The web-based medical record system to support clinical trials

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***Abstract*— In this paper the web-based medical record system that supports the medical device Cliniporator™ is presented. The system helps transferring data collected by device during the electroporation process to the central database, and enables filling of medical records through the web-forms. It is based on the technologies like ASP, HTML, Flash, JavaScript, XML and others. The main features of this medical information system are easy and rapid data access, scalability and independence of client computer as well as easy application debugging and upgrading.**

I. INTRODUCTION

Biotechnological and biomedical applications of in vivo cell electroporation, like electrochemotherapy and in vivo DNA electrotransfer, also termed electrogenetherapy (EGT), are rapidly developing. Electrochemotherapy (ECT) is already used in clinical practice for efficient drug delivery to the tumor tissue [4, 5]. In the frame of Cliniporator project (QLRT-1999-00484), founded by European Community, a medical device called Cliniporator™ was developed. This device is designed for controlled electroporation of the tissue. [1, 2, 3].

For a successful electroporation a voltage applied for a given electrode tissue geometry, pulse duration and number of pulses should always be in the range between reversible and irreversible threshold value. If the voltage applied exceeds the irreversible threshold value, a change in a cell membrane becomes permanent and destroys the cell. Pulses are generated in the high-voltage generator of the Cliniporator™ and delivered through needle or plate electrodes to the tissue. By measuring both voltage and current simultaneously the device is monitoring electrical property changes of tissue in real time. For efficient ECT the tissue has to be reversibly electroporated and drug delivered by local or systemic injection. For DNA electrotransfer in vivo the two key steps are the electroporation of the target cells and the electrophoresis of the DNA within the tissue. These two effects can be obtained separately using the appropriate sequence of electric pulses: short (100 μs) high voltage pulses that permeabilize the cells without substantial DNA transfer/transport to the cells and long (100 ms) low voltage pulses, that do not cause cell permeabilization but which facilitate DNA transfer into the cells. This method is much safer than gene transfer based on viral vectors [6]. Cliniporator is the first medical device of this kind designed for clinical applications.

Indeed, the medical device Cliniporator™ is already in stage of testing in clinical environment. Clinical trials in four approved medical centers in Europe are founded by European Community in a frame of ESOPE project

Figure 1: Cliniporator™

(QLK3-02002-2003). The aim of the project is to define Standard Operating Procedures (SOP) for ECT and EGT. Definition of the SOP can only base on the wide analysis of collected outcomes of ECT and EGT in clinical trials. Therefore, it is necessary to carefully follow and collect treatment parameters and their efficiency.

For collection of data acquired in ECT clinical trials a standard paper forms (Clinical Report Forms - CRF) were prepared. The CRF consists of a number of subforms, of which extent depends on the number of treated tumors and number of sessions required to treat the tumor. The CRF include patient's general data, his/her medical history, tumor treatment data and response data. A tumor treatment can be repeated if necessary. The melanoma nodules can efficiently be treated by ECT, therefore only patients with this type of tumor were included in the study. For every patient, medical personnel has to fill in 40 pages of forms on average. Since all forms are predefined and same for all patients, we decided to set up a unified database (*central database*) for collecting of medical records from all four medical centers involved in

