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Design of a Web-Tool for Diagnostic Clinical Trials Handling Medical Imaging Research

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New clinical studies in medicine are based on patients and controls using different imaging diagnostic modalities. Medical information systems are not designed for clinical trials employing clinical imaging. Although commercial software and communication systems focus on storage of image data, they are not suitable for storage and mining of new types of quantitative data. We sought to design a Web-tool to support diagnostic clinical trials involving different experts and hospitals or research centres. The image analysis of this project is based on skeletal X-ray imaging. It involves a computerised image method using quantitative analysis of regions of interest in healthy bone and skeletal metastases. The database is implemented with ASP.NET 3.5 and C# technologies for our Web-based application. For data storage, we chose MySQL v.5.0, one of the most popular open source databases. User logins were necessary, and access to patient data was logged for auditing. For security, all data transmissions were carried over encrypted connections. This Web-tool is available to users scattered at different locations; it allows an efficient organisation and storage of data (case report form) and images and allows each user to know precisely what his task is. The advantages of our Web-tool are as follows: (1) sustainability is guaranteed; (2) network locations for collection of data are secured; (3) all clinical information is stored together with the original images and the results derived from processed images and statistical analysis that enable us to perform retrospective studies; (4) changes are easily incorporated because of the modular architecture; and (5) assessment of trial data collected at different sites is centralised to reduce statistical variance.

KEY WORDS: Diagnostic clinical trial, Web-tool, medical imaging research, medical image analysis, database system

Abbreviations:

PACS	Picture archiving and communication systems
DICOM	Digital Imaging and Communications in Medicine
WIS	Web information system
CRF	Case Report Form
SQL	Structured Query Language
MySQL	My Structured Query Language

BACKGROUND

New clinical studies in medicine are based on patients and controls using different imaging diagnostic modalities[1]. Clinical trials use medical imaging to implement the most suitable diagnostic technique for a particular disease, to validate new diagnostic techniques and to monitor diseases under treatment[2]. The results are obtained by analysing a large number of images.

In diagnostic clinical trials, panels of experts collaborate at different hospitals and research centres. Medical imaging departments or radiological services can store and transmit images through picture archiving and communication systems (PACS) and make use of radiological information systems. Images are usually stored in Digital Imaging and Communications in Medicine format (DICOM)[3]. This format contains the patient and technical data of each image. Notwithstanding,

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it is not easy to store information about the clinical trial in addition to the images, e.g. the processing algorithm or methodology applied, parameters measured, information for quantitative analysis, etc.[4]. This requires the researcher to store this information in addition to the images files owing to this lack of connection. When medical images are used in this kind of clinical trial, the amount of data and the complexity of handling are enormously increased.

Our aim is to design and implement a Web solution to support diagnostic clinical trials involving different experts from hospital and research centres (distributed sites) mainly focused to medical imaging issue.

Similar technologies have been used with online database designed to be a repository of surgical[5] or clinical cases allowing clinicians to easily distribute and publish research[6].

Complementary tools have been developed for oncology multicentre trials[7], but no medical images were involved. Some previous works, regarding medical imaging, have designed a database oriented to support lung image analysis protocols[8], analyse mammograms[9] and support neuroimaging medical analysis.[10] In their systems, management is carried out at a central site. Besides, there are collaborative projects, such as the cancer Biomedical Informatics Grid (caBIG®) program or the Extensible Neuroimaging Archive Toolkit (XNAT®), whose mission are facilitating the exchange of cancer data or neuroimaging.

PROCESS MODEL: DESIGN

The image-analysis within this project is based on skeletal X-ray imaging. It involves a computerised image method using quantitative analysis of regions of interest (ROIs)[11–14] in healthy bone and skeletal metastases.

Each experiment will involve a subject with many data and multiple images. Each image will be analysed into multiple ROIs from which multiple measures and parameters will be derived. The patient data, original images, and the processed images with the quantitative results will be collected and stored. All patients gave informed consent for retention and analysis of their clinical information for research purposes, and the Institutional Review Boards of the participating centre approved the study. Figure 1 illustrates the stages of the process of our model.

Clinical Trial Protocol

A clinical trial for research follows a well-known methodology defining categorised subjects, experimental conditions and pathology validation. A parametric or nonparametric analysis is performed after arranging the data and the experimental conditions into a matrix organisation.

