Intelligent technologies for real-time monitoring and decision support systems

Djumanov, Dilshatbek

QUEEN MARY UNIVERSITY OF LONDON
DEPARTMENT OF ENGINEERING

INTELLIGENT TECHNOLOGIES FOR REAL-TIME MONITORING AND DECISION SUPPORT SYSTEMS

Dissertation

MPhil

Dilshatbek Djumanov
Supervisor: Dr P. Dabnichki
2011

Abstract

Automation of data processing and control of operations involving intelligent technologies that is considered the next generation technology requires error-free data capture systems in both clinical research and healthcare. The presented research constitutes a step in the development of intelligent technologies in healthcare. The proposed improvement is by automation that includes the elements of intelligence and prediction. In particular automatic data acquisition systems for several devices are developed including pervasive computing technologies for mobility. The key feature of the system is the minimisation/near eradication of erroneous data input along with a number of other security measures ensuring completeness, accuracy and reliability of the patients' data. The development is based on utilising existing devices to keep the cost of Data Acquisition Systems down. However, with existing technology and devices one can be limited to features required to perform more refined analysis. Research of existing and development of a new device for assessment of neurological diseases, such as MS (Multiple Sclerosis) using Stroop test is performed. The software can also be customized for use in other diseases affecting Central Nervous System such as Parkinson's disease. The introduction of intelligent functions into the majority of operations enables quality checks and provides on-line user assistance. It could become a key tool in the first step of patient diagnosis before referring to more advanced tests for further investigation. Although the software cannot fully ensure the diagnosis of MS or PD but can make significant contribution in the process of diagnosis and monitoring.

Acknowledgements

I would like to thank my supervisor Dr Peter Dabnichki for his guidance and support throughout this research project. In addition, I am grateful to the directors of Richmond Pharmacology Ltd and the staff members from each department for the opportunity they have given me to develop and test data acquisition systems.

Content

List of Figures and Tables

1 Literature review

Intelligent technologies are gradually encompassing different areas of our life including medicine, biology and bioinformatics. A survey on IT-related publications in medicine shows, that within the last 6 years the application of various intelligent technologies had an exponential increase compared to the previous decade [1].

1.1 Applications of Intelligent Technology Systems

One of the simplest examples of smart technology is smart control system, house security monitoring and smoke alarm systems. A combined system presented in [2] uses bi-directional communication for monitoring and giving warnings in case of emergency situations.

A similar system is used for monitoring elderly and disabled people at their homes [3-4]. Once equipped with imperceptible wireless sensors communicating with a central system, patients can have normal lives. The system traces any out of range vital signs and sends a warning message or calls an ambulance if necessary. It can detect the physical behaviour of bedridden elderly using an acceleration sensor. This wireless system is used in order to prevent elderly patients from falling down and injuring themselves.

Many similar systems have a bad reputation of generating false alarms. The main reason for this is that the performed analysis is based on results taken solely from a patient. Whereas there are many factors which could affect the state of a patient e.g. patient's activity, environment, etc.

Medical Data Acquisition Systems as described by Show et al [5], aim to facilitate efficient medical data management, including data collection, storage, retrieval and transmission using wireless technologies. One of the benefits is the timely access of critical data, inclusion of user-friendly interface and the ease of medical data management, making it more presentable, distributable, efficient and cost-effective. This system is expected to aid medical staff to monitor and update each patient's database efficiently by collecting personal and medical data from the patient using Near Field Communication (NFC) technology embedded in a Remote Unit. The data are transmitted from the Remote Unit to the Base Unit for storage via Bluetooth technology. Monitoring medical data is a crucial part of any data capture system, so using intelligent technologies for selective data query and even selective data capture would significantly increase the data transmission and effective use of storage space.

Compared to most analogue systems which lack this flexibility, data capture is performed at certain predefined time intervals which generate megabytes and gigabytes of unnecessary information. This might lead to shortage of storage space and slowing down of the entire system due to decreased access speed.

New technologies using future innovations in disease management are key factors for providing cost effective care of patients. For example, care at home nurses that currently manage 10 patients a day could care for 20 or 30 with the help of telehealth technology. Patients whose conditions have already been diagnosed can be monitored as frequently as necessary, and their therapies adjusted without home or practice visits [6]. As a result, telehealth boosts efficiency and increases access to medical care and disease management services. Instead of visiting a patient, a nurse would provide care management using mobile technology for data monitoring. This conversion from a visit based to "intervention" based system is growing in home health, setting the stage for faultless and efficient integration between home care and disease management providers.

Lau et al [7] demonstrated that an asynchronous web-based telemedicine system could be successfully implemented with low-cost components already available off the shelf. The system was tested on 6 patients for 6 months and the results indicated that the system was received well by physicians as all patients used it successfully and found some aspects of the system useful. Even novice computer users were able to operate the system, although the web browser user interface was too complex for some. E-Medicine system is a web based system allowing communication between patients and surgeons on offline basis, by monitoring patient records and treatments online. Surgeons can use questionnaires and answer patient's questions through the system. Patients can observe their treatment, history and receive instructions. However, such a system requires direct participation of both patients and doctors in the process, where the aim of telemedicine is to decrease human interaction by automation.

The term telemedicine refers to the use of telecommunication technology for medical diagnosis, treatment, and patient care [8]. Telemedicine makes possible a physician or specialist at one site to deliver health care, diagnose patients, provide intra-operative assistance, provide therapy, or consult with another physician or paramedic at a remote site. Thus, the aim of telemedicine is to provide expert-based healthcare to remote sites and to provide advanced emergency care through modern telecommunication and information technologies. Such a system using web-based database system for intelligent remote monitoring of an artificial heart was developed

[9]. It is important for patients with an artificial heart implant to be discharged from the hospital after an appropriate stabilization period for better recovery and quality of life at reduced cost of care. The authors developed remote monitoring system consisting of a portable monitoring terminal and a database for continuous recording of patient and device status. A web-based data access system was developed so clinicians could access real-time patient and device status data and past history data. An intelligent diagnosis algorithm module that non-invasively estimates blood pump output and makes automatic classification of the device status is a central part of this system.

More recently, Huanga and Cheng [10], presented a web-based medical diagnostic system named Chinese Medical Diagnostic System (CMDS) which can serve as an educational tool and assist physicians. It was proposed a unifying framework for intelligent disease diagnosis system CMDS where the medical ontology[1] has been integrated in the system development, and the methodologies of its implementation for digestive health. Nowadays, the Internet has been increasingly used in a variety of applications for medical purpose, i.e. to provide an easy access to information and facilitate building and sharing knowledge about clinical diagnosis experiences, disease treatments and even prescriptions. In this respect, there is a real need of an intelligent system because of the nature of the problem evolving complex methods of diagnosis and treatment. This allows not only the treatment of fully manifested diseases, but also to assist in maintaining health and balance to prevent illnesses.. CMDS uses web interface and expert system technology to act as human expertise and diagnose a number of digestive system diseases. CMDS provides a truly precise analysis for digestive system disease and the prototype system can diagnose up to 50 types of diseases, and uses just over 500 rules and 600 images for various diseases. The satisfactory performance of the system proved that it could serve the educational purpose, act as a consultant role and the functionality can be extended to the whole body health system. The drawback of the system is that it expects active involvement of patients in the process of diagnosis.

Ontology provides the framework for the domain knowledge base. With the help of ontology, the knowledge is not only readable by human- but also by machines.

---

[1] Ontology represents a set of concepts or objects within a domain, where the concepts contain their properties and attributes and have relatively complex relations amongst each other.

Figure 1.1 below shows the knowledge hierarchy of the medical ontology. The root of medical ontology is the medical entity; it covers four major sub-trees: physical medical entity, conceptual medical entity, resources, and events.

(1) Physical medical entity: The Material class shows the related ontology structure concerning a physical structure and body substance. In physical structure subclass, it shows the classification of the human body. The Non-Material class shows the patient's spirit, feelings and state. The physical medical entity plays an important role in the knowledge hierarchical and medical diagnosis.

(2) Conceptual medical entity: Conceptual medical knowledge is very important when physicians observe and diagnose each patient's disease. According to the different features of each disease, pathology, aetiology, pharmacology, and pharmacy knowledge are required know-how in this field.

(3) Resources: In medical ontology hierarchy, there are some components that do not belong to physical or conceptual medical entity. However, those activities can influence the medical diagnosis; e.g., the working qualification and experience of physicians should be recorded for reference.

(4) Events: Events are those activities that can affect the medical diagnosis, e.g., Erroneous diagnosis can impact on the medical service quality.

Figure 1.2 below shows the architecture of the CMDS expert system based on its functionalities. CMDS consists of three main components: Java Expert System Shell (JESS); Database Set (DS); and Knowledge Extractor (KE). JESS is composed of an inference engine, an XML-based knowledge description, and an explanation system Figure 1.2(1). DS is constructed as a general database and a knowledge base (Figure 1.2(2)). KE is made up of a web-based knowledge elicitation tool and an object-oriented knowledge acquisition editor (Figure 1.2 (3)). Further, CMDS still has a user interface and a physicians' information system.

In addition, an attempt was made to diagnose all of the diseases (50 types of diseases) in the application domain, the results illustrated that CMDS has a highly reliable and accurate diagnostic capability by high CF (certainty factor) values. The summary of the results are as follows:

- 60% → CF = 1.
- 90% → CF > 0.9.
- 5% → CF: 0.7–0.9.

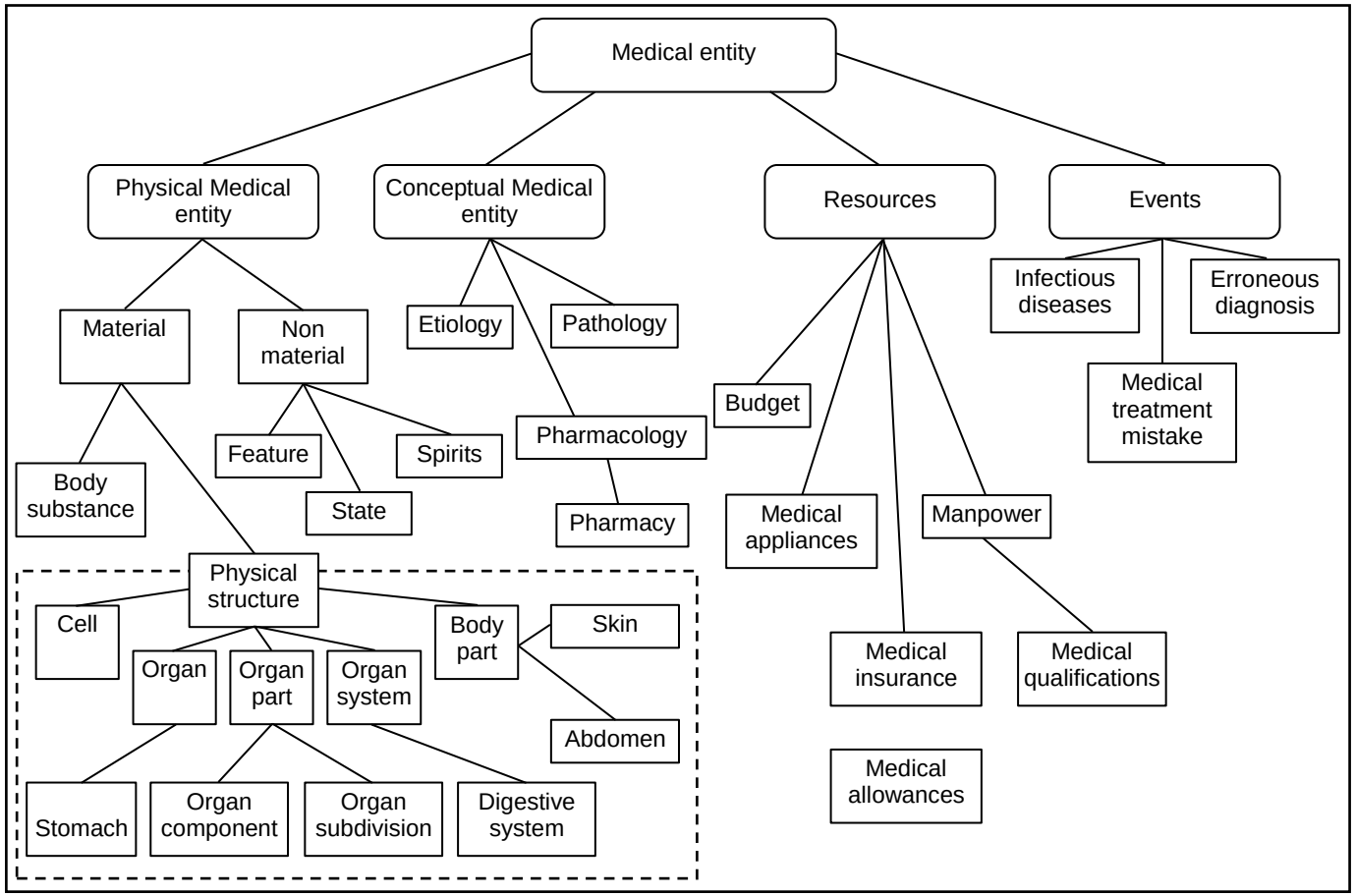


Figure 1.1. The knowledge hierarchy of the Medical Ontology.

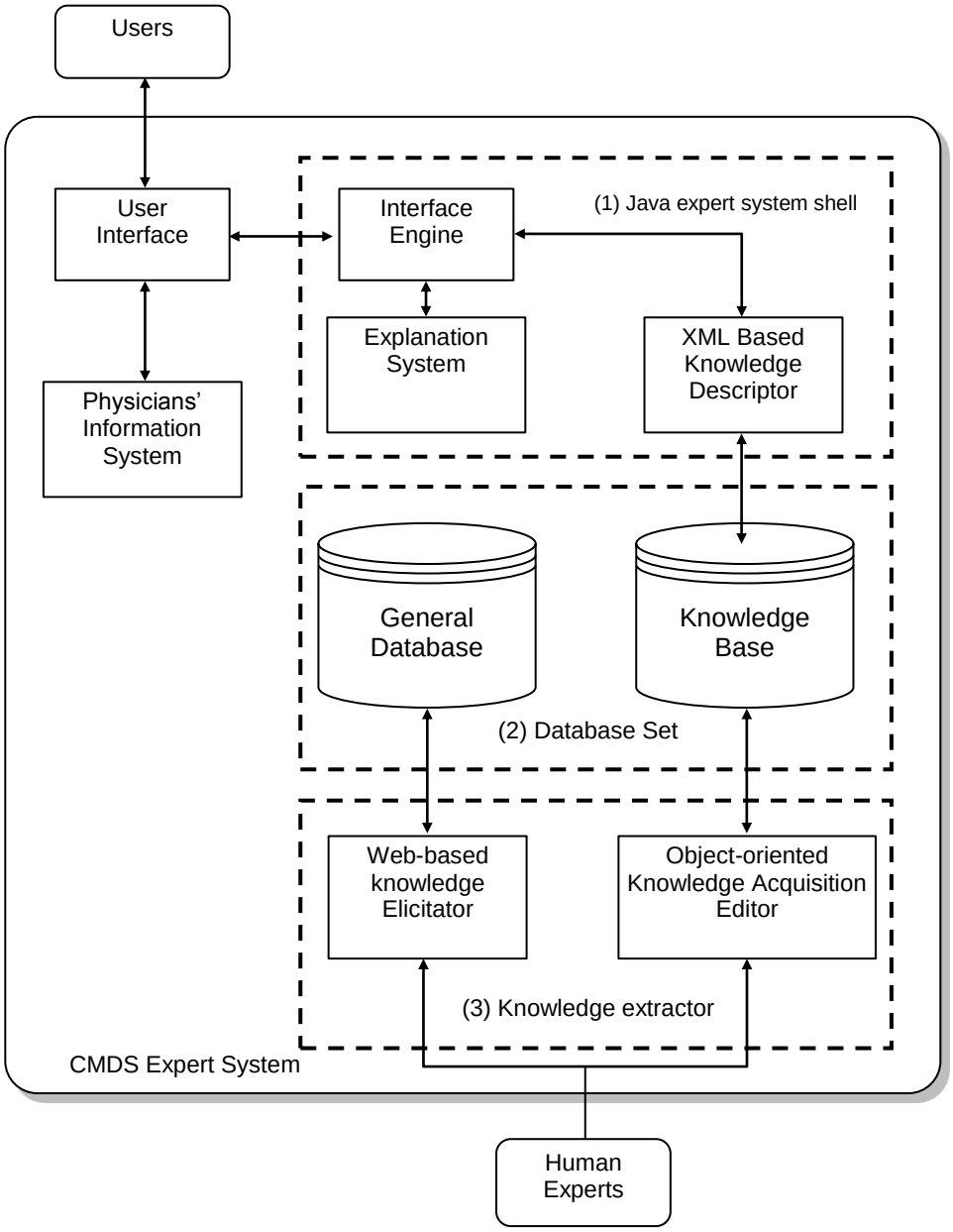


Figure 1.2. System architecture of CMDS.

An Introduced Intelligent autonomous agent for medical monitoring and diagnosis "Guardian" uses several algorithms to produce diagnoses and treatment plans in real time [11]. The system was tested on a set of scenarios, identical to human test subjects in order to compare Guardian with human physicians. Some of the algorithms used to maintain the system are:

- embedded simulator, to run testing procedures on a system;
- "Focus" – data selection algorithm, which filters the acquired data and reduces their volume by removing unnecessary entries;
- MFM algorithms using multilevel flow models of the human body.

This information is collected in a single format in six central knowledge base files, containing cardiac, pulmonary, haematological, neurological, urological, and general topics. Guardian contains about 1000 rules and is considered the largest rule based medical system. Mock testing showed that in most cases it gave correct diagnosis and prescribed action. However, test scenarios indicate that two nurses and one physician would have managed the patient perfectly, but with "Guardian's" help they would have received correct diagnosis and suggestions for corrective actions promptly. Thus, it is likely that they would have performed better. On the other hand the system is not ready to be put into action in a real hospital setting. The reason for this is the need to build a more or less complete knowledge base.

Povalej et al [12] attempted to experimentally find the influence of various intelligent system development features on the accuracy of the system in the case of decision trees. Different tests were done on most frequently used purity measures in the process of greedy decision tree induction. Greedy top-down decision tree induction is a commonly used method for "tree growing". Starting with an empty tree and training set an algorithm (set of rules) is applied until no more splits are possible. Also new hybrid purity measures were introduced which compared their efficiency on 54 UCI (University of California at Irvine) databases. In order to improve the induced decision trees the AdaBoost algorithm (algorithm derived by Freund and Schapire [34]) was used. With regard to average class accuracy boosting it proved to be more successful on majority databases. Newly introduced hybrid purity measures used in the algorithm for decision tree induction improved the accuracy on some test sets.

Effective trend extraction procedure which is based on a simple but powerful representation is described by Charbonnier et al [13]. Examples are given to illustrate the effectiveness of the procedure for complex system monitoring and decision support. The method extracts semi-qualitative temporal episodes on-line, from any univariate

time series. Three primitives - Increasing, Decreasing, Steady are used to describe the episodes. The method uses a segmentation algorithm, a classification of the segments into seven temporal shapes and a temporal aggregation of episodes. It acts on noisy data, without pre-filtering. It is dedicated to decision support in intensive care units. The signals contain information and noise at very different frequencies, and smoothing must not mask some interesting high-frequency data features.

The methodology of extraction on-line trends from a univariate time series consists of four steps, completed on-line in the following order:

1. On-line segmentation of data into linear segments.
2. Classification of the last calculated segment into seven temporal shapes: Steady, Increasing, Decreasing, Positive or Negative Step, Increasing/Decreasing or Decreasing/Increasing Transient;
3. Transformation of the obtained shape into semi-quantitative episodes, using three primitives Steady, Increasing, Decreasing ;
4. Aggregation of the current episode with the previous ones to form the trend.