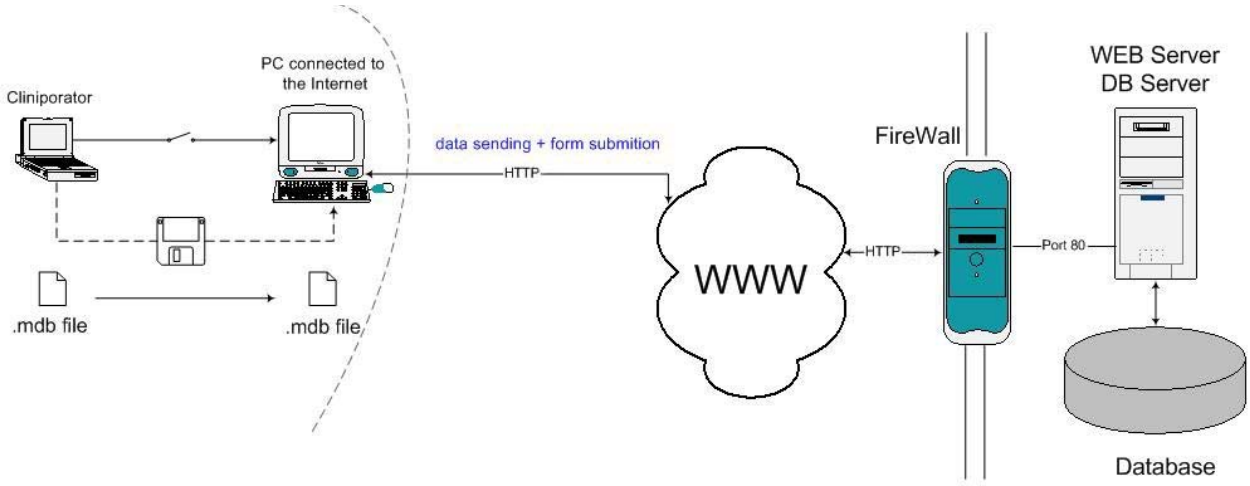

Figure 2: Diagram of the web-based medical record system.

the study. For submission of relatively high number of data into the central database we developed a web-application, which enables access to the central database and filling of forms from any computer connected to the World Wide Web.

II. CLINIPORATOR™

Cliniporator™ (Fig. 1) is a medical device for electrochemotherapy and electrogenetherapy. It consists of two parts: a console (industrial PC compatible computer) and an electroporator (control unit, high voltage and low voltage amplifier and measuring unit). User controls electroporator through graphical display and a keyboard of the console unit. He/she can enter relevant patient data, choose appropriate electrodes, and define pulse number, amplitude, length and frequency. All users' presets are stored in a local database (Microsoft Access Database), which is integrated into the console. By pressing a foot switch, user triggers a pulse generation. During the pulse application, control unit measures voltage and current through the load (a cell suspension or a tissue) with a 10 MHz sample rate and 10 bit A/D conversion. In preparation is the algorithm, which will allow device to adjust a pulse voltage according to the current and voltage measurements in the real time and thus prevent irreversible changes in the cell membranes. After the pulse application voltage and current measurements are stored in the local database. A storage space needed for storing voltage and current measurements is about 100 kB per pulse. User of the device can use locally stored data for later analysis of the treatments.

III. CENTRAL DATABASE

The central database (Microsoft SQL Server 2000) stores following data collected from the medical centers involved in the study:

- patient's data (demography, medical history, physical examination,…etc.),
- treatment's data (sessions, evaluation visits, follow-ups,…etc.),
- data submitted from local databases of Cliniporator™ medical devices,
- images of tumor nodules in a different phases of treatment.

A backup copy of central database is automatically generated once per week. The database storage expansion is estimated to few gigabytes per year (60 patients per year), mostly dependant on the number of uploaded images and local databases.

Each medical center has limited data access. It can not read or modify data submitted by other centers. The data are protected by username and password. Every medical center can have more authorized users, who all have access to the same data. Users can lock parts of the filled forms, so they can not be modified any more (like signing a medical forms).

IV. WEB-BASED SYSTEM

Medical centers that contribute data in the central database are spread all over the Europe. Due to the distances between the centers, we had to develop a system easy to maintain and debug. It had to imply two main services:

- digital CRF – digital forms for submitting CRF data to the central database, and
- local database upload – a module for transferring data from the local Cliniporator™ databases to the central database.

The system had to be set for the researching purposes, so it had to be simple for upgrading. Services like *statistic service*, and *virtual doctor service* had to be easy to add. Statistic service should offer statistic charts for already submitted data. The virtual doctor service should be a decision-make support system, which can help clinicians in choosing the optimal treatment for a particular tumor lesion, based on analysis of previously collected similar treatments.

