaroni M, Barlassina C, Soldati L, Cusi D. Towards Personalized Nutrition. American Medical Informatics Association Annual Symposium AMIA; 2015.

[34] Ickin S, Wac K, Fiedler M, Janowski L, Hong J H, Dey A K. Factors influencing quality of experience of commonly used mobile applications. IEEE Communications Magazine; 2012:50(4).

[35] App memory limits for Windows Phone 8. Available at https://msdn.microsoft.com/en-us/data/jj681682(v=vs.85) (last accessed 11 June 2018)

[36] Mandl K D, Kohane I S. No small change for the health information economy. New England Journal of Medicine 2009; 360 (13):1278-1281.

For Review Only

[37] Mandl K D, Mandel J C, Murphy S N, Bernstam E V, Ramoni R L, Kreda D A, et al. The SMART Platform: early experience enabling substitutable applications for electronic health records. Journal of the American Medical Informatics Association 2012; 19 (4):597-603.

[38] Office of the National Coordinator for Health Information Technology "SHARP (Strategic Health IT Advanced Research Projects) Program". Available at https://www.healthit.gov/policy-researchers-implementers/strategic-health-it-advanced-research-projects-sharp (last accessed 11 June 2018).

[39] Dobkin B H, Dorsch A. The promise of mHealth: daily activity monitoring and outcome assessments by wearable sensors. Neurorehabilitation and neural repair 2011; 25 (9):788-798.

[40] Choi W, Park M A, Hong E, Kim S, Ahn R, Hong J, et al. Development of mobile electronic health records application in a secondary general hospital in Korea. Healthcare informatics research 2013; 19 (4):307-313.

[41] Landman A, Emani S, Carlile N, Rosenthal D I, Semakov S, Pallin D J, Poon E G. A mHealth App for Securely Capturing and Transferring Clinical Images to the Electronic Health Record: Description and Preliminary Usability Study. JMIR Mhealth Uhealth 2015; 3(1):e1.

[42] Silva B M, Rodrigues J J, de la Torre Díez I, López-Coronado M, Saleem K. Mobile-health: A review of current state in 2015. Journal of biomedical informatics 2015 ; 56 :265-272.

[43] FDA "Mobile Medical Applications - Guidance for Industry and Food and Drug Administration Staff". Available at https://www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/default.htm (last accessed 11 June 2018).

For Review Only

[44] European Commission “Green Paper on mobile Health ("mHealth")”. Available at http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1433318086120&uri=CELEX:52014DC0219 (last accessed 11 June 2018).

[45] European Commission “Summary Report on the Public Consultation on the Green Paper on Mobile Health” Available at https://ec.europa.eu/digital-single-market/en/news/summary-report-public-consultation-green-paper-mobile-health (last accessed 11 June 2018).

[46] A 10-Year Vision to Achieve an Interoperable Health IT Infrastructure. Available at https://www.healthit.gov/resource/10-year-vision-achie-ve-interoperable-health-it-infrastructure (last accessed 11 June 2018).