The first step is a data processing step and the three others are abstraction steps. The interest in the method was shown on three very different examples. The first one is a medical application dealing with patient monitoring in ICUs (Intensive Care Unit). In these Units, medical staff is in charge of several patients in critical condition, whose state requires close attention. Trends are useful because they provide a summary of what has happened to the patient since last visit. During an alarm situation, they enhance latest changes in the monitored parameters, and enable medics to determine quickly potential hazards. The decision making process is then accelerated.

Researchers at the University of Pennsylvania Medical Centre have developed a "smart" intensive care unit (ICU) system that improves vital-sign monitoring of critically-ill patients. By collecting and analyzing several vital signs simultaneously, the smart ICU system could be used to assist physicians and nurses in monitoring patient's physiological parameters, thus enhancing patient care.

Collecting data such as heart rate, blood pressure, and blood flow measurements is critical to patient care, but it requires a great deal of time and must be analyzed by an experienced clinician. To enhance productivity, advanced computer intelligence can be used to convert a patient's vital-sign measurements into easy-to-follow visual models. The system is designed in a way that it takes available information and translates it into a three-dimensional graphic analysis. With the smart ICU, it is possible to spot

potentially dangerous deviations from a patient's 'ideal' vital-sign range and remedy problems quickly.

The system utilizes two artificial computer intelligence tools: neural networks and fuzzy logic. The smart ICU system's neural network can quickly learn the ideal vital signs for a given patient. The integration of the two tools allows for the optimal "smart" system with the ability to learn and adapt to varying situations.

One medical application of artificial computer intelligence is hemodynamic analysis: the evaluation of blood pressure, heart rate, and blood flow to the heart. Hemodynamic analysis is typically performed manually by clinicians who compile information from various monitors in order to evaluate each patient's condition. In the study hemodynamic data was collected non-invasively from 10 patients' electronic bedside instruments to measure cardiac performance. This data consisted of pulmonary artery occlusion, or blockage, pressure (PAOP), heart rate (HR), and cardiac output (CO). The artificial computer intelligence system produced three-dimensional maps/graphs, on a computer screen illustrating each patient's hemodynamic status over designated periods of time ranging from one hour to one week. The smart ICU is designed to support rather than replace clinicians; these tools can perform complicated tasks and help to recognize important trends in patient's health status.

1.2 Technology behind Intelligent Systems

The fuzzy logic approach became common in biomedical engineering because of its effectiveness as a theoretical, methodological, and design tool for addressing some of the problems in developing intelligent patient-supervision systems [14-16].

The validation of the knowledge base of the intelligent patient monitoring and alarm system built on fuzzy logic is described by Beckera et al [15], who compared to commercially available monitoring systems with threshold alarm functionality.

The presented approach offers a problem oriented modelling technique for medical domains where the inter-individual differences between patients have to be considered. Due to the high complexity in biological systems, accurate mathematical models fail whilst the fuzzy approach offers a well-defined solution of higher level of abstraction. The expert's knowledge of both experienced physicians and biomedical engineers is an important source of information for the design of intelligent machines. Today, sufficient commercially available tools support the process of building and testing fuzzy models and therefore the time to arrive at a working solution is decreased by rapid prototyping and simulation techniques.

Thang et al [17] presented an application of soft computing into a decision support system RETS: Rheumatic Evaluation and Treatment System in Oriental Medicine (OM). Inputs for the system are observed symptoms of patients and outputs are a diagnosis of rheumatic states, its explanations and herbal prescriptions. An outline of the proposed decision support system is described considering rheumatic diagnoses and prescriptions by OM doctors. "RETS" diagnoses the most appropriate rheumatic state of the patient, then gives an oriental prescription recommending suitable herbs based on neural networks. Training data for the neural networks is collected from experienced OM physicians and OM text books.

In Oriental Medicine terms rheumatism is described by 12 disease states and 32 typical clinical symptoms. The number of rheumatic treatment herbs is 63. Based on observed symptoms, doctors diagnose and classify rheumatic states, then give a corresponding herbal prescription with reasonable amounts in grams. Based on this one can understand that the system training is to large extent based on combinatorics. Figure 1.3 below shows the process of rheumatism diagnosis and treatment prescription by OM doctors. Such a process can be effectively assisted by Expert System (ES) or Decision Support System (DSS) as shown in

Figure 1.4 below. Roles of the functional parts in the figure are as follows:

- Knowledge Acquisition: Surveys symptoms, prescribing rules, explanations and sample prescriptions.
- Knowledge Base: Consists of symptoms, disease states, inference rules, training data and explanations.
- Fuzzy Inference: Checks rules, calculates weights and advises the most serious rheumatic state.
- Neural Networks (NN): Issues prescriptions with reasonable herbal adjustments.
- Interface: Obtains symptoms and their severities from users and shows inferential results.
- Explanation: Helps users to understand OM, rheumatism, and explains the results.

So far many useful NN applications have been developed. In RETS, trained by rheumatic treatment knowledge collected from skilled OM doctors, NN is used to give herbal prescriptions with reasonable amounts (Figure 1.5 and Figure 1.6).

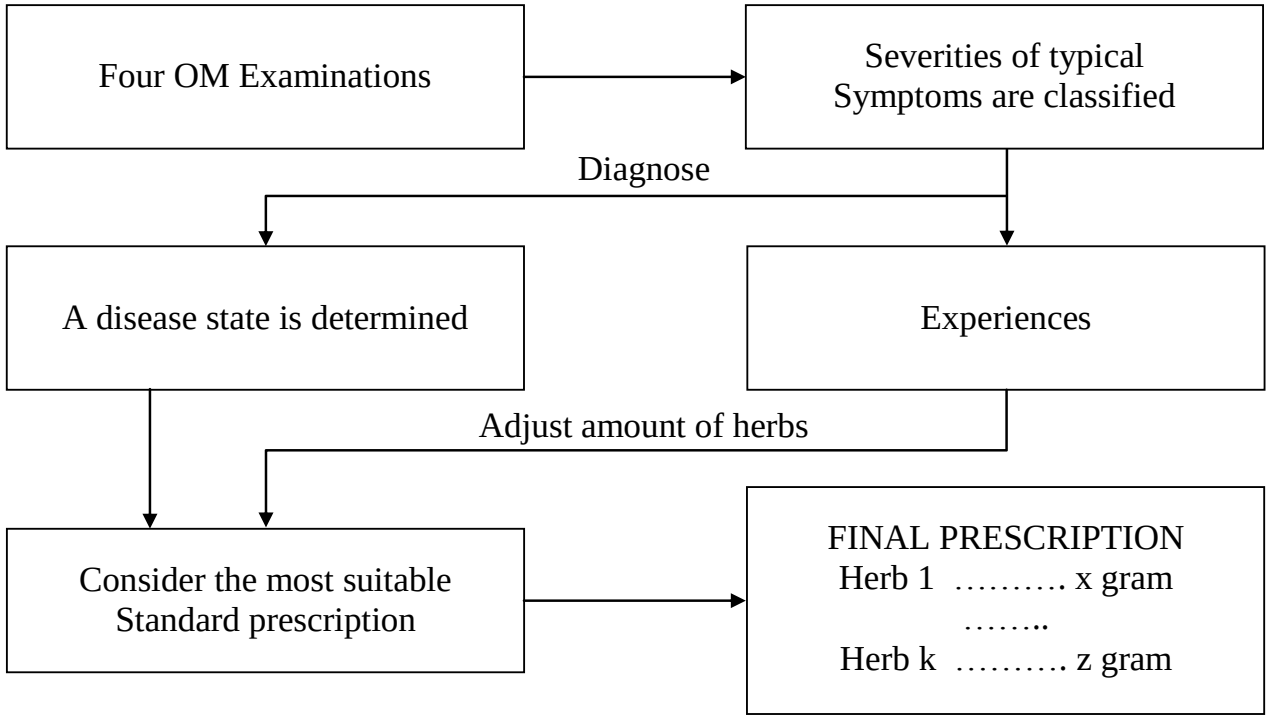


Figure 1.3. Diagram of diagnosing and prescribing rheumatism by OM doctors

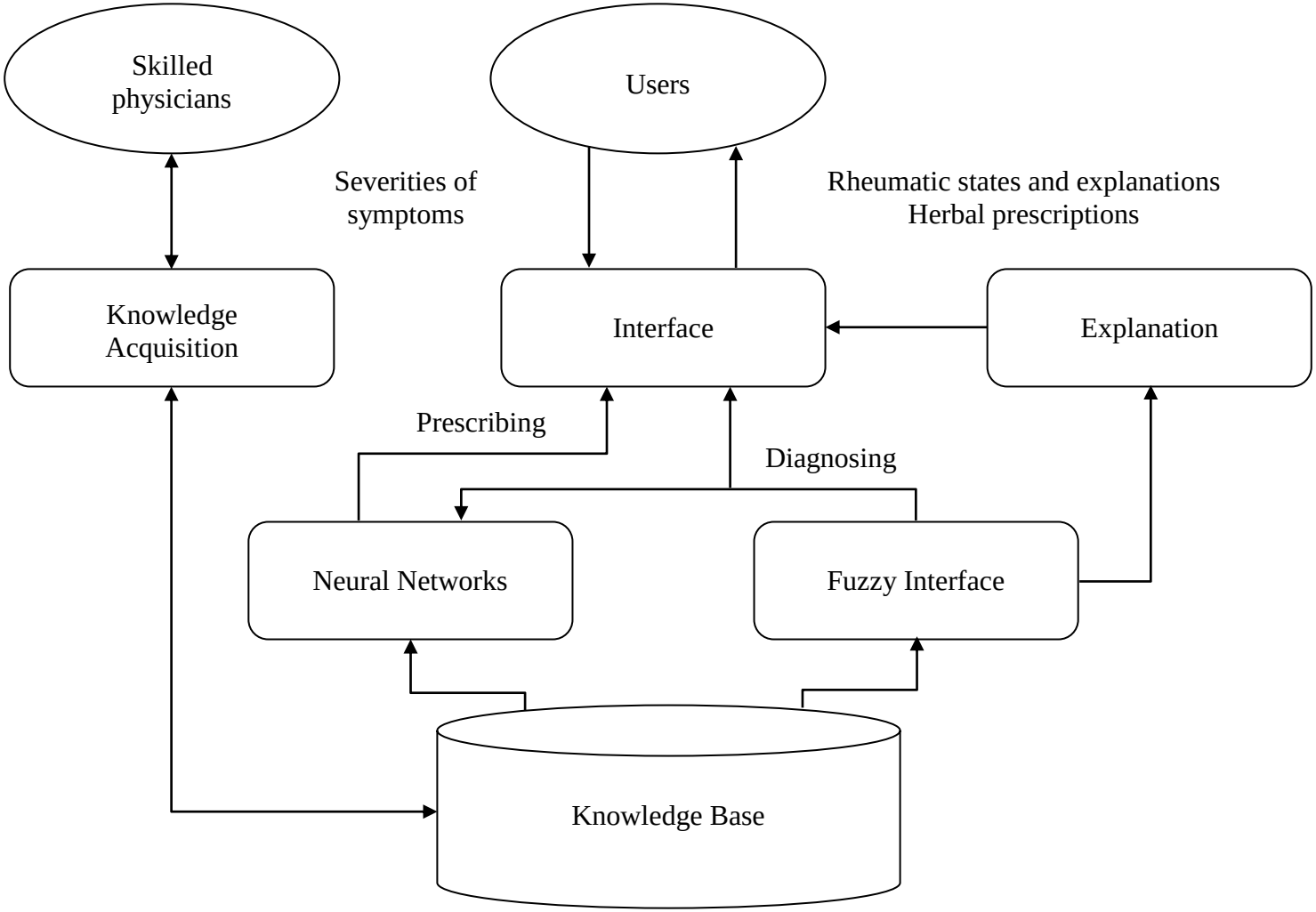


Figure 1.4. DSS for diagnosing and treating rheumatism in OM

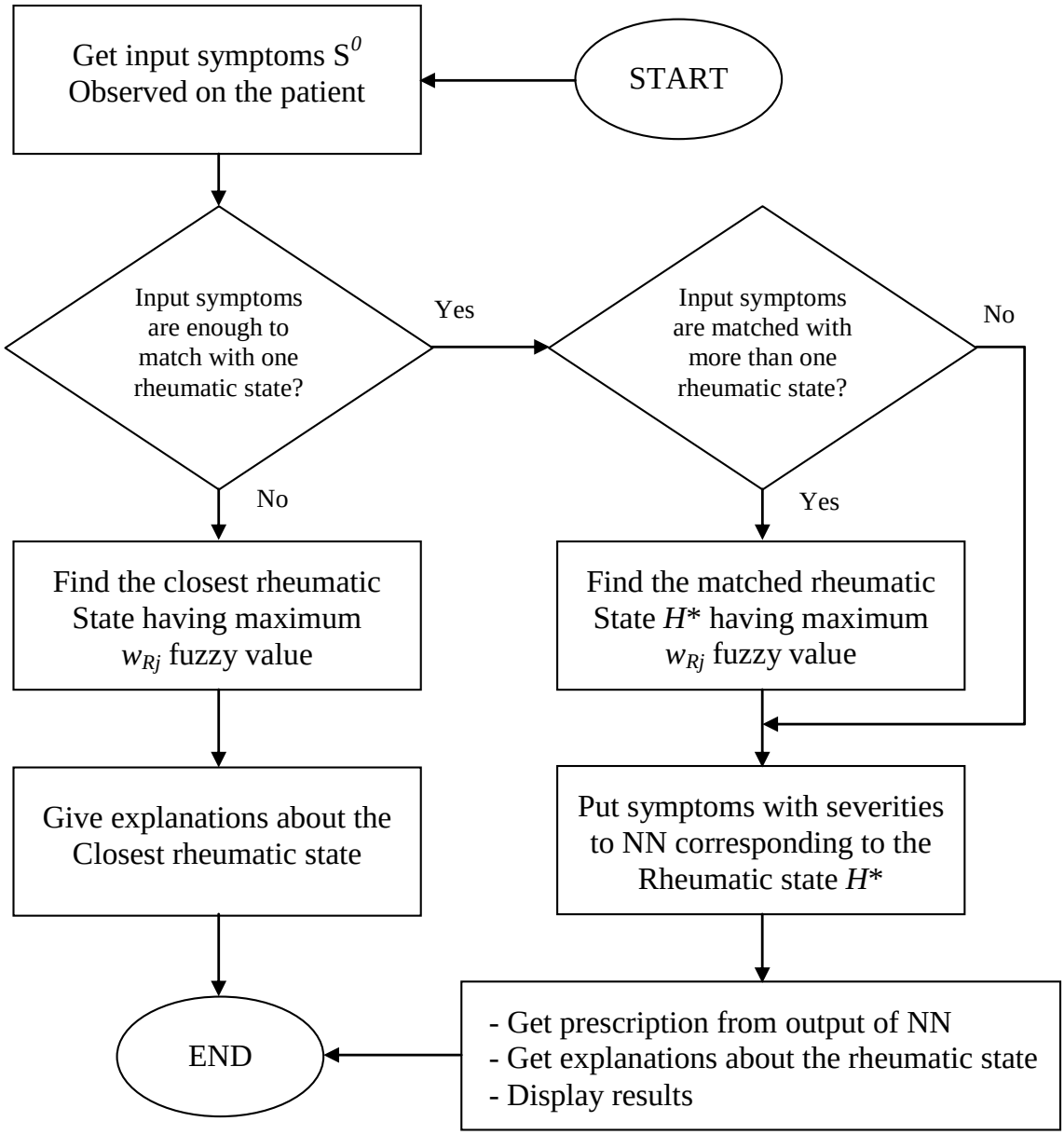


Figure 1.5. Illustration of steps of applying NN in herbal prescribing stage of RETS.

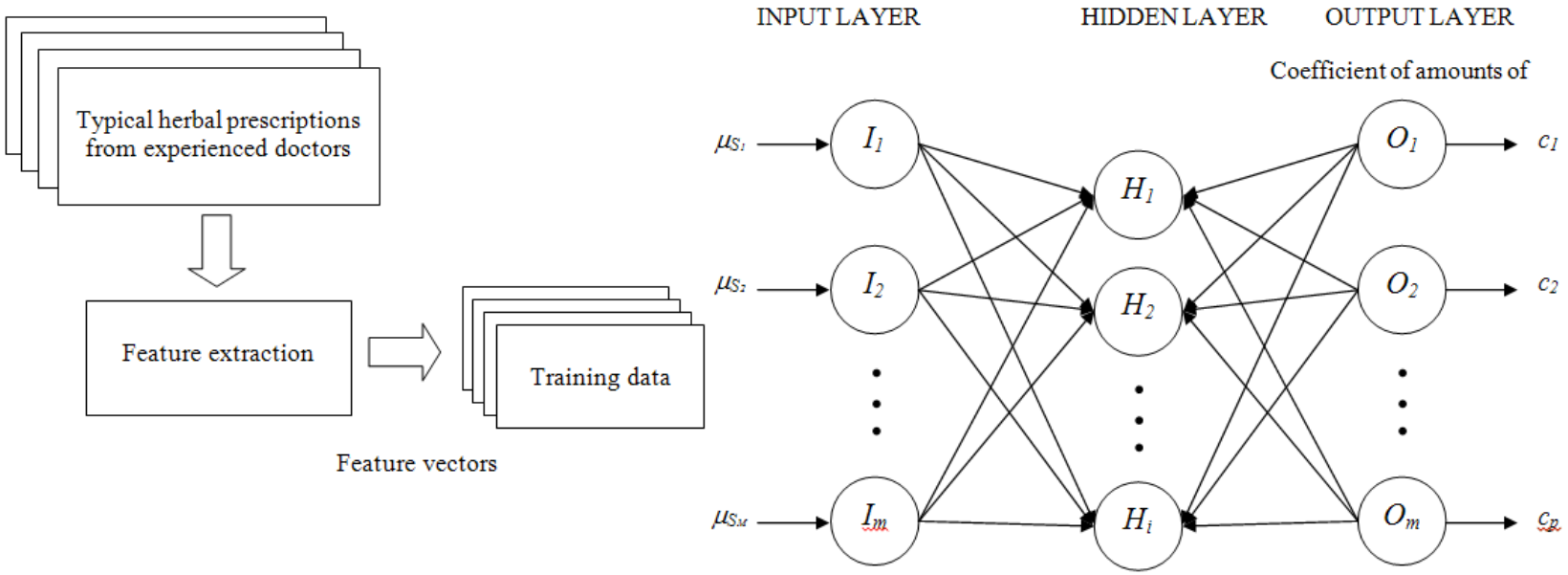


Figure 1.6. Neural Network for prescribing applications in OM

An important point in pre-processing training data is to select the right sets of inputs and outputs. Raw data are prescription rules and herbal treatment prescriptions with typical observed severities gathered from experienced doctors. Features should be reasonably chosen so that from trained NNs we can get appropriate prescriptions in accordance with observed symptoms and diagnosed rheumatic states. One of indispensable features of ES and DSS are their capabilities in offering explanations. Logical explanations of RETS can help users, especially young doctors or medical students, to deeply understand inference results. Explanations also make it easier for experienced doctors to revise related sample cases in training data.

Currently RETS has general and detailed explanations about rheumatic states and prescriptions.

- General explanation: after fuzzy inference process, from the knowledge base RETS obtains a general explanation about the most serious rheumatic state, then shows a fuzzy graph of all related states and fuzzy weights of rules.
- Detailed explanation about similar cases: in training data RETS finds similar cases that have same severities of observed symptoms and same infected rheumatic states with the diagnosed patient, then shows prescriptions of these cases and their explanations from experienced doctors.