An optimal solution was web-based system (Fig. 2). It doesn't need any installations on a client computer and is independent on its operating system. The only required software on a client computer is web browser (Internet Explorer, Netscape, Mozzila,…), which is, nowadays, standard PC software equipment. Access to the system is possible from any computer connected to the Internet, by simply submitting username and password. All the services are running on the web-server (MS IIS 5 running

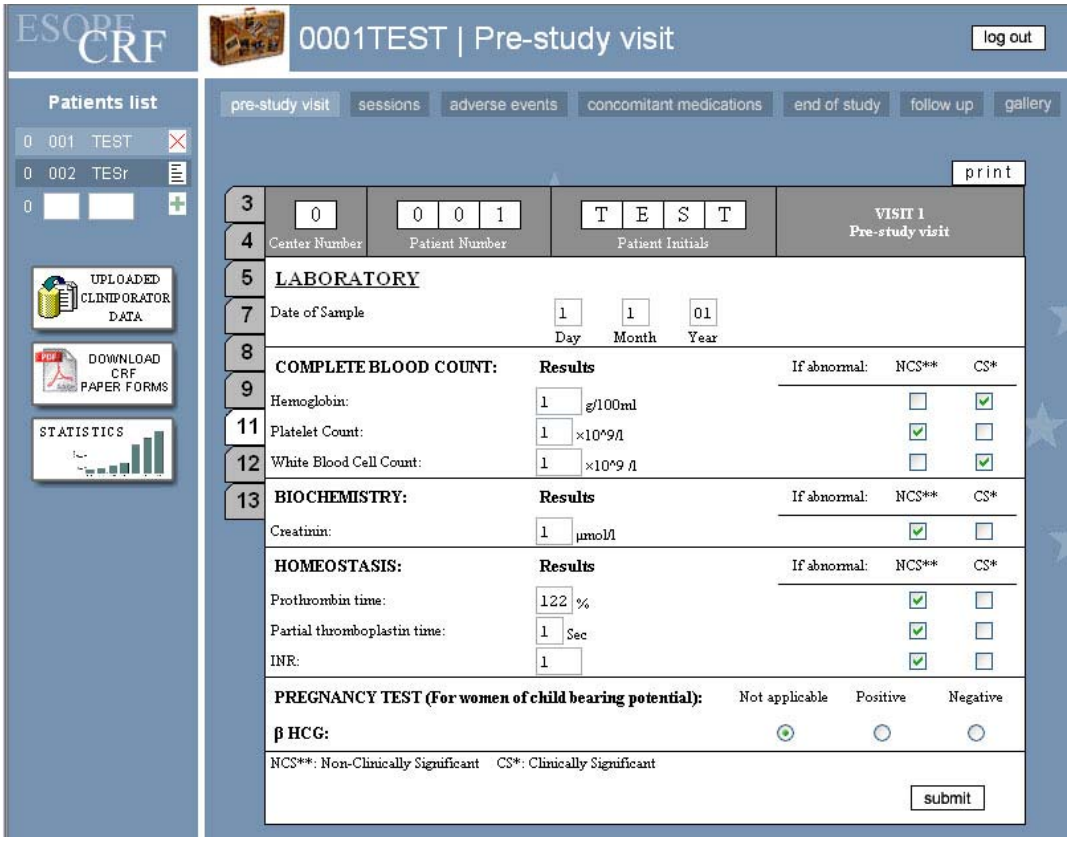

Figure 3: Digital CRF

on Windows 2000 Server). Client PC doesn't affect application speed. The speed depends only on the web-server capabilities and internet communication bandwidth.

System maintenances and upgrades are performed only on the web-server and the database server. This is the quickest and the most effective way for debugging and upgrading the system. During the system development users have a possibility to participate in testing, which is very important for timely detection of irregularities in the system.