For Review Only

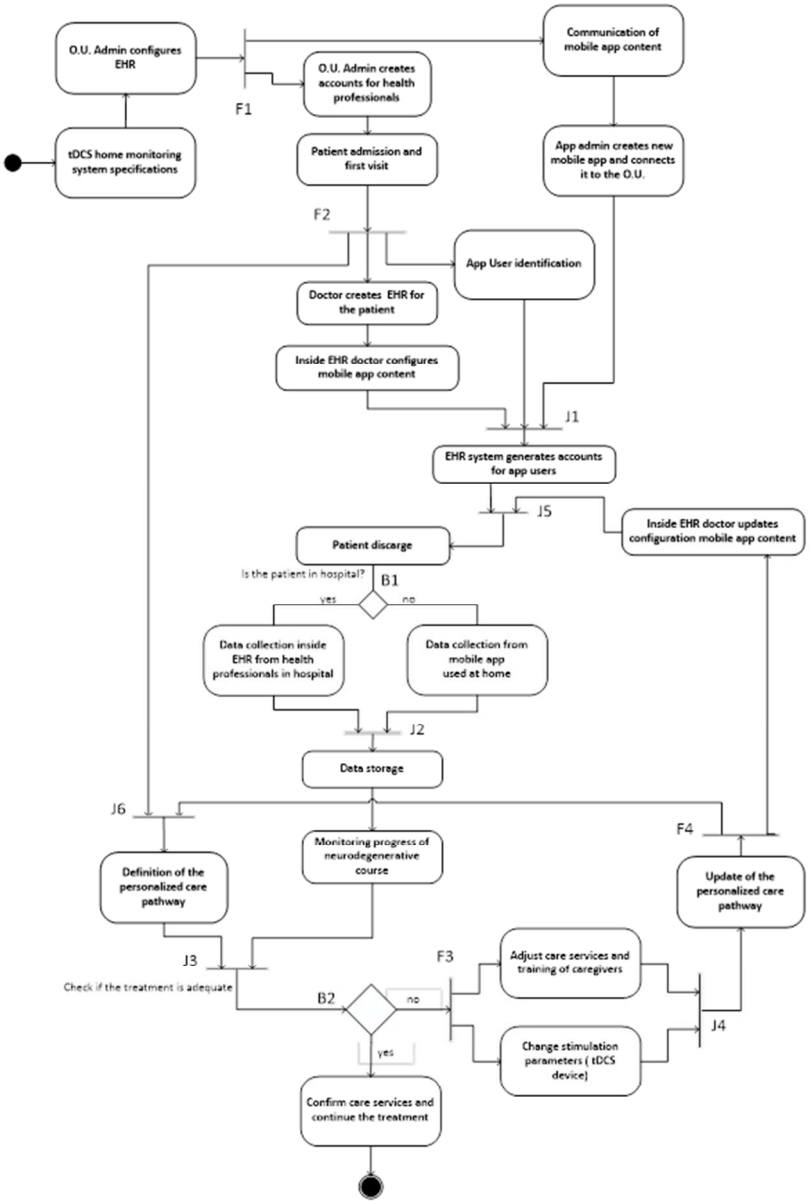

Figure 1: UML (Unified Modelling Language) activity diagram of the integrated tDCS care process. F1, F2, F3, F4 are AND splits; B1, B2 are XOR splits; J1, J3, J4 are AND joins; J2, J5, J6 are OR joins.

207x306mm (72 x 72 DPI)

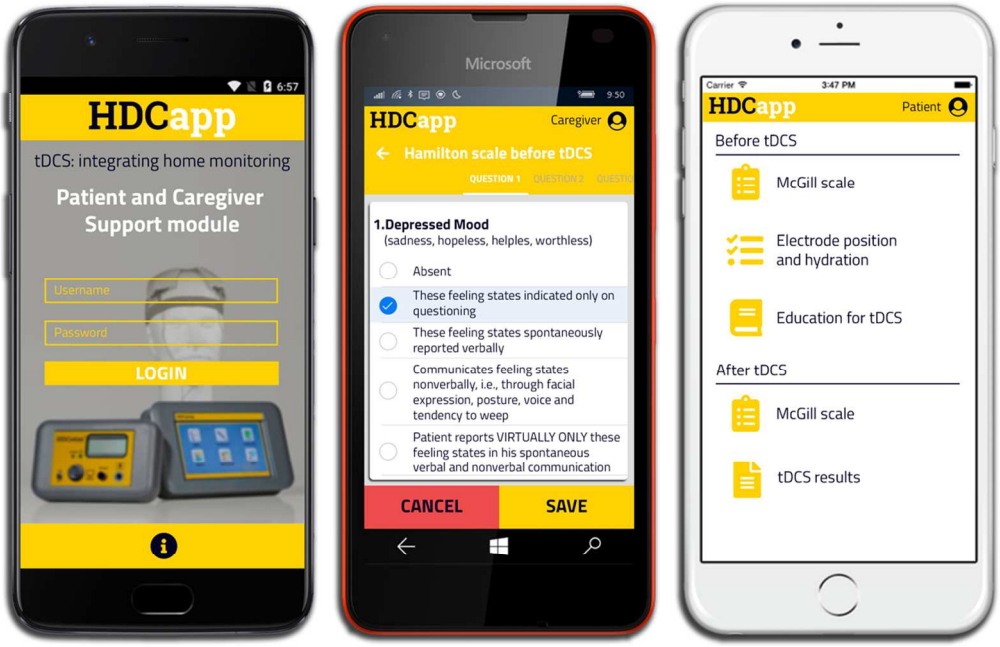

Figure 4: mHealth app on Android, Windows and iOS mobiles. Different devices show different pages (from left to right): landing page, evaluation scale page, menu page.

461x297mm (72 x 72 DPI)

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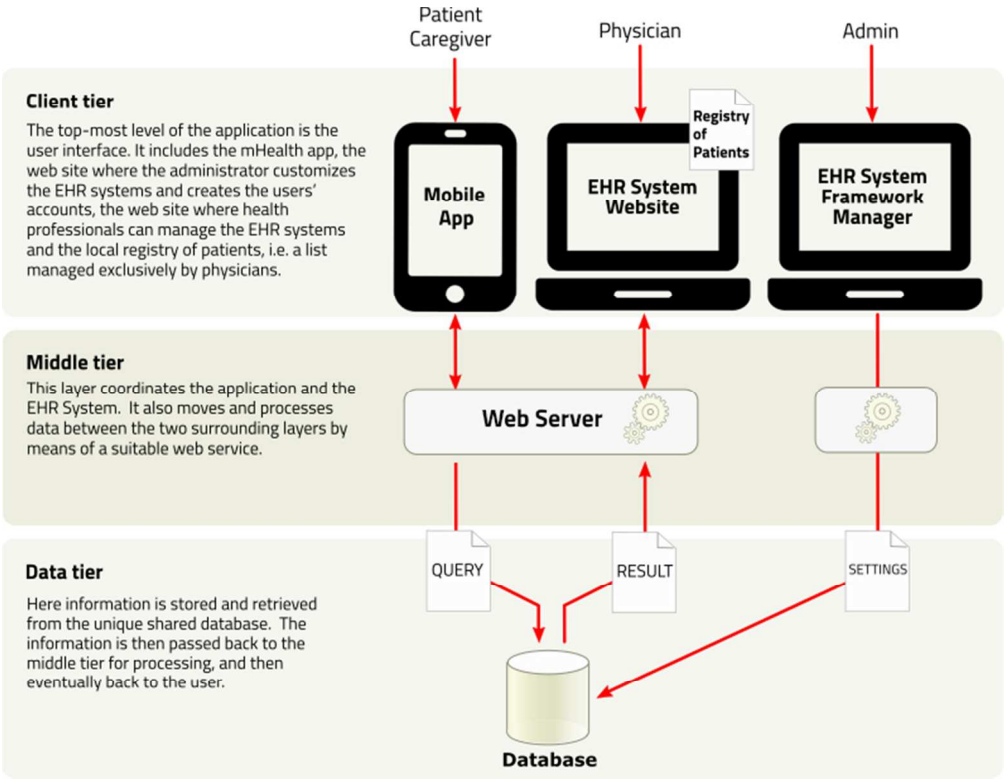