If input values into RETS are not recognized by the system - it provides the list of infected rheumatic states and recommends most proper state in which the patient seems to be infected, then shows the advised prescription with appropriate amounts of herbs.

For an evaluation with doctors in Hanoi Oriental Medicine Institute, doctors were asked to consider and provide 50 rheumatic cases including real cases that they had treated, RETS' results were compared with doctor's opinions. Herbal adjustments including additional herbs and amounts of herbs in the final prescriptions showed that 94% of prescriptions from RETS were in total agreement and 6% were fairly accepted. Experienced doctors even used RETS to illustrate treatments of clinical rheumatism cases for medical students.

If a patient has other diseases besides rheumatism, doctors cannot solely rely on this system since they do not have evidence to control potential effects of the herbal prescriptions on the other concurrent diseases. Hence, it is recommended that the system is used only for patients with rheumatism alone and not for those with other concurrent diseases.

1.3 Concepts

There are different types of approaches to introduce artificial intelligence into medical practice, from a simple advisory system to a complex decision support system. In all cases crucial and final decisions are taken by the doctor as the system sole function is to provide different options.

Figure 1.7 below illustrates the design of a well-structured knowledge-base system that maintains patient medical records. The system is equipped with data mining and AI techniques such as statistics, neural network, fuzzy logic, generic algorithm, etc., so that it becomes an active distributed medical advisory system.

A number of advisory systems are available for medical and educational purposes. DXPlain, Gideon and IIiad are three online decision support systems that provide possible diagnoses based on the laboratory reports and reported symptoms. These systems store extensive medical information on various diseases, but none of them truly utilises data mining. The web-based design of an active Medical Advisory (MEDADVIS) system possessing knowledge base, data mining and X-ray image analysis tools is a further step in improvement of the systems support abilities and intelligence.

A full MEDADVIS server has four layers: User access, System memory, Intelligent toolbox and External resources, each containing some functional units as summarised in Figure 1.7 below.

User Access. This layer plays a role similar to that of the human sensory system. Authorised users, including patients, and staff from hospitals, clinics, government offices, etc, can use any Web browser to access a MEDADVIS server.

System Memory. The System Memory module plays a role similar to that of human memory. It is to hold patient records and expert factual knowledge. The Expert Knowledge base stores both medical expertise and reasoning strategies.

Intelligent Toolbox. The Intelligent Toolbox layer mimics human sub-conscious. The tools are operated off line, i.e., whenever a server has available computation time, the tools will be operated. Some MEDADVIS soft-computing intelligent tools are: X-Ray Image processor, Data Mining, Knowledge Pruning and Decision Support units. The X-ray Image processor extracts higher-level information from X-ray images of a patient and puts them in the patients' records. The Data Mining unit, equipped with soft-computing techniques like statistics, artificial neural network, Fuzzy logic, Generic algorithm, etc., enriches the expert knowledge base with additional rules that are hidden

in patient's data. The Knowledge Pruning unit enhances the expert knowledge base with the addition of rules. Important rules that have a strong effect on decisions will have greater weights, and rules with negligible weights are excluded from the knowledge base. The Decision Support unit is the most intelligent one of MEDADVIS. It examines a patient's record and gives necessary advice to the patient, e.g. special and routine checking schedule, preliminary treatment and medication, proposals to see medical general practitioners or specialists if necessary.

External Resources. MEDADVIS has links to online external resources: pharmacy library, hospitals, clinic, diagnostic centres etc. Online pharmacy libraries are important resources that contain medication information, such as new medicine, new diseases and syndromes, which are used by the Decision Support unit.

Before performing analysis data it has to be collected, processed and saved in right format and structure for easy access and manipulation. One such system is detailed by Liu et al [19], who described a data collection system which was used to collect patient monitor data along with annotations of clinical events. The system was designed to reduce the number of false alarms. One disadvantage of the annotation collection system is that it exists separate from the monitor, which in practice means that primary data values can only be obtained once every five to six seconds. More sophisticated analysis techniques might work better on data collected at frequencies of 1Hz or higher.

A process for disease diagnosis support system (DDSS) was been developed by Negoita et al [20]. The inputs to the proposed process are the symptoms of a patient and the results of potential diseases that the patient is suffering from. It includes checking the golden rules, processing artificial neural networks, interacting diagnosis process and determining diagnosis process by rules. Diagnosis of enteron pathology has been used as a case study using the process and the results were encouraging.

The model including essential procedures for determining diagnosis process of a doctor is shown in Figure 1.8 below. The process includes:

Entering symptoms: patients are required to answer a sequence of questions.

Checking the golden rules: this is a comparison between patient's symptoms and the golden criteria of each disease. If patient's symptoms and golden criteria are matched, the disease can be positively identified; otherwise the patient's symptoms will be fed to the artificial neural networks as the inputs.

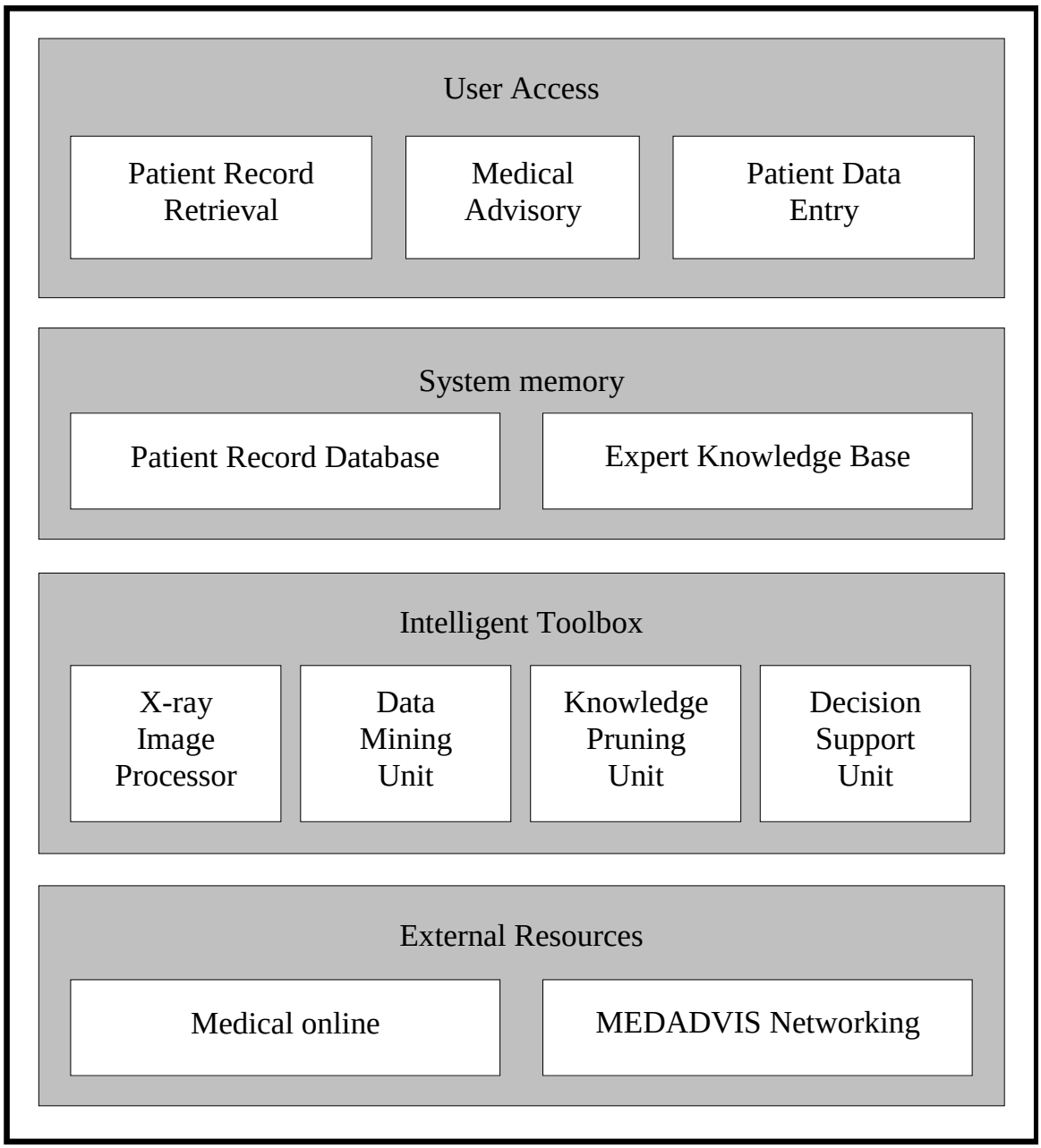


Figure 1.7. Structure of a Full MEDADVIS Distributed Web Server

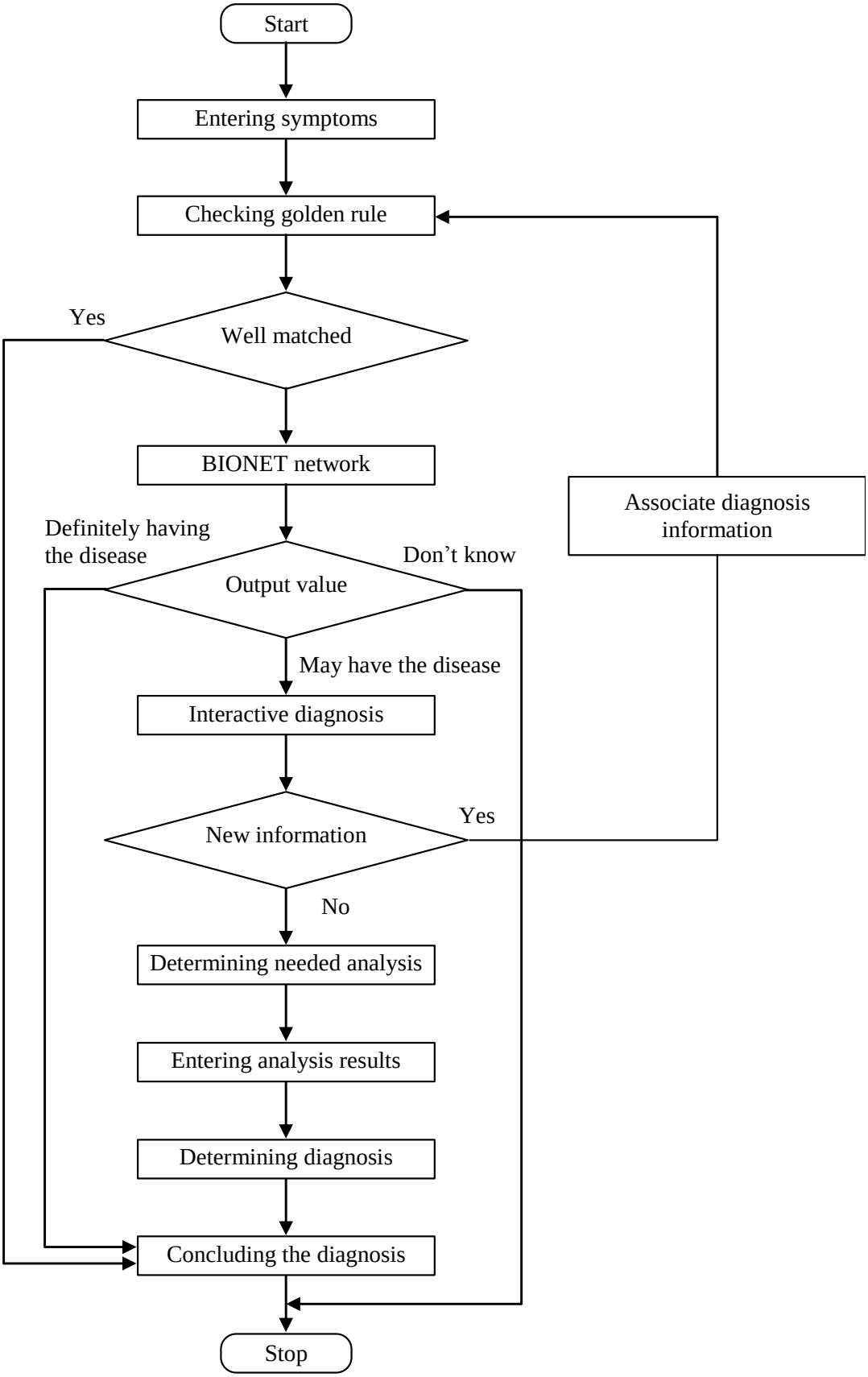


Figure 1.8. Diagnosis of Disease Process

Interactive diagnosis process: if after processing by the BIONET network, the system still cannot figure out the disease, it will utilize doctors' experiences to contact the patient interactively. Interactive process uses bound criteria that are set of rules extracted from the training data set. It represents experiences of experts, and helps the doctor to accurately determine each patient's symptoms. Section 4 presents the detailed interacting algorithm.

Determining required analysis: in many cases, the patient's clinical symptoms are not sufficient to determine the disease and then DDSS needs to use paraclinical analysis.

Determination of diagnosis: this is based on fuzzy rules provided by experts. Detailed presentation on the design of a fuzzy logic system for diagnosis support systems is presented in Section 5.

Concluding the diagnosis: the results of each preceding steps are interpreted in suitable forms so they can be understood by the users.

Taking advantages of the golden rules provided by experts, the benefits of artificial neural networks model was utilized. The artificial neural networks model used in the process is derived from BIONET, where each output value of BIONET is between 0 and 1. The mappings of the output values are given below:

- If output ≥ 0.95, the patient is definitely having the disease at the representative neuron.
- If $0.6 \leq$output < 0.95, the patient may have the disease at the representative neuron.
- If output < 0.6, don't know what is wrong at the representative neuron.

In a case when a patient may suffer from more than one disease two neurons fire.

To compare the result of EPDSS (Enteron Pathology Diagnosis Support System) proposed disease diagnosis support system, three medical experts performed a blindfolded study. The percentages of correct diagnosis are listed in Table 1.

Table 1. Rate of success for correct diagnosis

Disease	No. of samples	Percentage of correct diagnosis			
		Dr Quos	Dr Minh	Dr Chuong	EPDSS
AA	50	98	95	94	99
AC	50	99	96	96	98
AP	50	98	97	96	96
PGU	50	100	98	97	98
Overall percentage		98.75	96.50	95.75	97.75

So called intuitionist fuzzy sets can be used in order to perform intelligent data analysis in medical diagnosis [21]. It is achieved by measuring the performing diagnosis on the basis of the calculation of distances from a considered case to all considered illnesses, taking into account the allocated values of all symptoms. The distance is calculated between 0 and 1 for each symptom and described by three numbers: membership μ, non-membership ν, hesitation margin π. For example, for malaria: the temperature is high (μ=0:7, ν=0, π=0:3), whereas for the chest problem: temperature is low (μ=0:1, ν=0:8, π=0:1). As a result, this approach makes it possible to introduce relative weights for all symptoms (for some illnesses some symptoms can be more important). A solution is obtained by looking for the smallest distance between symptoms that are characteristic for a patient and symptoms describing the considered illnesses.

A further step is taken by implementing self-learning fuzzy logic control in medical application by Mason et al [22]. Based on the principles that fuzzy logic by itself is not an "intelligence" but an action based on a set of predefined rules, they introduced a technique where the system can correct the rules and create them on an on-going basis.

Self-learning fuzzy logic control has a key property of accommodating uncertain, non-linear and time-varying process characteristics. This intelligent control scheme starts with no fuzzy control rules and trains itself on how to control each process presented to it in real-time without the need for detailed process modelling. Self-learning fuzzy control requires another processing layer added to the conventional simple fuzzy controller.

Ubiquitous computing has been one of the popular research and development topics around the world. One of the best utilization of this technology can be in the field of computer aided diagnosis and prediction. Authors in [23] are going towards defining a framework for the computer aided diagnosis and computer aided prediction of the high risk patients. It will help the medical system to do early detection of high risk diseases, reduce diagnostic errors and prevent sudden death situations. One of the limitations of this system using hospital domain knowledge is the different diagnosis pattern of the doctors. Health monitoring and Computer Aided diagnosis is useful for high risk patients for prevention of sudden death. As a specific example, it is defined as four clusters of patient level (regular, careful, serious and dangerous) using vital signal

data. It is achieved by setting up 3 kinds of health care modules which are called home care module, emergency call centre module and an ambulance module (Figure 1.9 below).

After acquiring vital signs from the patient by electronic devices, network protocols such as IEEE 802.11b are used for wireless communication between sensors and the home medical server. Subsequently, the home healthcare server suggests an emergency treatment using MLP (Multi-Layer Process).

System Framework of home healthcare system (Figure 1.10 below) consists of 4 systems and a knowledge database. The database supports sharing of hospital diagnosis knowledge to CAD (Computer Aided Diagnosis) system. The vital signal data processing system is used for data normalization, after detecting the vital data. These filtered signals will be used as input data to the neural network based CAD system. With the help of this information, regular monitoring of patient is ensured. It can measure the level of risk by applying regular monitoring and prediction techniques like time series analysis. CAP (Computer Aided Prediction) system predicts vital data and the severity level of the disease. The last module classifies emergency state of action system for classification of the patient's unstable condition level. If the patient's condition is not normal, the system reacts to the emergency situation by suggesting an immediate action.

Computer Aided Diagnosis (CAD) system (Figure 4.1) uses neural network algorithms. It acquires input data from patients' database. Generally, pulmonary disease patients need to check, SPO2, Co2, HP, BP etc, which should be passed as input data to MLP. The target used by CAD is based on the previous case studies. In addition, the outputs and learning weight results are automatically saved in the database and a message is sent to the server.

Computer Aided Prediction (CAP) system framework (Figure 4.2) works similarly to a CAD system. But acquires input vector about patient's previous and current data (Yt-1 ~Yt-n) for the prediction of level of risk in the future.