A core of the system is a web-application, Cliniporator Web-Recorder. It involves the following functionalities:

- web-forms (digital CRF),
- image upload,
- interactive human map for marking tumors,
- local database upload,
- basic statistics (statistical processing of the submitted data).

A. *Web-forms*

Web-forms (digital CRF) are form-like web pages. Through digital CRF users submit patient and treatment data to the central database. Digital CRF have the same form as the paper-based CRF. They are organized in sections (pre-study visit, sessions, follow-up,…etc.), and every section is divided into several pages. Some of the pages are dynamically generated, according to the already submitted data (e.g. according to the number of patient's tumor nodules, pages for their descriptions are generated).

An important advantage of digital CRF is automatic data checking. Application warns user if he mistypes or enters meaningless data. This functionality is performed by client-side JavaScript code, which is very user-friendly.

The other advantage is easy navigation through numbered forms. The forms are organized into the sections (Pre-Study Visit, Session, Follow-Up,…), and sections into the pages. By selecting the section and the page number (it corresponds to the page number of the paper based CRF), user can easily access any patient's data (Fig. 3).

At the end of every section user has an opportunity to "digitally sign" the section. By signing a section the corresponding forms are "locked" and all further modifications disabled.

B. *Image upload*

Image upload enables storing of tumor images into the central database. Images, captured with digital camera, can be uploaded in the original size. A smaller image, suitable for displaying, as well as a thumbnail of the image, are dynamically generated and also stored in the database. All the images are in the JPEG format. User can add a caption and a description to every image. Images can be added in every phase of the treatment (pre-study, sessions, follow-up,…). In the image gallery user can watch all the uploaded images of one patient. Thumbnails of images are grouped by tumor nodules, and sorted by date. By selecting appropriate thumbnail, user can see the large image subtitled with user's comments. He can also download the originally submitted image. Image gallery is very useful for the visual observation of tumor changes.

C. *Interactive human map*

The purpose of the interactive human map is a visual presentation of the tumor locations. According to the

patient's sex, appropriate body map is displayed. User can switch between four views: front, rear, left and right. By simply clicking on the map, user can "add" a tumor, and then submit some principal data about the tumor (location, measurement lesion,…) and upload corresponding images. During the sessions, user can select on the map which of the pre-submitted tumors are treated. The map was developed in Macromedia Flash 6, and it exchanges

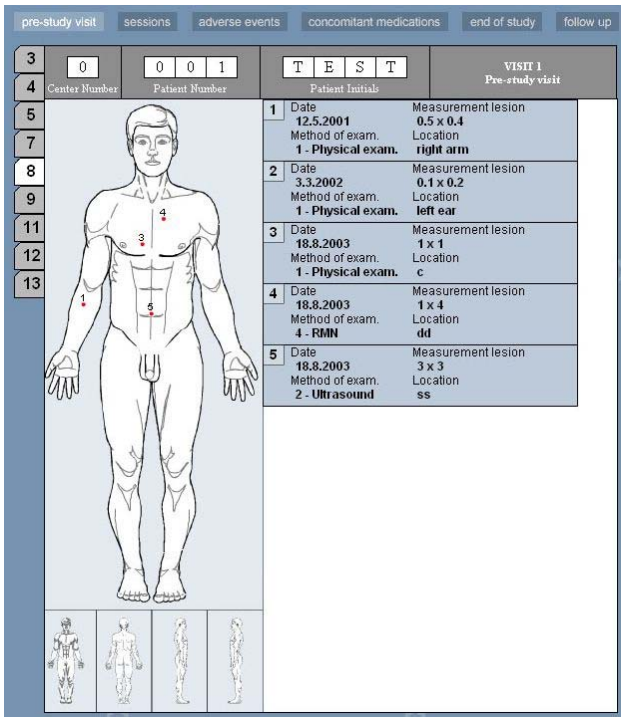

Figure 4: Interactive human map

XML structured data with the web-server. The interactive human map is shown in the Fig. 4.