The protocol involves the precise study plan for executing, objectives, design, methodology, statistical considerations, safety and ethical considerations and organisation of the planned trial[15]. In this study, the protocol provides a template for a trial conducted by clinicians, technicians and researchers at multiple locations (“multicentre” trial) to perform the study precisely as designed (see Fig. 2).

Users

The Web includes an access security system whereby all users should log in using a username and password. This is validated before accessing the system. This will confirm the user's role and access is only given to those parts that can be completed by the user.

Selection Criteria

Once registered, the first screen includes the selection criteria of patient. If a patient does not meet the requirements, he or she automatically excluded from the study. If the patient meets the criteria, he or she is eligible and identified by a code.

Case Report Form

The Case Report Form (CRF) is designed specifically for each “role” assigned to the clinician, radiologist, researcher, etc. Thus, the clinician will complement data on patient, tumour staging, biochemical markers, etc. The radiologist will assess the X-rays and the researcher of medical imaging laboratory will process and measure the different parameters of images ROIs.

Fig 1. Process model described in this work.

Image Data Acquisition

The acquisition of images is performed during outpatient appointments. The images can be uploaded in DICOM format or other formats, like JPEG, BMP, etc., in case when they are to be acquired by a scanner. They are transferred to an image server. The image data are too large to be stored directly in the database, so the database stores a path to the image data files on the server. Patient name and other identifiers are replaced by an identifier in the image header prior to transfer. Thus, patients enjoy full anonymity in the database.

Quantitative Image Analysis

Quantitative data and parameters derived from the analysis of ROIs[11–14] must be stored in the database and associated with the appropiate patient and image identifier.

Double-blinding

The technical personnel, clinicians and investigators all work independently. Therefore, the assessment and processing of images is double blinded.

Reporting

Automated report provides a real-time summary to the users via Web. This will be applied as soon as it is introduced into the system.

Statistical Analysis

There is a direct connection from the database to the statistical analysis software.

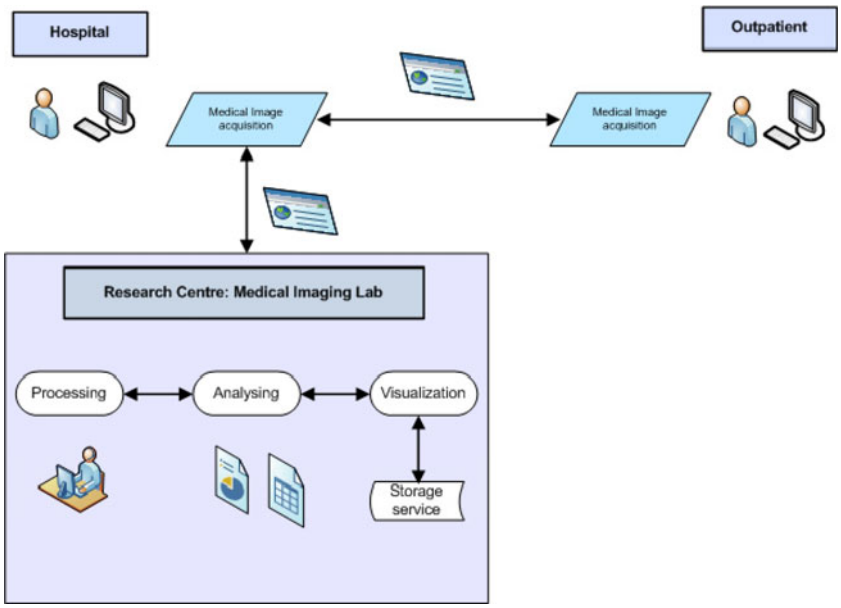

Fig 2. A simplistic approach to data access at different locations.

IMPLEMENTATION

The solution chosen to implement is a Web application. We chose a Web information system (WIS) as a platform for the following reasons: It allows the user to communicate with the central database; it has a system of authentication for each user; it isolates the data included for the different users; and it renders the application dynamic. Figure 3 shows the architectural representation. The Web architecture is made up of the following technologies and components:

- Web server: Microsoft Internet Information Services (version 5 or higher).
- Database server: MySQL v.5.0
- Implementation techonologies: ASP.NET 3.5 and C#.

The Web application has been structured in the following layers:

Presentation layer This shows the communication interface with the user (Web–user interface) for data input and uploading images (image-file uploader). The technology used is ASP.NET and C#. This layer is served to the user through the Internet Information Services (IIS) Web server.