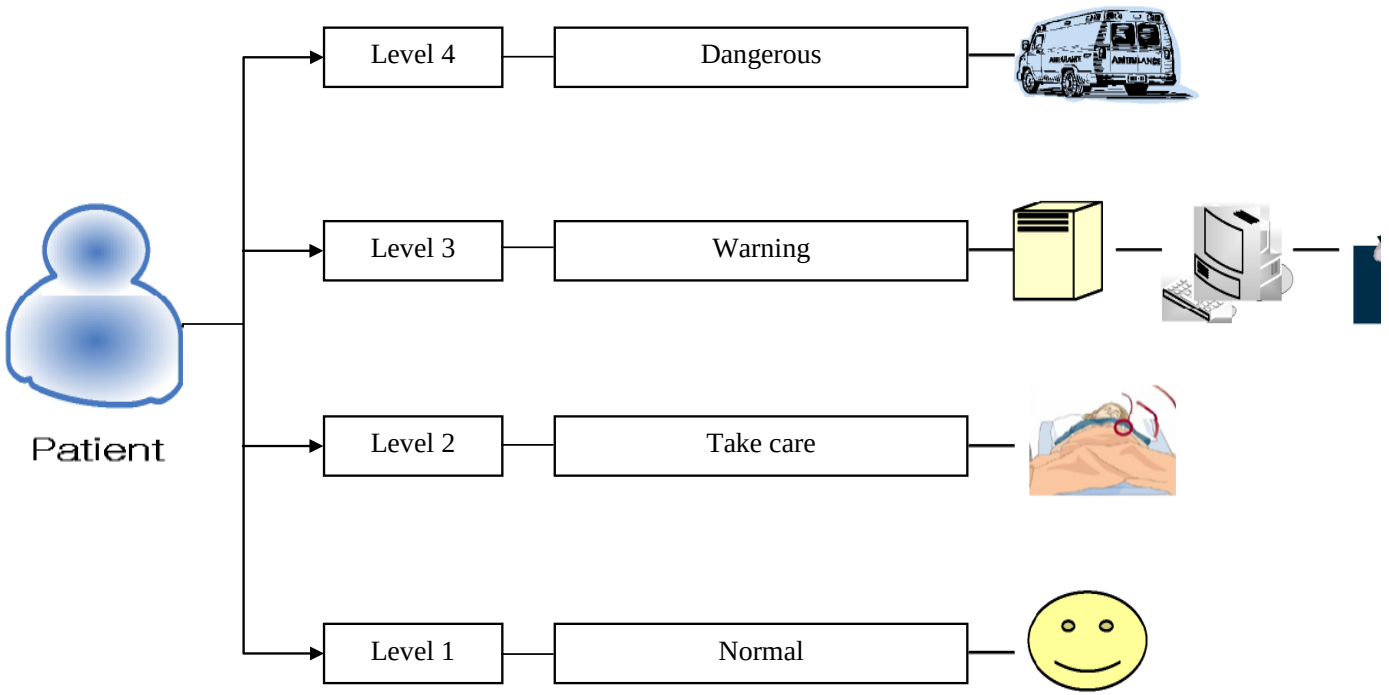


Figure 1.9. High risk patient system service scenario

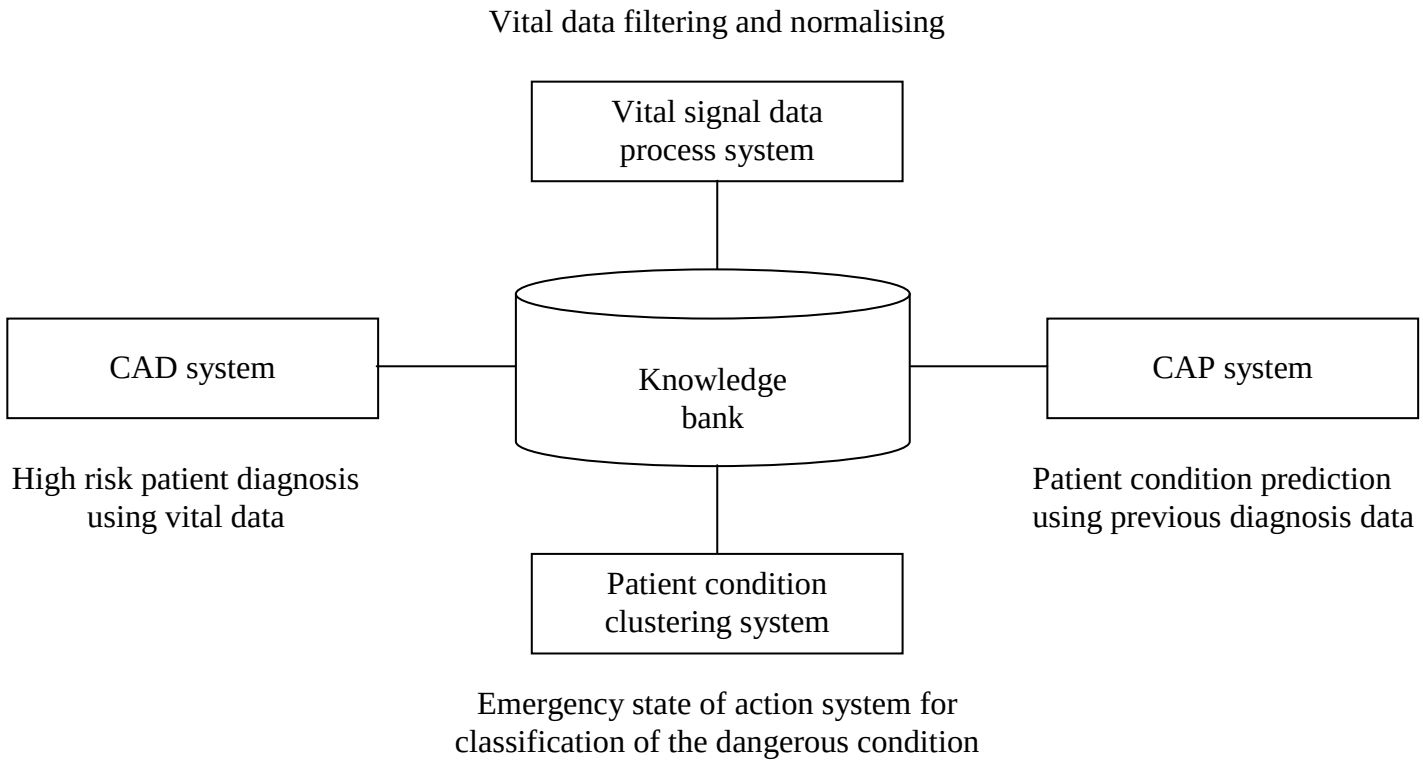
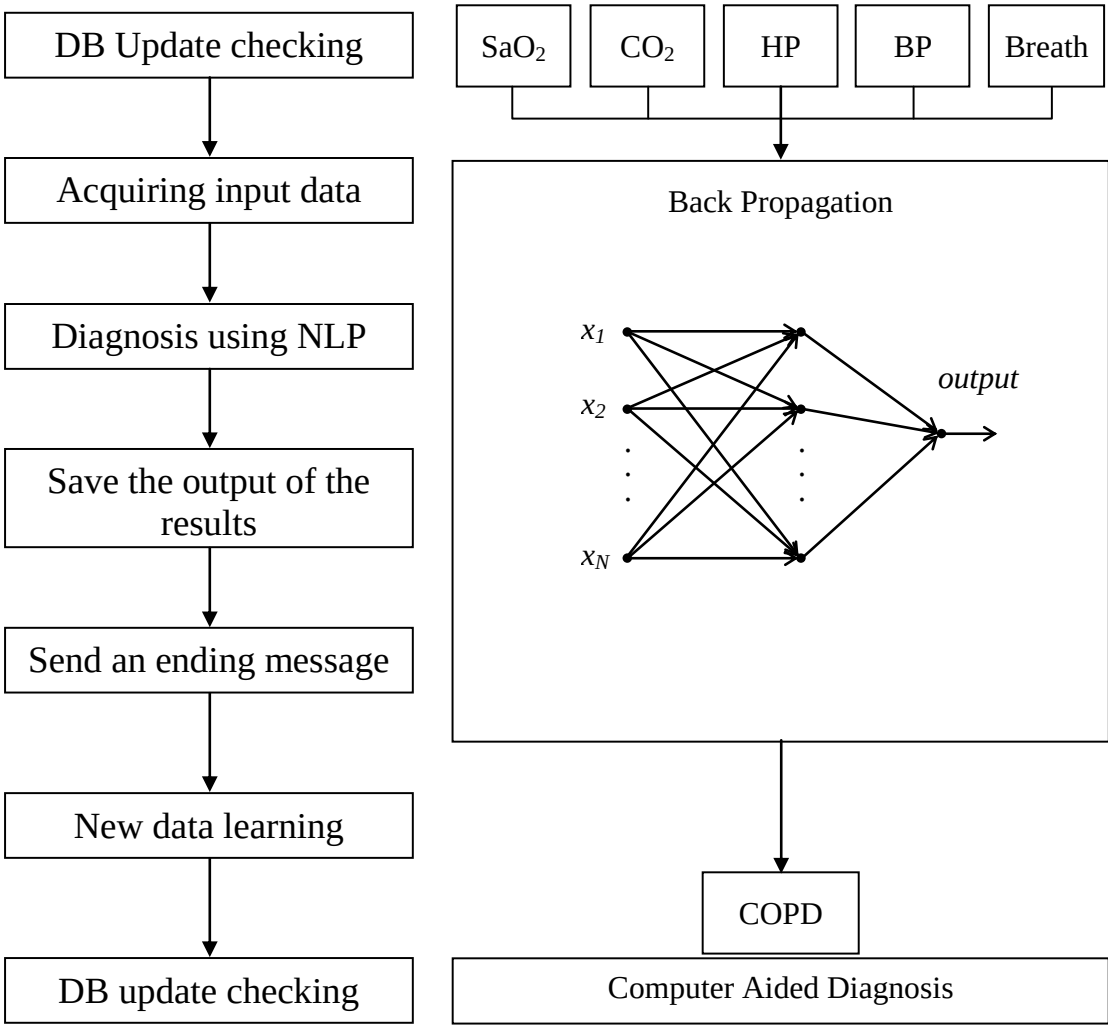
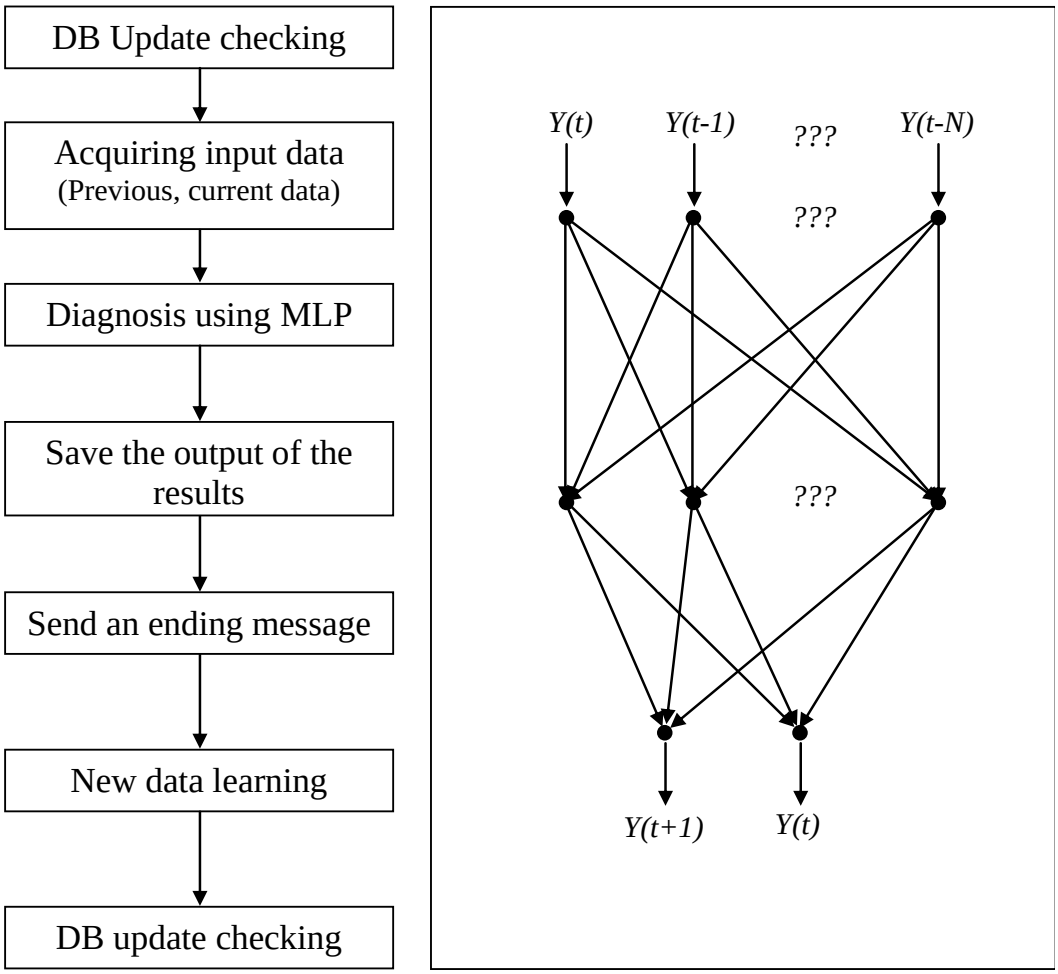


Figure 1.10. System framework



<CAD system>

Figure 4.1. Computer Aided Diagnosis framework



<CAP system>

Figure 4.2. Computer Aided Prediction framework

1.4 Aims and Objectives

Research of intelligent applications in medicine shows that substantial volumes of papers have been published confirming the increase of intelligent system applications used in medicine. Substantial funds are invested in research which is justified by encouraging results. However, the presented findings indicate that it is not possible to take into account all factors potentially affecting human health or state. In situations where assumptions have to be made, false alarms are generated. As these developments are almost entirely research projects, the costs of such systems are not taken into consideration. To develop a system that monitors the person's health status from different angles requires high cost equipment and some new sensor technologies.

Monitoring and diagnosis rely heavily on the quality of the collected data. To achieve data accuracy one has to obtain reliable data from appropriate devices.

Due to communication problems some intermediate data can be misinterpreted or lost leading to incorrect diagnosis. Furthermore, data storage systems, amended incorrectly, will not be able to remove changes without an audit trail.

The aim of this work is to develop Intelligent Data Collection Systems to be used in clinical research. The work consists of two main parts: Automated Electronic Data Capture systems to be used in clinical research and a system for analysis and diagnosis of patients with multiple sclerosis.

As the matter of fact the current traditional methods of data processing and storage requires large amount of paper based records. During a clinical study, in average, one subject's records stacks to about 200 pages, this requires thorough quality control (QC) and usually double data entry. There is always a possibility for errors while manually recording data on paper, which is then followed by electronic format conversion.

The proposed data capture systems aims to increase the accuracy of data collection processes such as vital signs, ensuring data consistency, and can also provide ongoing data monitoring and management.

To keep the cost to a minimum and ensure speedier approval for medical use, approved and certified devices are utilised in the development of the Data Acquisition Systems. This will also increases the reliability of the data, since some devices became industrial standards and thoroughly validated and checked by years of use.

The second part of the research project aims to provide a set of diagnostic tools for patients with Multiple Sclerosis. This includes building online assessment applications for patients which saves the results to a web server for further analysis. Saved results will be analysed by the system and displayed to medical professionals in a more easy readable form. These tools intend to significantly reduce the visits to a doctor by monitoring the disease progression achieved by analysis of test results.

2 Integrating Intelligence in Monitoring Systems

The main purpose of Intelligent Technologies is to minimize human involvement in processes by the use of different techniques such as neural networks and fuzzy logic. The process of decision making starts from data collection that forms the basis for further analysis. Hence the reliability and consistency of the collected data is the most important part of the procedure, which affects not only the final decisions but also the speed of decision making. Data can be collected unsystematically capturing every single detail as well as intelligently collecting only the necessary segments. As an example, it has been observed that in the process of 24 hour ECG holter monitoring, a junior Cardiologist prepares a report containing on average only 10% of the whole recorded data in addition to other statistical information. This is sufficient for a senior cardiologist to make a decision as the focus concentrated on crucial segments of the data.

The pharmaceutical industry is one of the largest and rapidly changing environments where many progressive technologies have been developed over the past decades. Development of new medicine is the core business for many Clinical Research Organisations (CRO). Clinical trials are conducted by CROs in different phases ranging from I to IV. The trials at each phase have a different purpose and help scientists assess possible health hazards and establish the efficacy and safety of the proposed therapy. Regulatory bodies such as the Food and Drug Administration (FDA) decide whether to approve the new drug compound based on the documentation and trial results produced. As a result, large volume of data is collected from volunteers during a trial including vital signs, ECGs, blood samples etc. Data, collected during clinical trials depend on the tested type of medical treatment. All relevant information is always provided in a Clinical Trial Protocol, a document describing the organization of a clinical trial, objectives and methodology. The protocol usually describes eligibility criteria for volunteers, tests schedule, procedures, medications and dosages, and the length of the study. All measurements are recorded on CRFs (Case Report Forms) - questionnaire specifically used in clinical trial research and found as a primary data collection tool for the investigator site. Provision of full, complete and accurate data including all associated documents is essential; hence the paper based approach creates a number of problems including document storage and reliability of the collected data. Furthermore, data collection and especially data entry are prone to mistakes, since they are

monotonous and repetitive processes. Hence, after double data entry quality control (QC) checks are performed.

This chapter will outline the results of utilizing a pervasive computer system that successfully addressed the problems described above by directly recording measurements from a device to a proprietary database without intermediate manual recording to CRF and subsequent manual data entry. In addition to that the system provides administrative control tools such as Online Schedule planning tasks and times for nurses; Administration unit providing the means to Study managers monitoring tasks completion and emergency situations.

2.1 Modular approach in designing software

The concept of software architecture is illustrated in Figure 2.1 below, which consist of the development of each separate module as a standalone application using one single repository for data storage. Subsequently all modules are combined into a single application without any change in separate modules. Such an approach is dictated by the possibility of updating or upgrading separate modules which will not affect the performance of the other modules. The use of a single central repository with normalized tables allows for the elimination of possible data redundancy in the database.

The software is linked to a Scheduler Database where all tasks for clinical staff are stored in a structured manner. Special software tools reduce and at some points eliminate data entry into the data records in real time while taking medical measurements.

Some measurements require patient data such as weight, height and age, which the system database accesses directly from the Volunteer database that contains all information for registered volunteers.

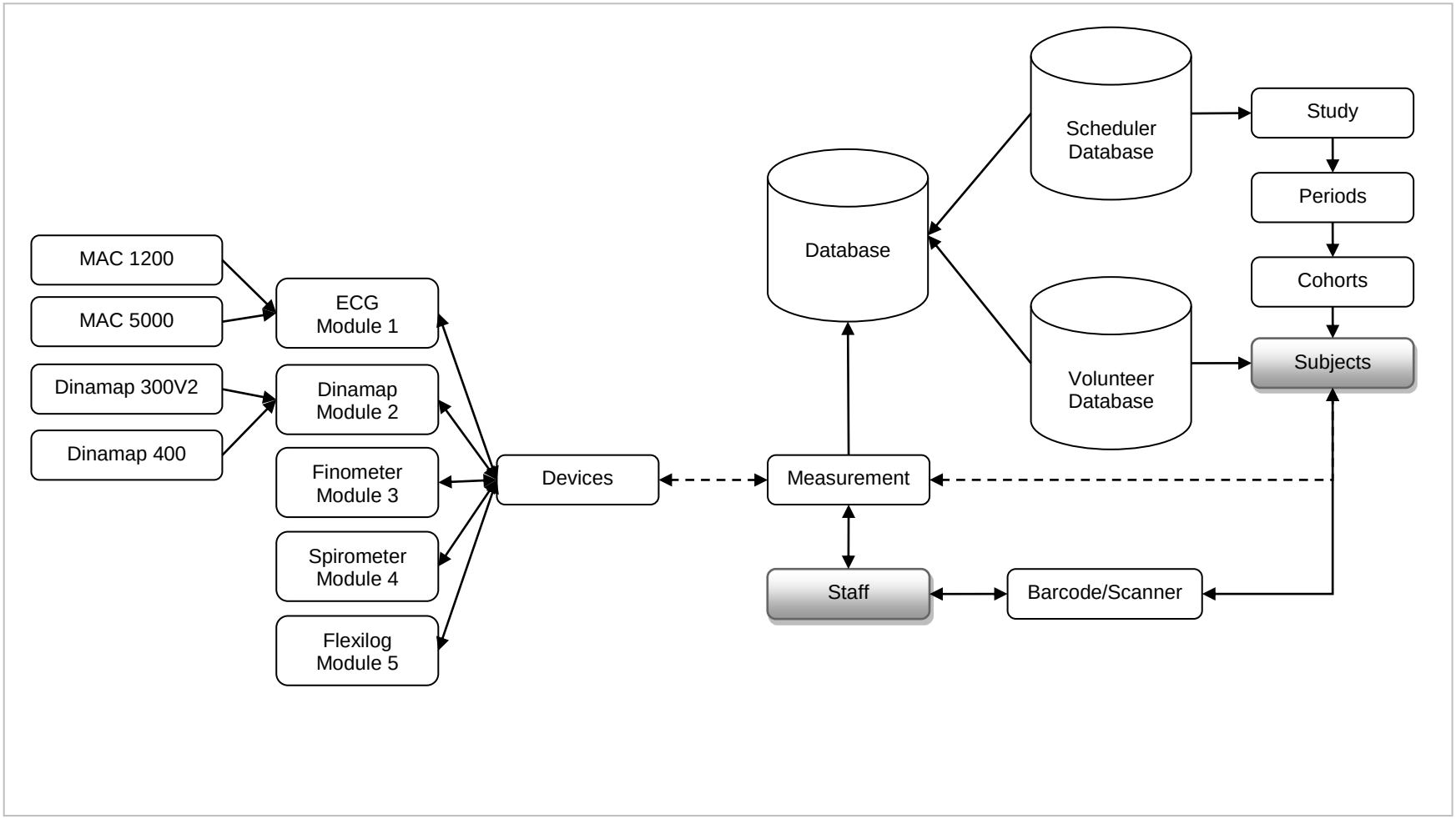


Figure 2.1. The concept of the software architecture.