D. Local database upload

Local database upload is also performed trough the internet browser. The user simply selects the local database file and fills in comments. The rest of the process is automatic: application saves uploaded file on the server, records in the central database some upload information (date and time, user id, name of the file,...), and then copy data from the uploaded file to the central database. A DTS (Data Transformation Service) package takes care of copying data and their overwriting – the newer data will overwrite the older ones. At the end of the upload process user is informed of the upload success. In the list of the uploaded data user can check all the data uploaded from his/her center.

E. Basic statistics

Basic statistics, which allow the follow-up of the project progress, are dynamically generated from the data in the central database. Therefore, they offer information about the number of treated patients per center as well as number of ended therapies, number of tumor sessions and uploaded corresponding local databases, distributions of applications of different electrode types and different drugs. Every center has access to these statistics and can compare its activities with others. Some of statistics (usually local statistics) can be dedicated to a particular center and therefore hidden to the others. Statistics are presented in Macromedia Flash 3-D charts.

V. APPLIED TECHNOLOGIES

For the purpose of developing the web-based medical record system we used the following technologies:

- HTML + JavaScript,
- XML + XSL,
- ASP (MS IIS4.0) + JScript,
- T-SQL (MS SQL Server 2000) + DTS packages + Visual Basic,
- Flash (Macromedia Flash Player 6.0).

VI. CONCLUSION

We have developed a web-based medical record system that consists of a central database and a web-application (*Cliniporator Web-Recorder*) which can be accessed by unlimited number of the Cliniporator™ medical device users. The aim of the system is building patients' records during the testing period of the Cliniporator™ medical device in clinical environment. The system enables central collection of the data from Cliniporator™ devices, which is important for fast detection of device malfunctions and for following stocks of single use electrodes. A huge number of uniformed data collected in a database gives us an opportunity for excessive data analysis and further research. The results of analysis will contribute to establish standard operating procedures (SOP) for electrochemotherapy and later on for electrogenetherapy. Results of analysis will also help us in improving Cliniporator™ device and determining algorithms for intelligent pulse delivery. Collected medical records can help clinicians in making decisions which treatment protocol for a particular tumor lesion to choose. Our future aim is to build a decision-making system that will be able to suggest an optimal therapy for a particular tumor based on the existing data.

The advantage of *Cliniporator Web-Recorder* is that the system can easily be upgraded without any user's disturbance. Due to the system centralization all modifications are implemented locally on the server, while users are just informed about the improvements.

REFERENCES

[1] Maček Lebar, A., Serša, G., Čemažar, M., Miklavčič, D., "Elektroporacija", Med Razgl, vol. 37, pp. 339-354, 1998.

[2] Neumann, E., Kakorin, S., and Toensing, K., "Fundamentals of electroporative delivery of drugs and genes," Bioelectrochemistry and Bioenergetics, vol. 48, no. 1, pp. 3-16, 1999.

[3] Satkauskas, S., Bureau, M. F., Puc, M., Mahfoudi, A., Scherman, D., Miklavčič, D., and Mir, L. M., "Mechanisms of in vivo DNA electrotransfer: Respective contributions of cell electropermeabilization and DNA electrophoresis," Molecular Therapy, vol. 5, no. 2, pp. 133-140, 2002.

[4] Serša, G., Čemažar, M., and Rudolf, Z., "Electrochemotherapy: advantages and drawbacks in treatment of cancer patients," Cancer Therapy, vol. 1 pp. 133-142, 2003.

[5] Mir, L. M. and Orlowski, S., "Mechanisms of electrochemotherapy," Advanced Drug Delivery Reviews, vol. 35, no. 1, pp. 107-118, 1999.

[6] Ferber, D., "Gene Therapy: Safer and Virus-Free?," Science, vol. 294, no. 5547, pp. 1638-1642, 2001.