Business logic layer This level defines the different functions of the system: (1) user communication with the database, (2) provision of rules to isolate data and (3) provision of rules for the dynamic nature to the application. This layer involved the framework .net resident in the application server, the execution of the code created and the IIS Web server.

Data layer At this level, we find both the physical repository of data with the engine for SQL[16] queries administered by the MySQL database server[17]. For data storage, we chose MySQL, which is one of the most popular open source related databases. All components are portable across platforms, including Microsoft Windows, Linux, Solaris and Mac OS X.

For security reasons, all data transmissions between the user and the Web server must be encrypted. To this end, the communications are conducted under the Hypertext Transfer Protocol Secure a combination of Hypertext Transfer Protocol and a cryptographic protocol such as Secure Socket Layer. This ensures the complete confidentiality of stored data. These security certificates are issued by recognised institutions and must be periodically renewed to ensure safety[18].

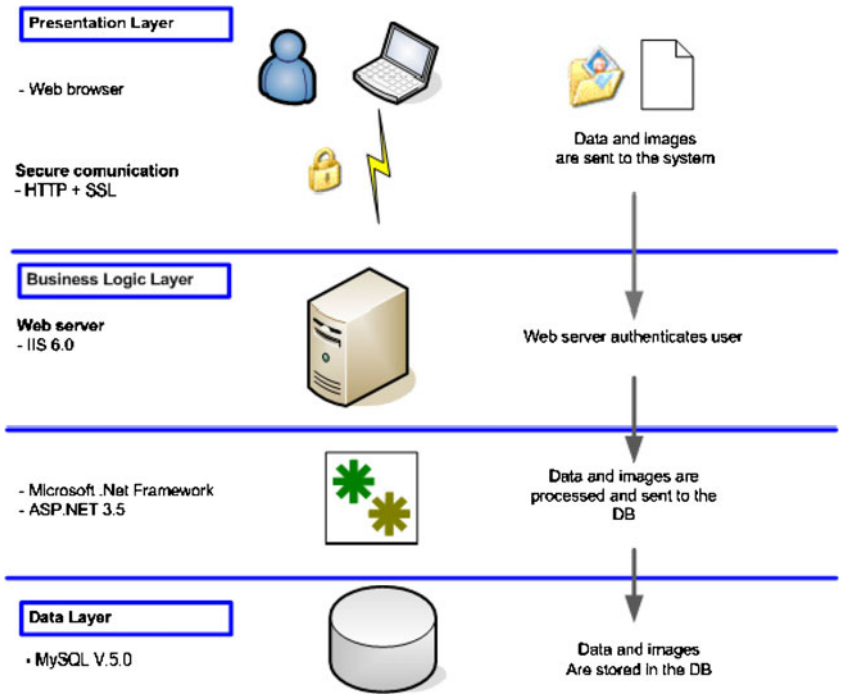

Fig 3. Architectural description. DB (database).

RESULTS

Figure 4 shows an example of workflow at the medical imaging laboratory. The general workflow is as follows:

1. The system administrator creates new entries (user and a password). Therefore, the system is accessible.
2. The experimental conditions of the clinical trial are defined, and they appear on the Web-user interface (selection criteria, the tasks to be performed by subjects, etc.) in order to avoid possible errors.
3. The sponsor or investigator first identifies the device to be tested. When initiating a clinical trial, study subjects are recruited following procedures using a signed document: the informed consent. Both patients and their images are anonymous and identified by a code before use by other researchers.
4. The technical personnel receives the instructions of the sponsor and uploads the images associated with a study by a patient code.
5. The clinicians, radiologists, researchers, etc. have a defined role and a specific CRF to be completed in the Web–user interface.
6. Researchers from the medical image laboratory process and analyse the images. Thereafter, the different measures and quantitative parameters are included in the study.
7. Statistical methods are applied to the processed image set and patient data.

Figure 5 shows a screenshot of image upload interface. This Web-tool allows us to share cases, studies, images and information with different hospitals, clinical or research departments involved in the same clinical trial.