2.2 Database and record system

Microsoft SQL Server 2000 was used as a back-end for database application. The system combines 3 databases: Scheduler Database – containing all information from the Scheduler software, Volunteer Database (VDB) - containing information about volunteers and a database for the developed system. Scheduler software is a tool for creating schedules for clinical staff based on knowledge, working hours and availability of employees. The software is designed to resolve possible clashes such as two synchronous tasks assigned to the same employee. The VDB database combines all information about volunteers taking part in clinical trials. Once a volunteer is registered, a permanent ID number (RPL-Id) is assigned automatically. RPL-Id is a unique number for each volunteer consisting of 6 digits. Finally, the database for the system is designed to prevent data redundancy by using normalized table structure. All tables are linked in the database level using key fields which create additional safety measures to the database by preventing accidental amendment or deletion of the data even through direct access to the database. As a clinical application the database comprises an audit trail feature where every single change to the database is recorded to an Audit trail table. In addition every single database server is backed up daily using a tape recording device.

The structure of the database is shown in Figure 2.2 - Figure 2.6 below. For the user management section of the system, a set of tables are used to store and manage the access to the system by storing user's relative information (Figure 2.2 below). Since every task contains similar fields such as date-time, period, visit etc., a set of Schedule management tables (Figure 2.3 below) are created for storing and manipulating such data. As an example: since one visit can contain hundreds of tasks, single information entity is used instead of creating copies of visit data in each task record. This falls into a database normalization rule allowing more efficient data management while maintaining the database in a structured manner. Each device produces specific data i.e. has its individual table. The system combines 6 devices, hence the system core table consists of 6 tables which are not directly related to each other (Figure 2.4 below). Software related data such as user information, software features and default parameters are stored in Admin tables (Figure 2.5 below).

Some devices produce large files as containing numerous measurements some reaching tens of megabytes. Such files are stored on a separate server but are linked to the central database, this helps to keep the database size smaller.

The ECG (Electrocardiogram) module of the system is considered as a separate entity, because of its size and features. Firstly, it is one of the most used modules and some studies produce of up to 30,000 ECGs. Part of these ECGs pass through different routes while being analysed by independent cardiologists. The system requirements outlined above were addressed in the database architecture by separating the ECG data management tables (Figure 2.6 below).

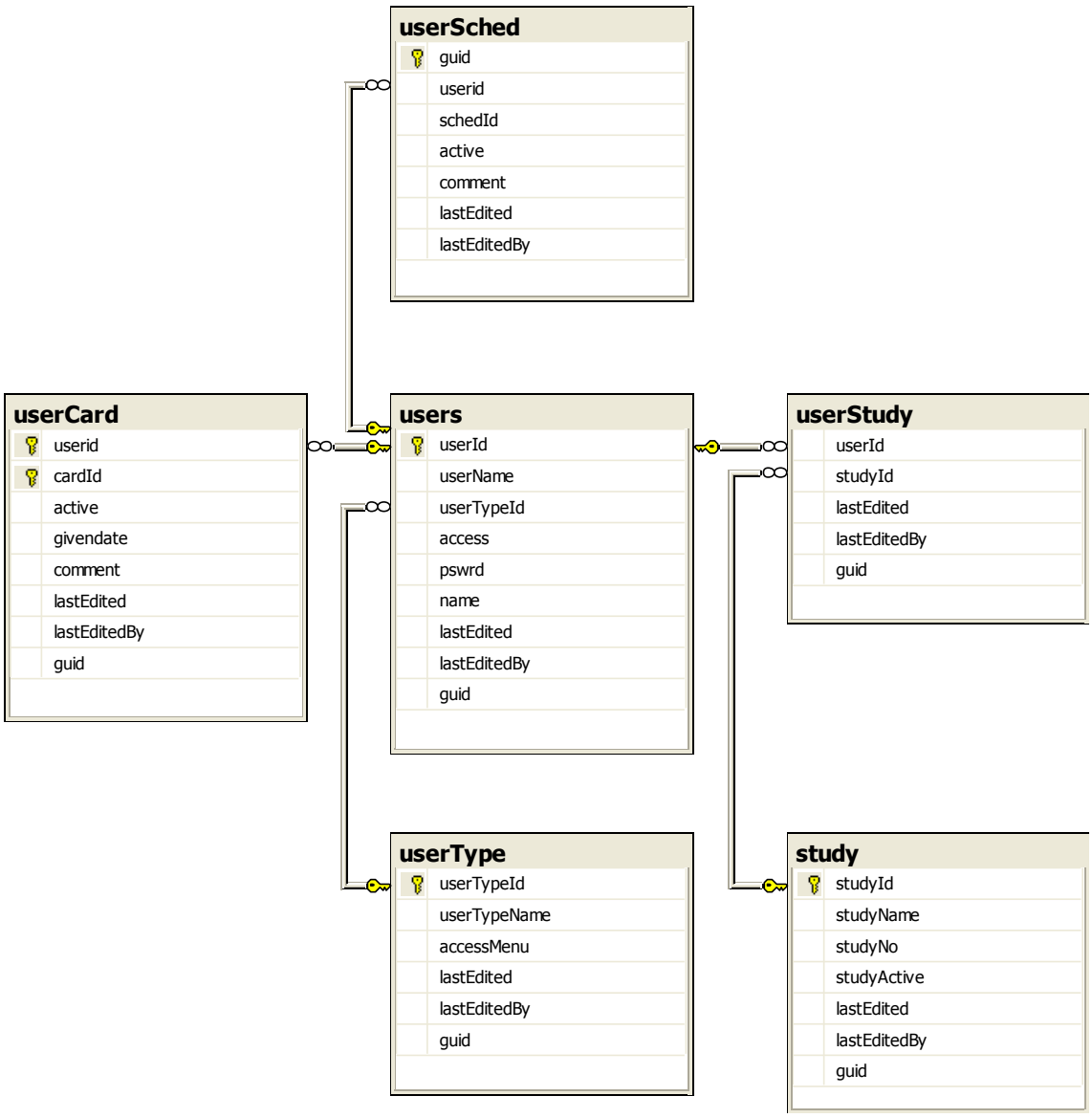


Figure 2.2. Database architecture – User management tables.

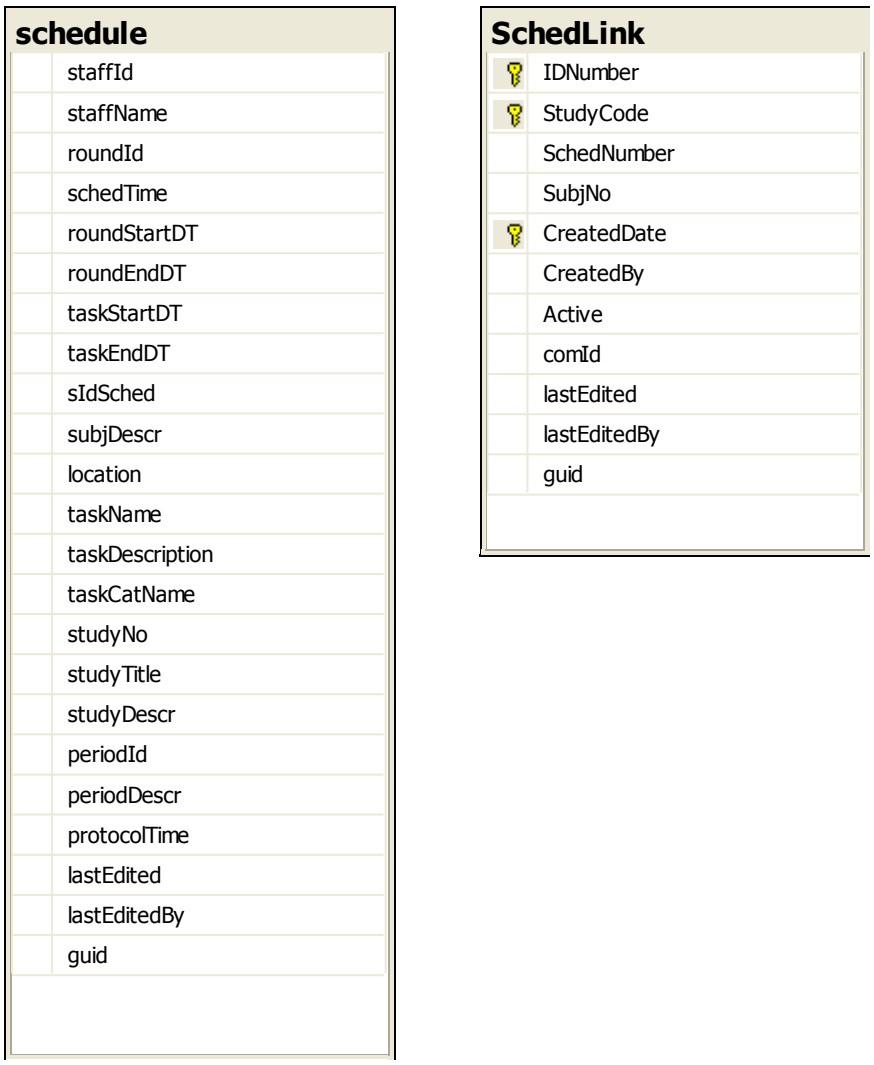


Figure 2.3. Database architecture – Schedule tables.

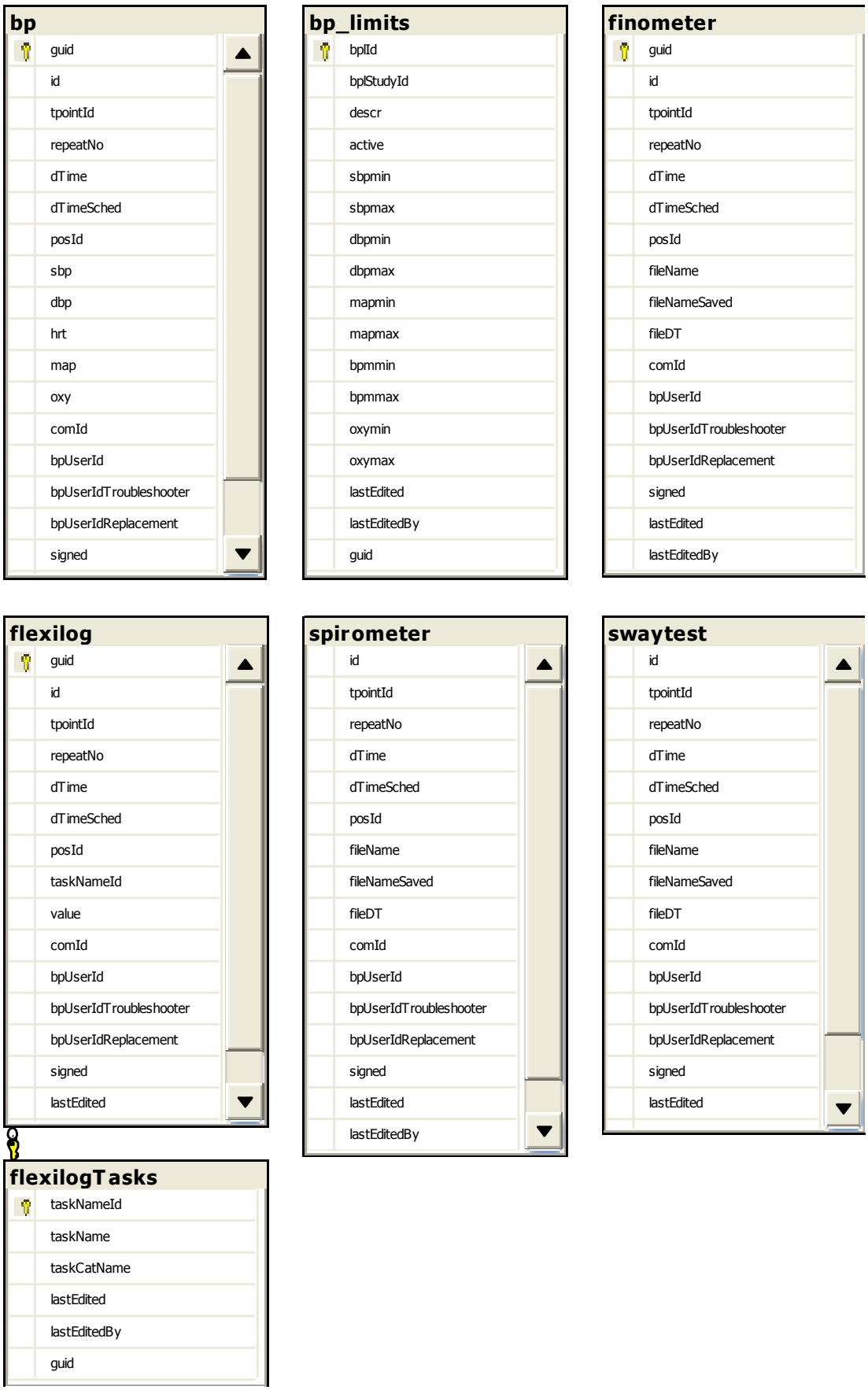


Figure 2.4. Database architecture – Device core tables.

Figure 2.5. Database architecture – Admin tables.

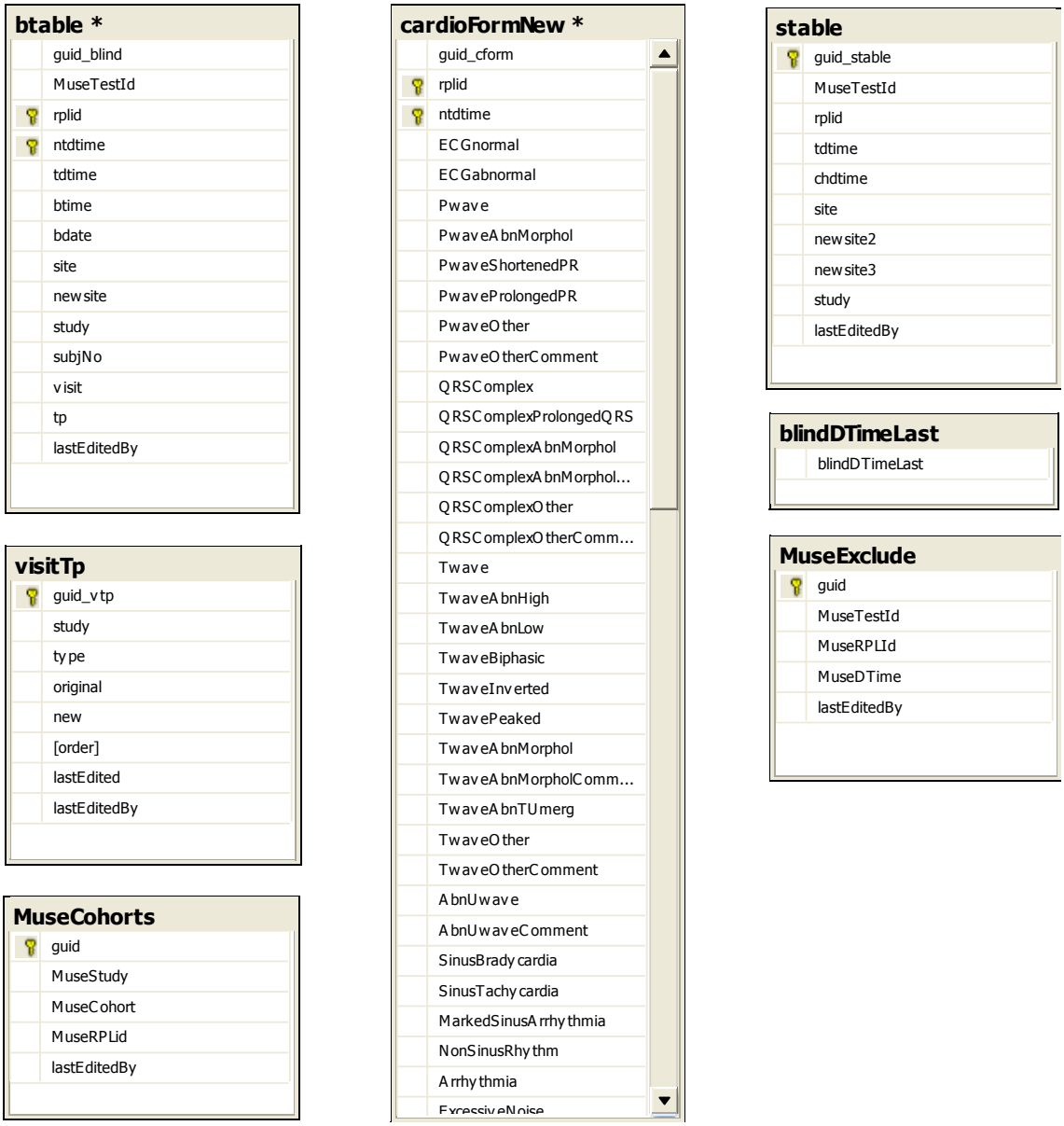


Figure 2.6. Database architecture – ECG Management tables.

2.3 ECG module

The “ECG” module for recording, storing and processing discrete electrocardiograph data has proven its usability by its use in several large clinical studies. Several software tools have been produced to reduce man hours and increase the reliability of the acquired data.

2.3.1 Background

ECG is a non-invasive transthoracic graphic produced by an electrocardiograph, which records the electrical activity of the heart over time. An example of an ECG trace is given in Figure 2.7 below and represents a 12 lead ECG of a 26 years old male. A typical ECG tracing of a normal heartbeat (or cardiac cycle) consists of a P wave, a QRS complex and a T wave (Figure 2.8 below).

The QT interval is measured from the beginning of the QRS complex to the end of the T wave. Normal values for the QT interval are between 0.30 and 0.44 (0.45 for women) seconds. The QT intervals as well as the corrected QT intervals are important in the diagnosis of long or short QT syndrome. The QT interval varies depending on the heart rate and various correction factors have been developed to correct the QT interval for heart rate. The QT interval represents the total time needed for the ventricles to de- and re-polarize.