Figure 5: Three-tier architecture model of the integrated home care system.

280x215mm (72 x 72 DPI)

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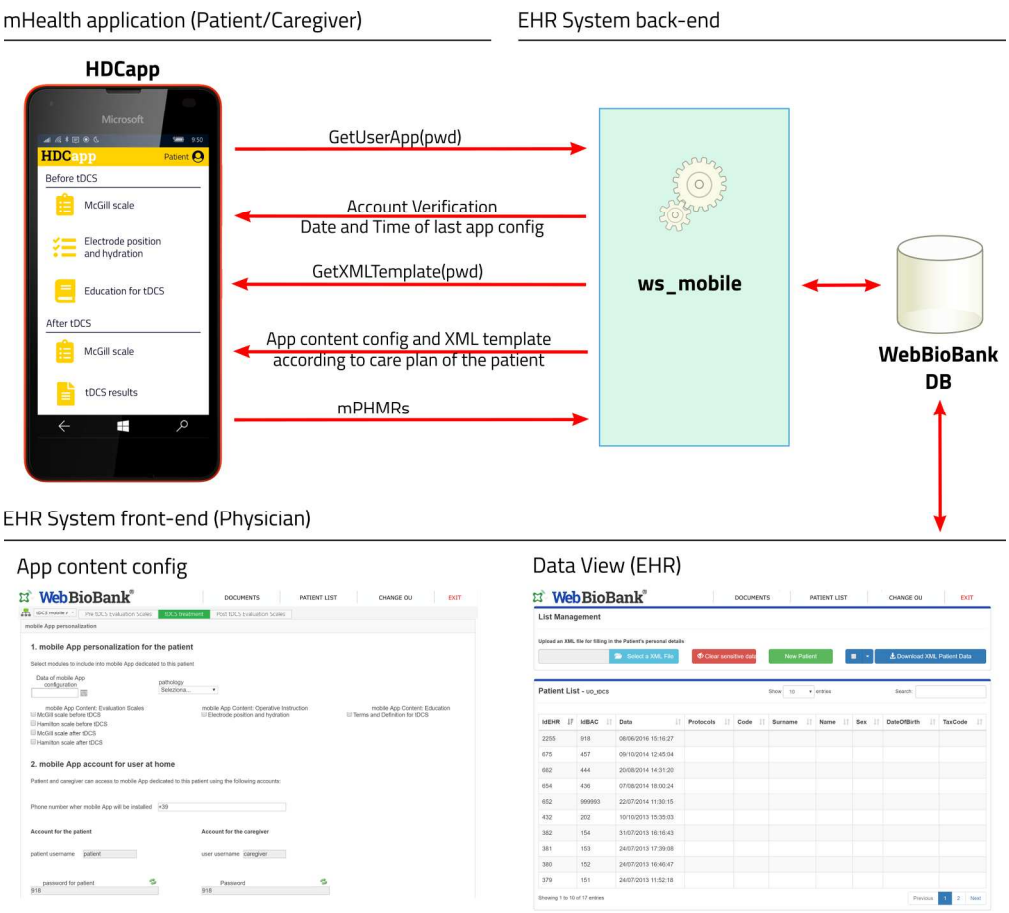

Figure 6: tDCS integrated home monitoring. The HDCapp is a mHealth application used at home by the patient and his/her caregiver; the EHR System is a web-based platform for the EHR management (namely, WebBioBank) and a web service (namely, ws_mobile) for anonymous data exchange with the HDCapp. Both the EHR System and the ws_mobile run on the same server. The ws_mobile manages user authentication on the mHealth app, customization of the app according to the latest prescription of the care plan of the patient; ws_mobile also pre-customizes the templates of the mPHMR according to the identification number of the patient and of the Operative Unit where the patient's electronic record is stored in WebBioBank. When the mHealth app receives the files, it locally archives them: next the Save button of mHealth app does not locally save data, but updates one of the received templates, generates a real mPHMR, and immediately sends it to the ws_mobile for its subsequent storage within the WebBioBank database.

815x734mm (72 x 72 DPI)