DISCUSSION

The research community recognises the importance of collaborative use of databases and analysis systems hosted by different institutions

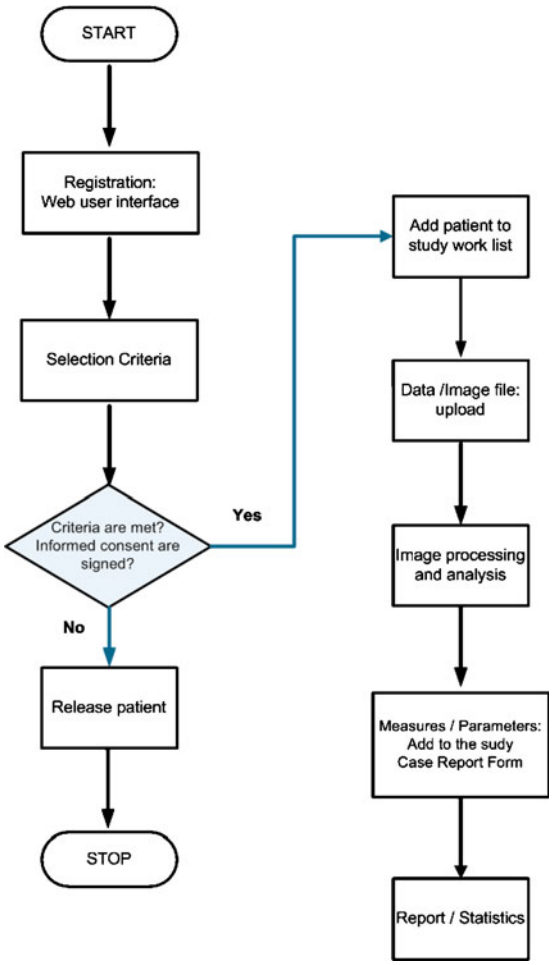

Fig 4. Workflow at the medical imaging laboratory.

in order to study complex diseases, such as caBIG® or XNAT®. Their workspace offer standard-based software tools designed to meet diverse clinical trials management needs. Notwithstanding, these tools do not meet all user expectation: Some functions are outside the scope of these tools (e.g. managing clinical data or imaging) or some technical key prerequisites are not appropriate (e.g. database type or application container).

The main reason for implementing this Web-tool is to make it available to users scattered at different locations. Thus, the easiest solution is to publish the tool via Internet. Along with the ease of publishing a Web application is the fact that, today, most users have access to Internet both at work and at home[19]. Moreover, Internet users are familiar with using Web browsers and the interface that interacts with this tool.

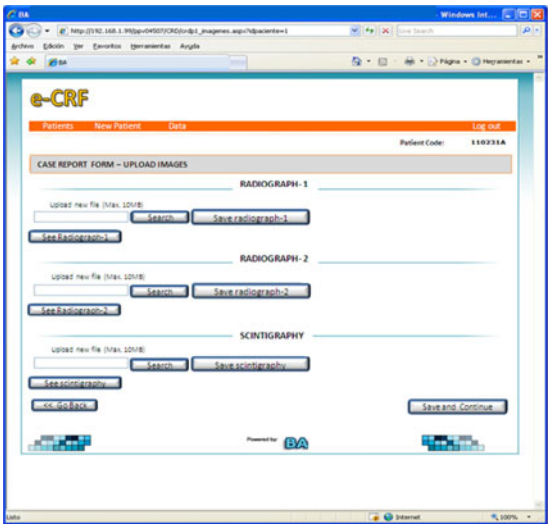

Fig 5. Screenshot: image upload interface.

The second reason is the role of electronic CRFs, which allows efficient organisation and storage of data and images.

The third reason is the possibility of defining roles, allowing each user to know precisely what his task is. In addition, controlled clinical trials (blinding) enable us to prevent both conscious and subconscious bias in research.

Physicians, specialists and researchers can then readily access information from their home or work sites using a generic Web browser. Our system, in addition to being Web-based, is also a tool that makes extensive use of open source components. This lowers the cost of software, ensuring robustness and reliability. Its open architecture and modular design also facilitate the adaptation of the system to new conditions [experimental data, image formats, hardware (scanner), etc.]. Clinical trials involving medical images require important computer support. However, commercial software tools have certain drawbacks when using processed medical imaging in conjunction with clinical data and are not adapted to multicentre studies.

CONCLUSIONS

Our Web-tool model for clinical trials using medical images from patients as a diagnosis test has the following advantages: (1) sustainability is guaranteed; (2) network locations for collection of data are connected with a central data management

server and associated database, ensuring security; (3) all the clinical information is stored together with the original images and the results derived from processed and analysis of images and the statistical analysis, enabling us to perform retrospective studies; (4) incorporation of changes, such as experimental conditions, methodology, image formats, etc., is facilitated because of the modular architecture; and (5) assessment of trial data collected at different sites is centralised to reduce statistical variance.

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