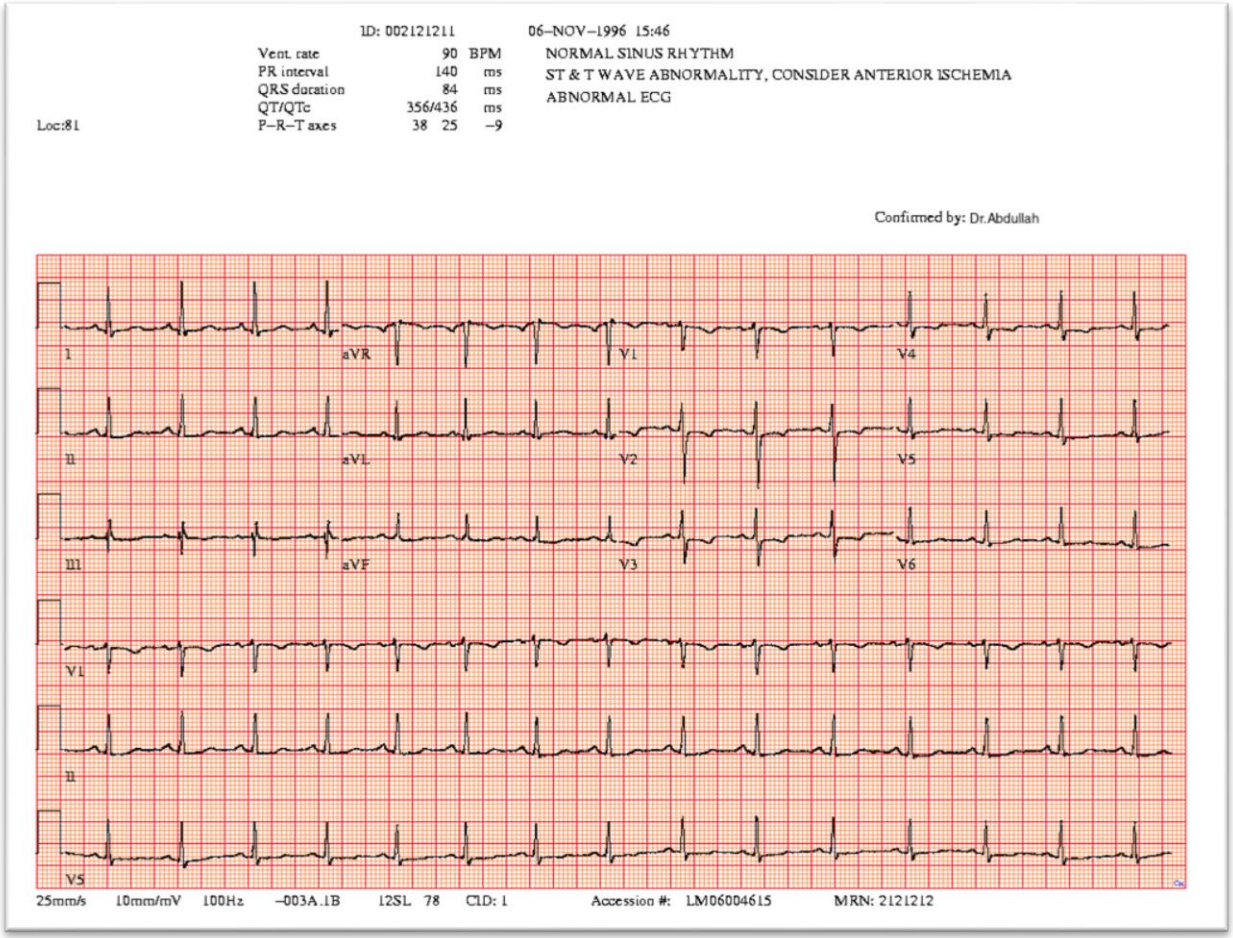


Figure 2.7. 12 lead ECG

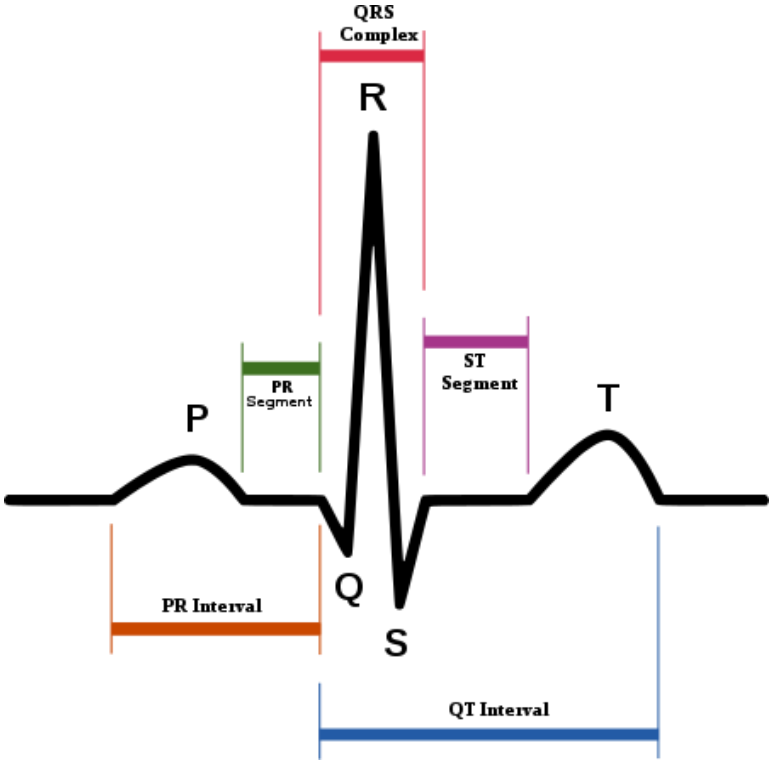


Figure 2.8. Schematic representation of normal ECG trace

In a QTc (QT corrected) clinical study the ECGs taken from different volunteers need to be over-read by cardiologists due to the fact that determination of the end of T wave is much more complicated. This process involves 3 cardiologists where the 1st cardiologist would either confirm the machine reading of QT interval or re-measure it and set the interval manually. Some ECGs were also marked as un-measurable due to the quality of ECG trace and rejected. In the case when QT interval was re-measured or ECG was rejected, these ECGs were checked by a 2nd Cardiologist who either agreed with the first or sets his/her own QT interval by setting the T mark. In cases when two cardiologists disagreed on ECG exclusion or QT interval measurement, the set of ECGs is re-examined by the 3rd Cardiologist (Senior cardiologist) whose decision is final. These ECG values are exported and analysed by a statistician. During an ECG review Cardiologists are also required to fill an ECG Review Form containing about 54 fields.

To keep the ECG readings clear from bias caused by other factors such as time of ECG, age and gender, all ECGs were blinded by removing all demographic data.

The Muse® system is server based software which allows ECG management and performance of different operations including measurements. Removing demographical and other data from ECGs manually requires 3-4 minutes per ECG using the Muse system. Having 26,000 ECGs blinding would take 1300 man hours or 162 days as a minimum. To automate this process a set of tools was developed for faster and more reliable management of the ECG review process.

2.3.2 ECG Management

The Muse system consolidates an interval editor allowing precise manual measurement of various ECG parameters but lacks automation. Since ECG review processes are hierarchical, ECGs are uploaded into different sites to be reviewed by cardiologists. In order to speed up the processes ECG Management application was developed to automate them. The application consists of four sub modules: **ECG Blind, Blind Database Query, XML Extract** and **Data management.**

2.3.3 ECG Blinding Tool

The application for exclusion of demographical data from ECGs was named **ECG Blinding Tool** which not only removes demographical data from ECGs but assigns selected ECGs to corresponding Muse system sites. A screenshot of the main window is shown in Figure 2.9 below.

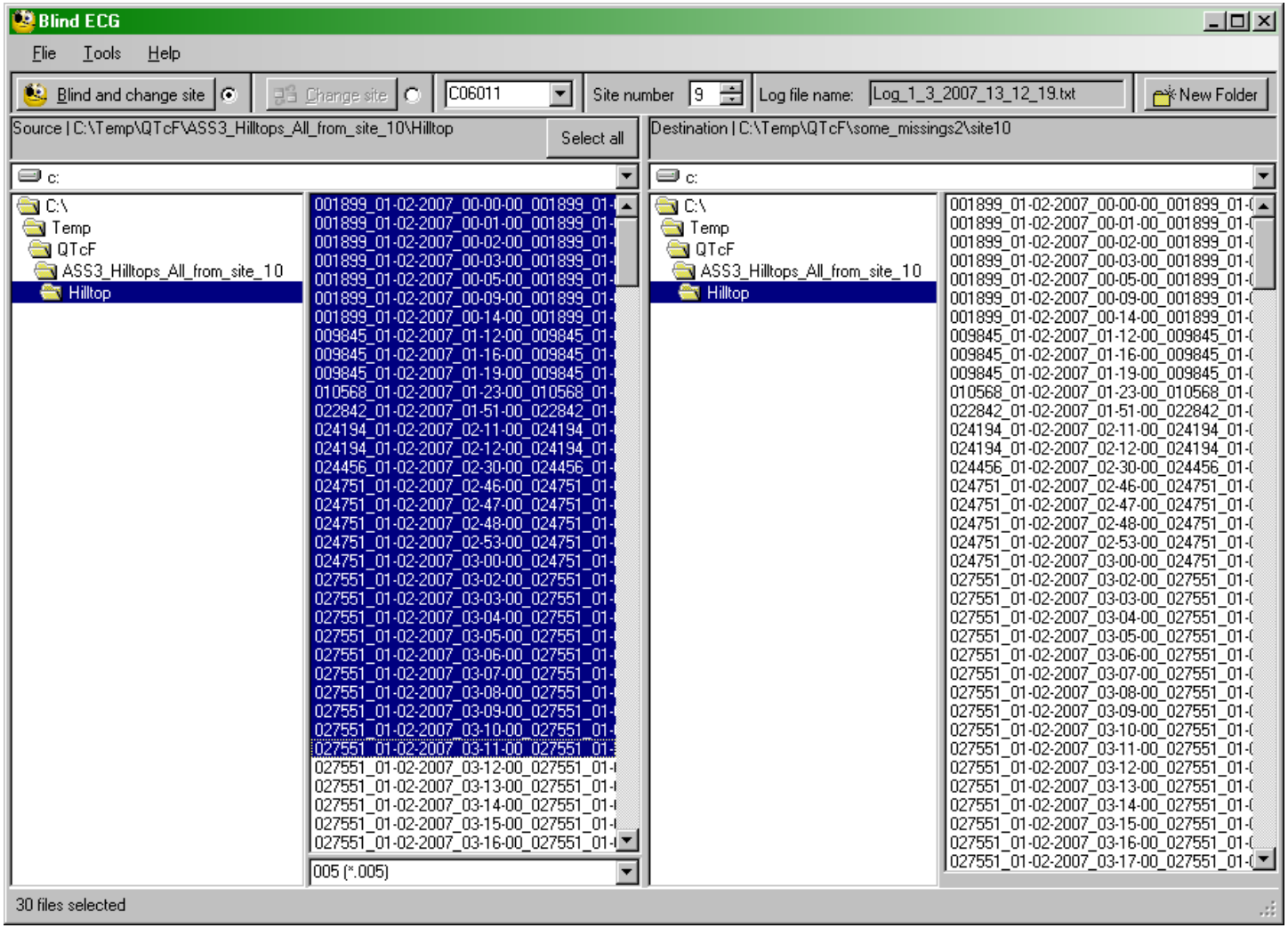


Figure 2.9. ECG Blinding Tool screenshot.

The process involves the following steps:

- ECGs are exported from the Muse system
- Demographic data from all ECGs are removed and stored
- Unique ID and Date-time codes are defined for each ECG
- The code is assigned to ECGs and matched to corresponding data removed from ECGs
- ECGs site is changed into relevant Muse site for review.

Software ensures that a unique ECG code is maintained throughout the study and one code represents only one ECG.

The whole process guarantees that Cardiologists perform blind reviews. Taking into account the same number of ECGs described above the process of extraction and processing with the use of the software takes about 5 days. The process has not only been accelerated 33 times but also improved by minimizing manual work and increasing data consistency.

2.3.4 Blind Database Query Tool

Stored ECG data can be viewed using the Blind Database Query tool (Figure 2.10 below). It has a number of filter options facilitating retrieval of large data volumes from the server. Initially the software was also used to create ECG Review Forms to reduce the cost of the review process. Later paper review forms were replaced by Electronic ECG Review forms.

2.3.5 Electronic ECG Review Form

The process of ECG review is means that cardiologist reviews an ECG by performing analysis and fills a paper form with over 50 fields. Every single form is entered into a database using double data entry technique with a mandatory 10% quality check. it should be pointed out that for the mentioned 26,000 ECGs data entry alone requires about 860 man hours.

Electronic ECG Review Form was developed to allow cardiologists to fill them as they go along with the review. This eliminates not only the data entry but preparation and printing cardio review forms and eliminates the use of printed paper.

ECGs are reviewed using a generic software Muse Interval Editor ® developed by GE Healthcare. By opening an ECG using Interval Editor, the Electronic ECG Review Form application opens the corresponding ECG Form automatically. Cardiologists fill the form after a review was performed and signs the form electronically (Figure 2.11

below). Colour coded table with the list of ECGs to review display the outcomes of reviewed ECGs and indicates whether the form was filled incorrectly.

The software is linked to the Muse server terminal using Windows API functions, where cardiologists review and analyse ECGs while filling the form. It is in a password protected environment and after a successful login, the program checks automatically whether the same user is logged into the Muse system. This feature is important representing a part of the intelligent management module, where by opening any ECG in Muse for review – the corresponding review form is automatically opened.

The form has different types of warnings for incorrectly selected patient or accidental error in ECG selection. If the form is filled incorrectly it is indicated by a red background for the cardiologist to be reviewed later. During the form filling, the system checks the data for inconsistency and prevents data entry mistakes. The layout of the form is identical to the forms previously used by the cardiologists.

In short, the data entry process for ECG review forms was removed and the process of ECG review significantly enhanced.

2.3.6 ECG Data Management Tool

The last software tool included in the ECG module is ECG Data Management tool. The main purpose of the tool is to assist with ECG preparation process for level 3 ECG review (Figure 2.12 above).

Features of the software tool:

- ECG preparation for the 1st 2nd and 3rd cardiologists;
- Import ECG values to database;
- QC of imported ECG values;
- ECG review reports, for monitoring and management of the ECG review process.
- Database management;
- Data Export.

The ECG module was tested and validated then used in a five real studies and proved to be highly effective. In particular: manual review progress monitoring has been replaced with electronic version where the number of ECG for review and outstanding number of ECGs are displayed in a table reflecting current ECG review state; 36 rule checks are performed on electronic data for possible erroneous ECG Review Form values; electronic data exchange between Muse server and Oracle Clinical databases.

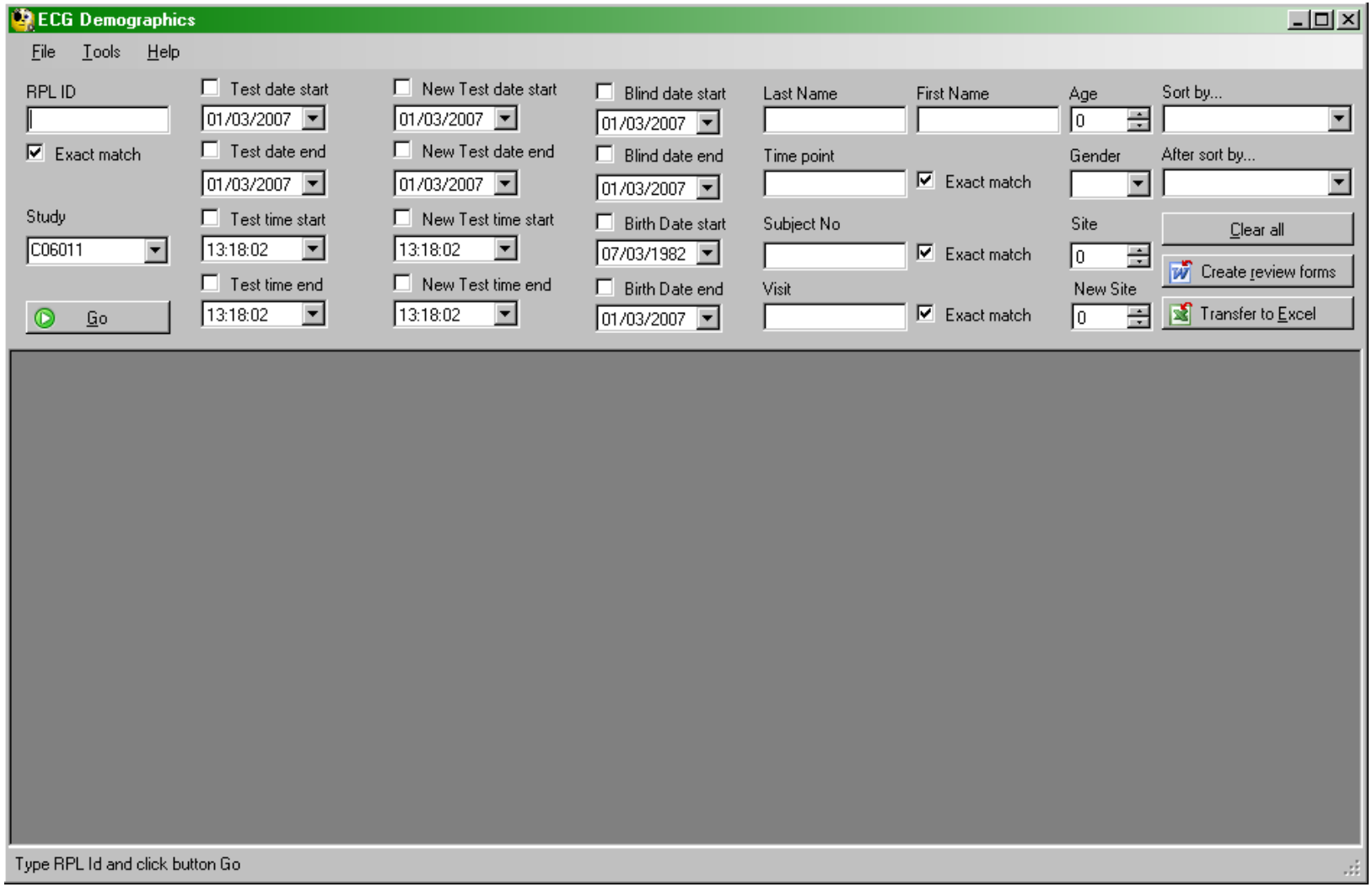


Figure 2.10. Blind Database Query screenshot.

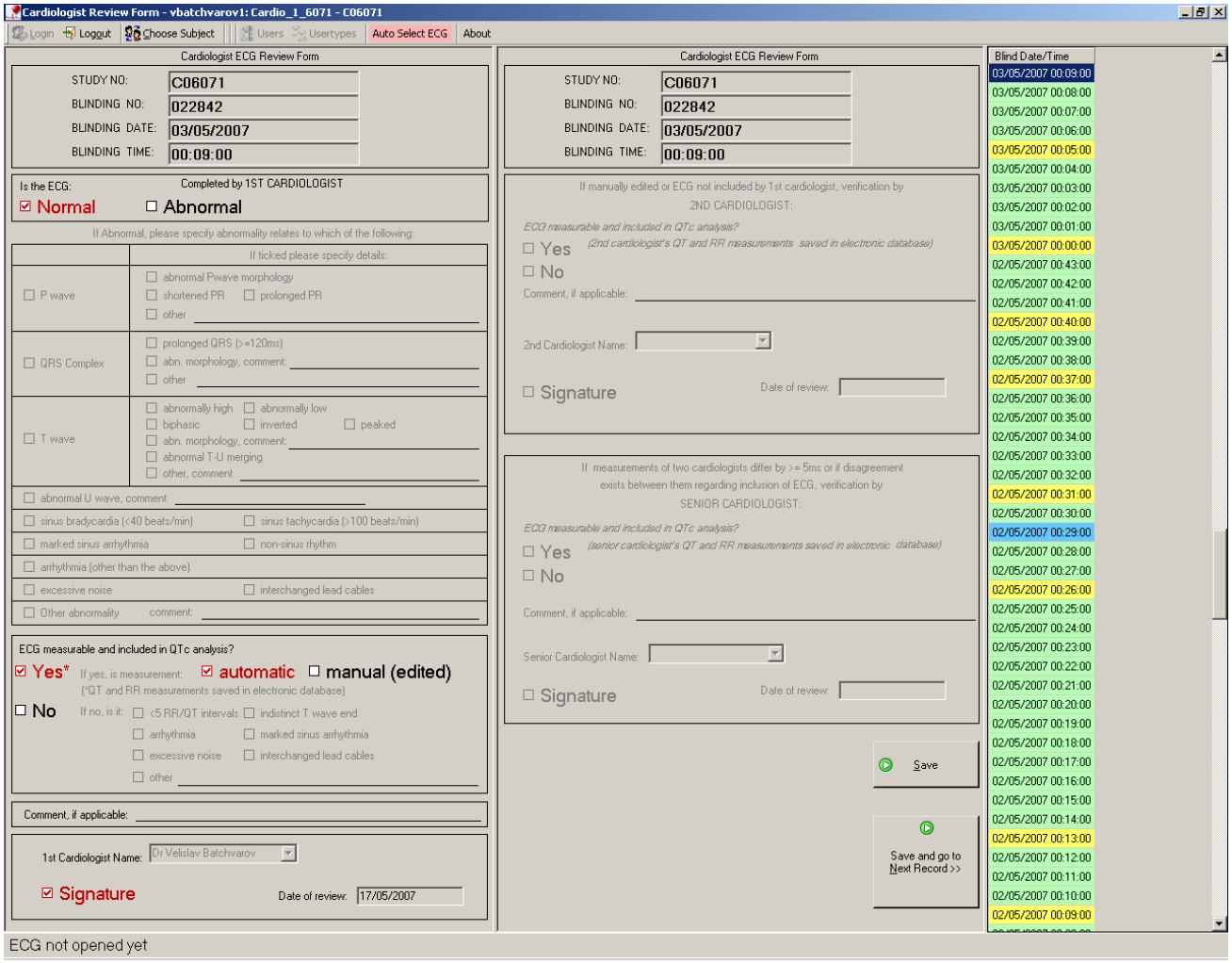


Figure 2.11. Electronic ECG Review Form screenshot.

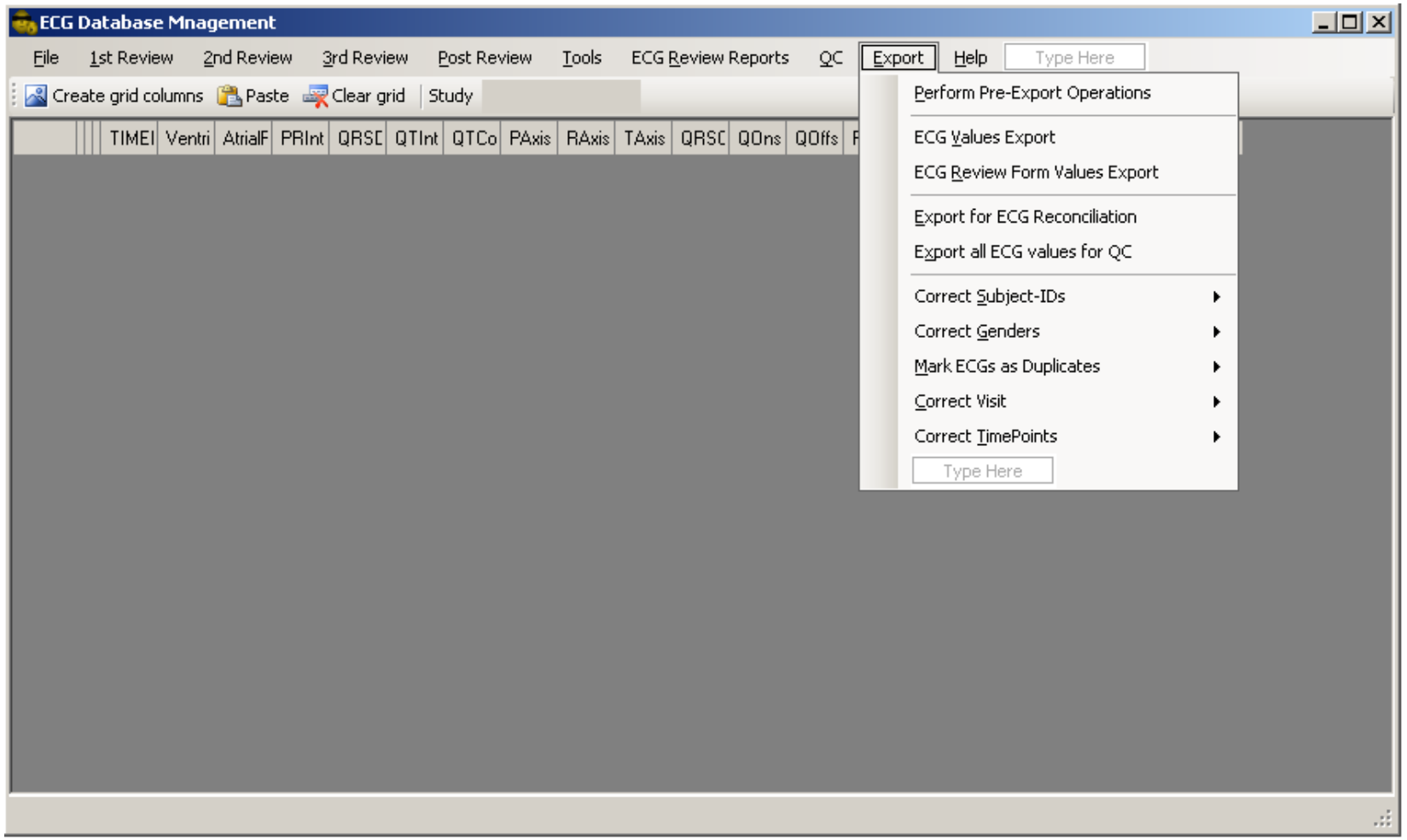


Figure 2.12. ECG Data Management Tool screenshot.

2.4 Blood Pressure and Finometer modules

Data collected during clinical trials depend on the type of medical treatment tested. However, the majority of Phase I trials require standard data such as blood samples and Vital Signs (blood pressure and temperature). All relevant information is always provided in a Clinical Trial Protocol, a document describing the organization of a clinical trial, objectives and methodology. The protocol usually sets eligibility criteria for volunteers, tests' schedule, procedures, medications and dosages, study length. Usually all measurements are recorded into CRFs (Case Report Forms) - questionnaires specifically used in clinical trial research as a primary data collection tool for the investigator's site. Provision of full, complete and accurate data and all associated documents is essential. However, the current paper based approach creates a number of problems including document storage and reliability of the collected data.

Clinical trial assistants (CTAs) are responsible for checking the correct input of data into CRF forms at scheduled times. The standard procedure is identical for every volunteer and requires

- Switching the device on,
- Putting the cuff on the volunteer's arm
- Performing a measurement
- Recording the Blood Pressure values from the Dinamap device immediately

Once the trial is finished, all collected data (CRFs) are entered manually and several independent checks are conducted to avoid data entry mistakes. Only then are the data records presented in electronic format to a sponsor (organisation funding the study, normally a drug manufacturer). Data collection and especially data entry are prone to mistakes, since they are monotonous and repetitive processes. Hence after double data entry quality control (QC) checks are performed.

The "blood pressure" module is for recording, storing and processing discrete blood pressure data. It was developed as a module incorporating Scheduler database. A pervasive computer was used to successfully address the problems described above by directly recording measurements from device to a proprietary database without intermediate manual recording to CRF and subsequent manual data entry.

The software has full control over the device through serial port connection and specifically developed communication protocol. Communication protocol involves a sequence of commands sent through the serial port to obtain data from Dinamap such as: device state, Diastolic and Systolic blood pressure.

2.4.1 Hardware design

The Automatic Electronic Data Capture System was designed for use in a ward hence the mobility of such a system is of prime importance. Following a thorough analysis of different technologies and related operating system (OS), the choice was Windows based system either using small size laptops or handheld PCs with Windows Mobile OS. They operate as an intermediary between the device and a database.

Dinamap is a portable blood pressure measurement device and can be carried around a ward using a stand on wheels. For added mobility either a laptop or Pocket-PC (PPC) (Figure 2.13 below) with wireless connection is used as a host data acquisition device. PPC is attached to Dinamap communicating through a serial adapter. The system incorporates a barcode reader for scanning Patient IDs from the volunteer's card. A security procedure is introduced to ensure that blood pressure is taken from the right volunteer at the right time by comparing the time slots to the scheduler database.

For a Pocket-PC the software code is written using a different set of libraries to address the operating system limitations. The connection scheme is also different as the Pocket PCs have neither USB nor Serial port connections.

Figure 2.14 below shows the system interface using different types of adapter cables to make possible the communication between the devices. Since PPC (a) has only one USB port a hub (b) is used to increase the number of USB ports. USB to PS2 adapter (c) is then used to connect a Barcode reader (d) to the PPC. In more recent versions the USB barcode scanner is directly connected to the USB hub (b). A barcode scanner is used for scanning barcodes on Volunteer's cards for taking blood pressure measurements and to scan Employee's cards during logging in to the software. USB to Serial port adapter (e) is used for connecting Dinamap (g) through serial cable (f).

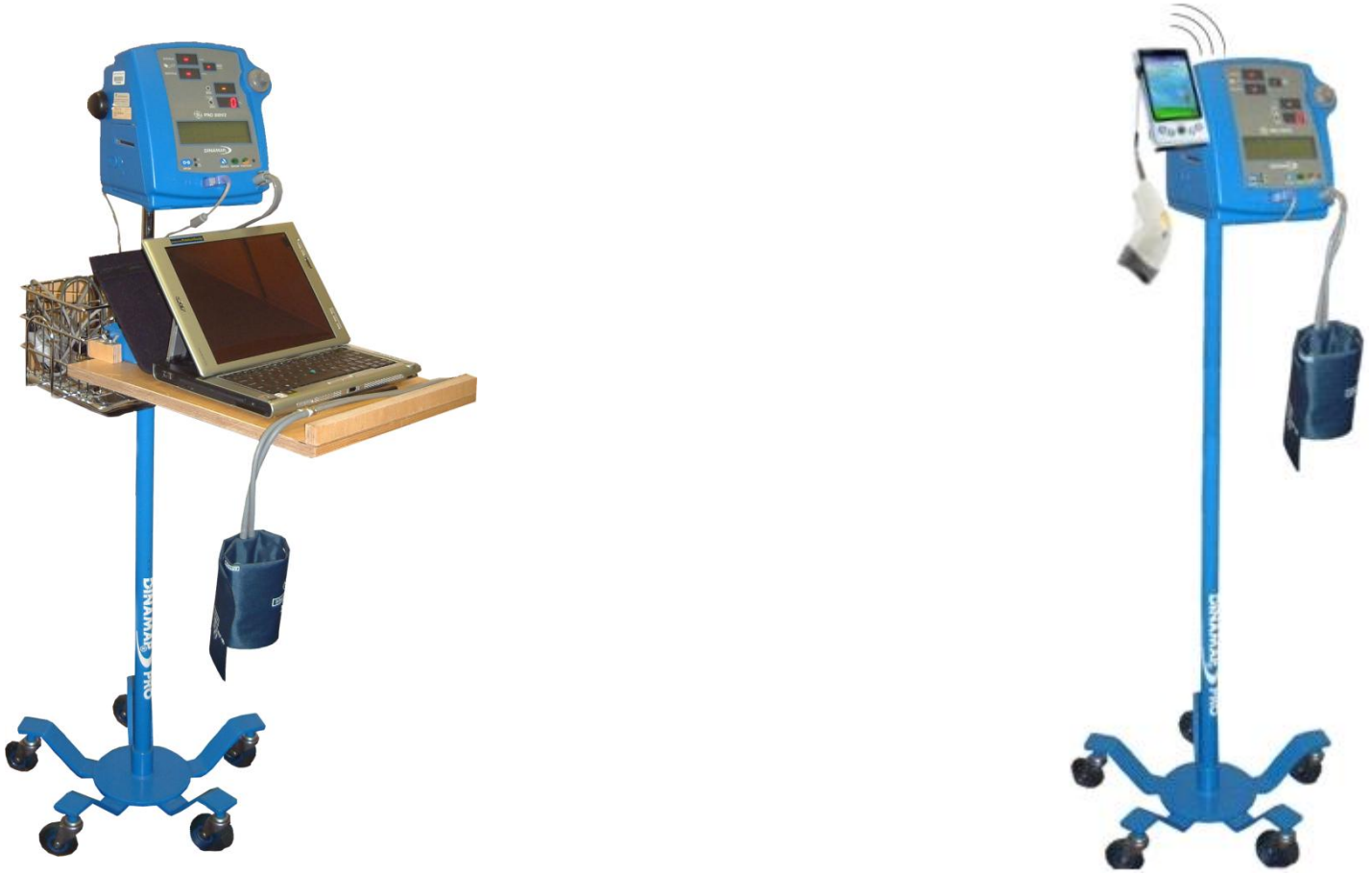
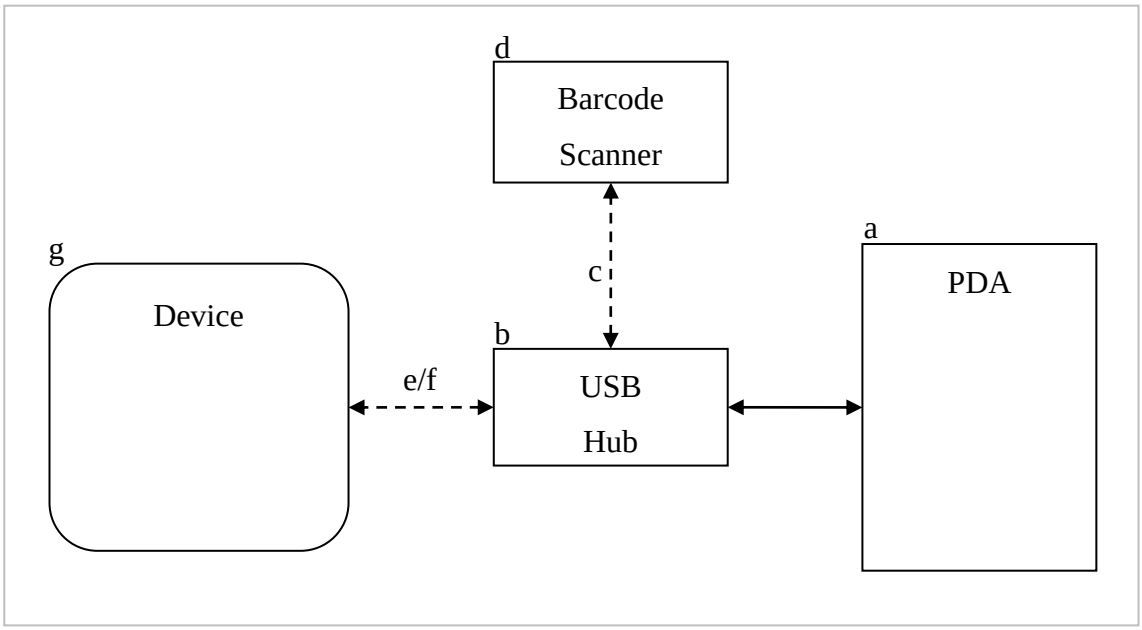


Figure 2.13. Hardware setup for Dinamap using a Tablet (left) and Pocket PC (right).



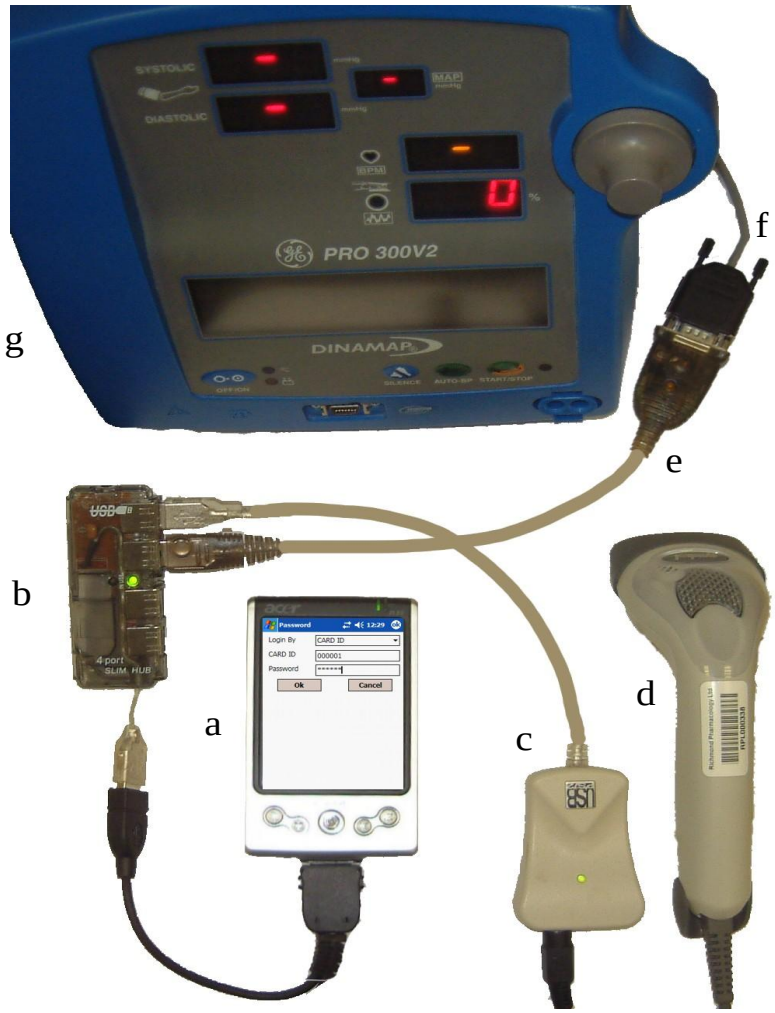


Figure 2.14. Hardware Design and Interfacing with pocket PC.

2.4.2 Software description

The screenshot of the software developed for a PC based system is shown in Figure 2.15 and its prototype for Pocket devices is illustrated in Figure 2.16 below.

For security reasons a password system was implemented into the application conducting a user check prior to using the software. Login can be performed using either Card ID or username. There is also a potential to replace the login system with a finger print reader. The graphical interface replicates the Dinamap device and its active buttons. Once logged in the user's schedule is automatically presented on the screen with active fields that allow either device specific or user tasks to be managed. Each task contains specific information as well as patient ID.

Every single measurement is followed by scanning and confirming patient's ID, therefore readings cannot be recorded unless the patient is identified and checked against the existing schedule. Barcode readers are implemented for this identification to simplify the process and prevent possible data entry errors. Hence patients IDs are printed using barcode font.

The system was developed with the intent to use it intensively during clinical trials and the drive was to be as user friendly as possible. Hence the approach was to emulate the use of the actual system that staff is already used to. Blood pressure is hence measured in just 3 intuitive steps:

1) CTA clicks on a scheduled task.
2) Confirms Patient Id by using barcode reader.
3) Blood pressure determination starts automatically after confirmation. After completion a record is created automatically.

Although a three step operation for taking a measurement is used, there are a number of processes running in the background.

- The system checks regularly the connection to the device used.
- After each task selection the system expects a patient ID to be scanned.
- During ID entry, another function is checking whether barcode reader is used and not a keyboard. In the latter case a warning message is displayed.
- Once patient ID is entered, which should be no more than 6 numeric values, the system performs another set of checks including whether it matches the task information and whether the scheduled date and time of the task is sufficiently close to current.

Figure 2.15. Blood pressure module screenshot (PC system)

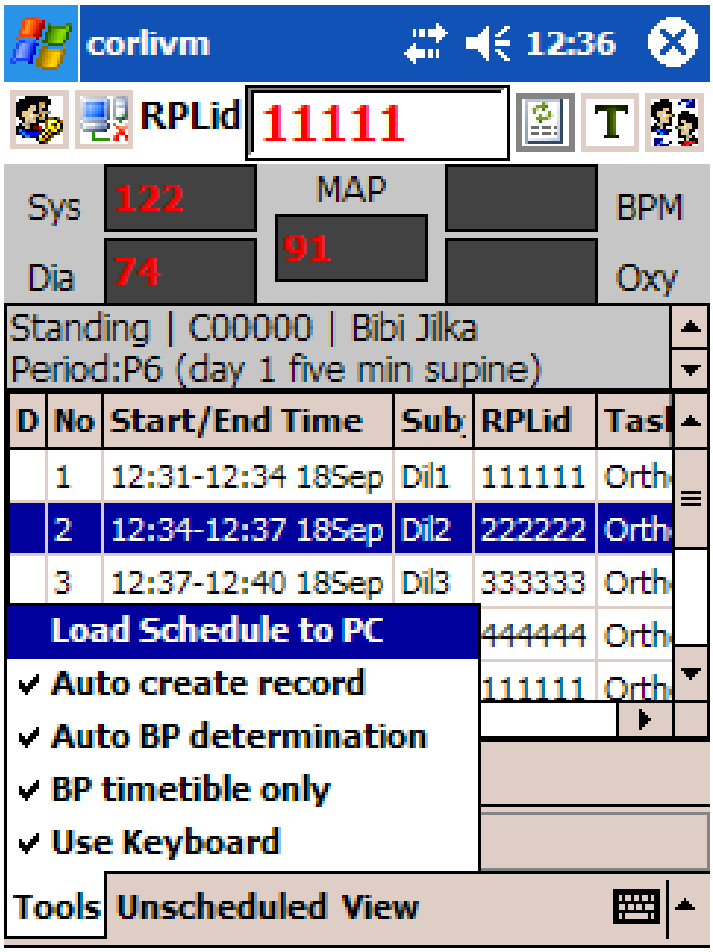


Figure 2.16. Blood pressure module screenshot (Mobile PC systems, PDA)

- If so, it starts a measurement automatically, after confirmation. This was achieved by full control of a device through PC software.
- Once a measurement is successfully performed, the system allows a comment entry if applicable. Then creates a record checking whether any records were created for the current task. If affirmative all consecutive records are created as a repeated measurement.
- During every single operation requiring server access, the system creates a local record if connection fails.
- Once measurement is created a query is also created to retrieve the same record and each value is compared against the data currently stored in the PCs temporary memory. This operation ensures the correctness of the record.
- Another function is responsible for checking whether the obtained readings are within the allowable thresholds by suggesting repeating the measurement.

In cases when a CTA becomes unavailable, then a nurse (trouble-shooter) can take over through scanning the ID card with a barcode reader. This technique is used for a quick change during emergency situations. A similar solution is provided for replaced nurse; they can login and retrieve the schedule of the person they are replacing. All actions are then recorded in the database that keeps track of user replacements.

The system is designed to run in the absence of direct database connection. In such cases the system saves all data into the local drive and once the connection is restored the data is copied over to a server.

The majority of the system features are adjustable. The simple interface features such as font size or schedule location can be set using menu items.

The schedule is fully colour-coded allowing a user to better manage tasks. Green colour indicates a successfully completed task while red background indicates that urgent attention is needed, i.e. tasks are either delayed or missed.

The PDA version of the system contains the most important features and modules of the main PC software, but limited by the device constraints.

The Finometer module is a similar application for management of a beat-to-beat arterial blood pressure data. This device allows noninvasive haemodynamic monitoring and developed by the creators of Finapres™, Finometer™ and Portapres™. Finometer is a stationary Finapres based new beat to beat finger arterial blood pressure and haemodynamic monitor featuring:

- non-invasive continuous beat to beat monitoring of the finger arterial pressure waveform;
- beat to beat Brachial arterial pressure waveform reconstruction and level correction from finger arterial pressure;
- cardiac output, stroke volume and peripheral resistance computation.

Since the device is supplied with its own software "Finolink", we utilised the capabilities of the "Finolink" by monitoring and controlling by use of Win API functions. Communication with the device is possible through "Finolink" only, therefore taking control over the software helped us to take control over the device. The device produces large output files as continuous information is recorded and subsequently analysed.

The hardware connection scheme is shown in Figure 2.17 below and consists of a Finometer – the continuous blood pressure measurement device, tablet PC and database server for storing the data.

The device consists of a main unit with a display, arm attachable Front End device, finger cuff, hand cuff and a height correction sensor. A finger cuff attachment is shown in the Figure 2.18 below.

A screenshot of the system is illustrated in Figure 2.19 below. The software has almost identical features to those implemented in the Dinamap module including quick user change, troubleshooting, replacement of an absent nurse, schedule, barcode reader and security checks.

The process of taking measurements is as follows:

- The application is started and a qualified user (CTA or nurse) logs in.
- The corresponding Schedule is automatically loaded to the screen consisting of a different set of tasks.
- User selects a task and confirms patient's ID.
- The system automatically starts the software for communicating with the device. All required settings, such as patient information, are automatically imported into the software.
- User performs a measurement using the software and closes it.
- Once closed the system takes over the results and saves them to the database.
- The performed tasks background colour will be changed to green representing a completed state.

To make the task schedule easy to follow a colour coding is used, where performed tasks are coloured in green and any missed tasks background colour will be changed to red.

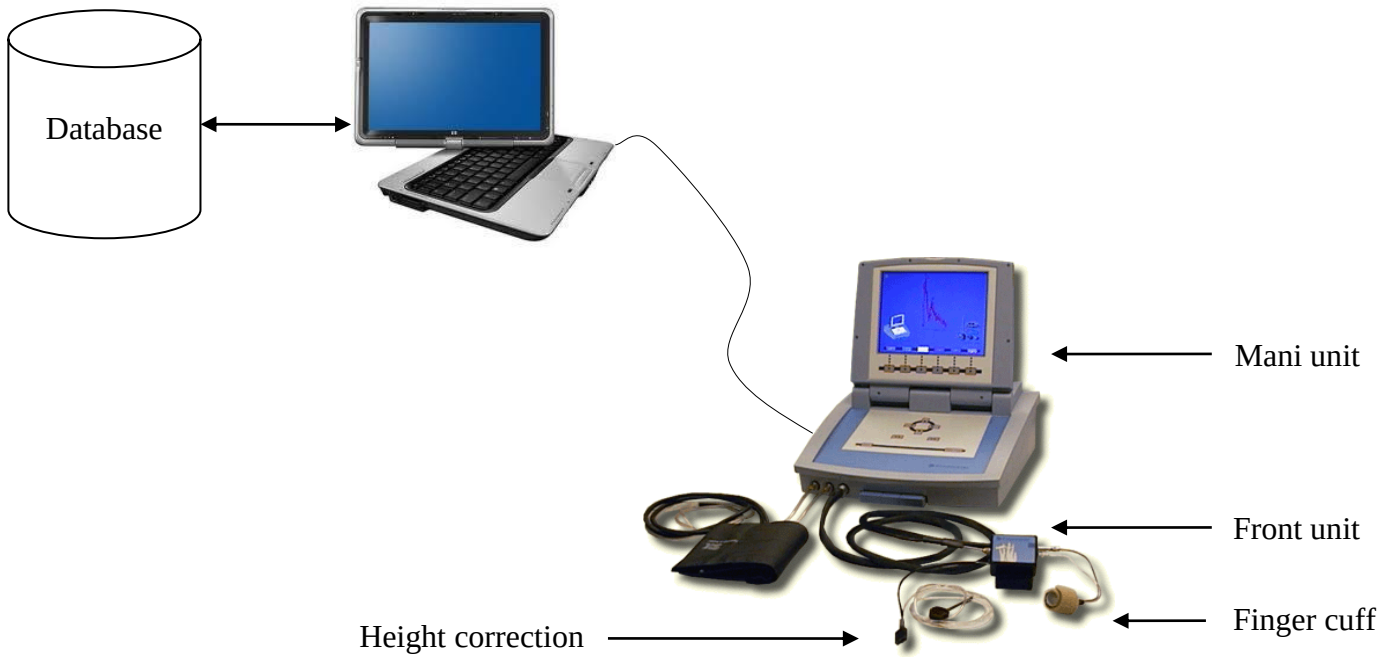


Figure 2.17. Hardware connection for Finometer.

Figure 2.18 Finometer cuff attachments.

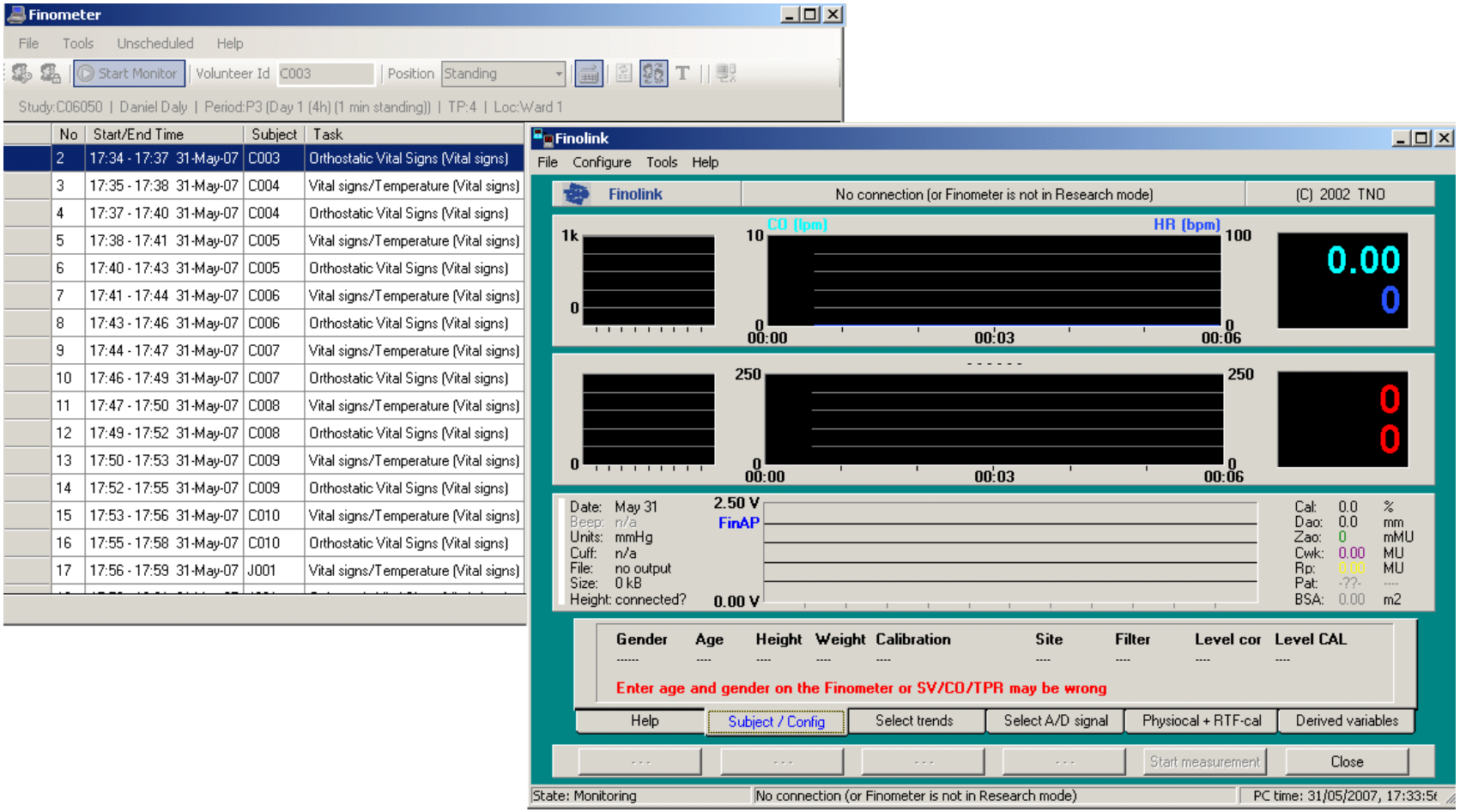


Figure 2.19. Screenshot of the Finolink software controlled by Finometer application.

2.5 Spirometer

Spirometer is a device for recording, storing and processing lung function data providing lung volume and flow measurements (Figure 2.20 below). Each device comprises of a main unit with built-in printer, a screen and a flow meter with detachable attachments. RS232 connection allows direct access to the device through Spida5 software. Due to the device specifications, every reading requires patient data such as age, height, weight etc. Initially, manually entered, these data can be saved and retrieved when needed.

Figure 2.20. Cardinal Health (Micro Medical) Spirometer device.

Standard procedure of using the device in clinical trials is as follows:

- The CTAs are given a schedule, according to which they perform different type of measurements for a number of volunteers.
- Before the start of a measurement round with a Spirometer, the CTA prepares the device by switching it on and entering patient's information such as Patient's ID, initials, weight, height and age then performs the measurement.
- After a measurement is performed the device produces a number of resulting values which vary between 12 and 25. Depending on a the Study Protocol, required values are selected and recorded by the CTA to a CRF (Case Report Form).

- At the end of the study all data are entered to a database using double data entry method with either 10% or 100% quality check depending on study requirements.

Data collection and data entry procedures are time consuming and have a predisposition for mistakes during transcription to CRF and data entry.

Procedures using data acquisition systems are comparable in complexity as intermediate tasks are simplified. In the particular case:

- CTAs do not have to carry their schedules since the software has an integrated schedule. Additional advantage is that the software displays the last version of the schedule in case it was amended.
- CTA prepares the device as usual with the difference that it has attached either laptop or PPC (Pocket PC) and starts the software by logging in and identifying themselves using a barcode reader. The system uploads the colour coded schedule automatically and activate appropriate task as shown in Figure 2.21 below.
- Once the CTA confirms the patent's ID by scanning the badge the system is ready to start the measurement. Additional precaution is taken, in order to start the measurement, the CTA has to confirm patient ID using the barcode reader. These eliminates the possibility of taking measurements from a wrong volunteer or from performing an incorrect task.
- The system automatically pre-populates the patient's information further reducing data entry, since the volunteer database is accessed directly.
- Once all measurements are taken, every single measurement value is automatically recorded to the database. This enables the data management team to retrieve them when required.

As described above no manual data entry is involved when a data acquisition system is used. This is a feature of the algorithm to ensure accurate and clean data. The only possibility for errors is during commented recording, for which the most frequent comments have been stored to the system. Hence in the majority of cases CTA can just select from a dropdown list. System flexibility allows storing and amending stored list of comments automatically by analysing the most frequently used comments. In effect this is a built-in low level learning algorithm.

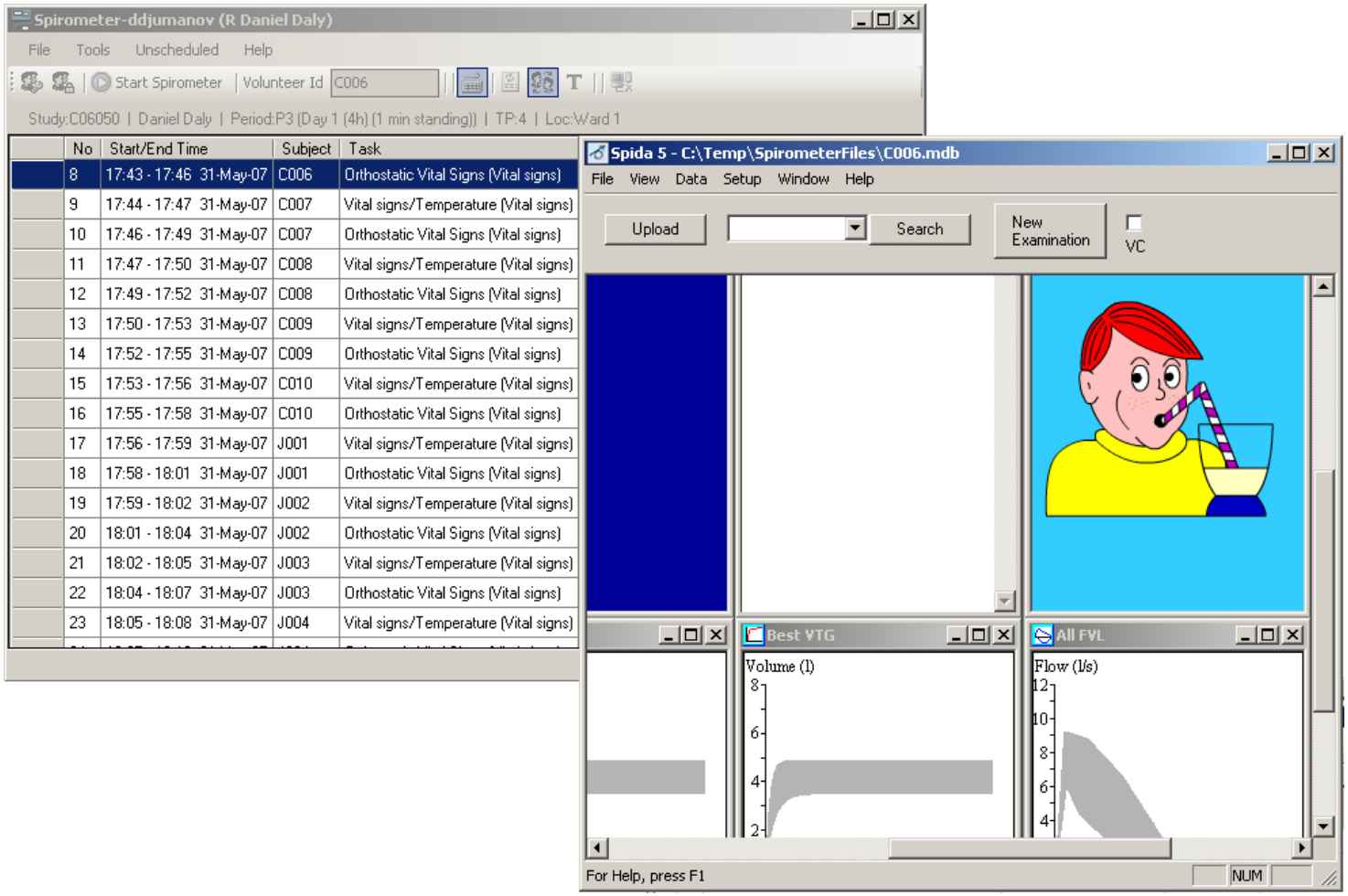


Figure 2.21. Spirometer Data Acquisition System application (left) executing Spida5 software (right).

2.6 Flexilog

Flexilog is used for recording, storing and processing gastric/intestine pH data. It is an ambulatory oesophageal pH recording device of acid reflux and for relating symptoms to reflux episodes. Controlled by three buttons the Flexilog records pH data continuously for 24 or 48 hours, depending on settings. Computer based analysis program "Flexisoft III", provided with the device, offers a comprehensive range of display and analysis options. Figure 2.22 below shows the Flexilog device with associated peripheral attachments.

The usual procedure of measuring PH data is:

- Flexilog is calibrated using provided fluids.
- At set date and time the catheters are inserted into a patient and recording is started.
- Patients are free to move within ward area and can be even sent home with the attached device.
- Once recording is finished the data is downloaded using Flexisoft software utilizing serial port of a PC.
- The data then analyzed and report is created by the software.
- All produced reports are saved in a network drive which is included into a daily backup.

The developed software incorporates partial automation to the standard workflow and is used only when downloading data from the device. Since the device has its own software module Flexisoft, the Flexilog data acquisition module integrated into the Flexisoft by the means of Windows® API functions, and has similar features to the Spirometer module. Once the module is started a clinical schedule of a user is displayed. Schedule consists of a list of tasks where each task is linked to a study, visit, timepoint and a subject. Selecting a task and clicking a button loads automatically the Flexisoft application for downloading data from the device. Once the downloading is finished and the application is closed, the downloaded file is processed by the Flexilog module and saved into a database by linking it automatically to subject's record and other task identifiers such as Visist and Timepoint. Figure 2.22 shows the Flexilog device with associated peripheral attachments. Screenshots of the developed Flexilog module are shown in Figure 2.23.

An advantage of the developed system is not much significant, although increases the reliability of the data by automatic linking study and subject details to measurements.

Figure 2.22. Flexilog device.

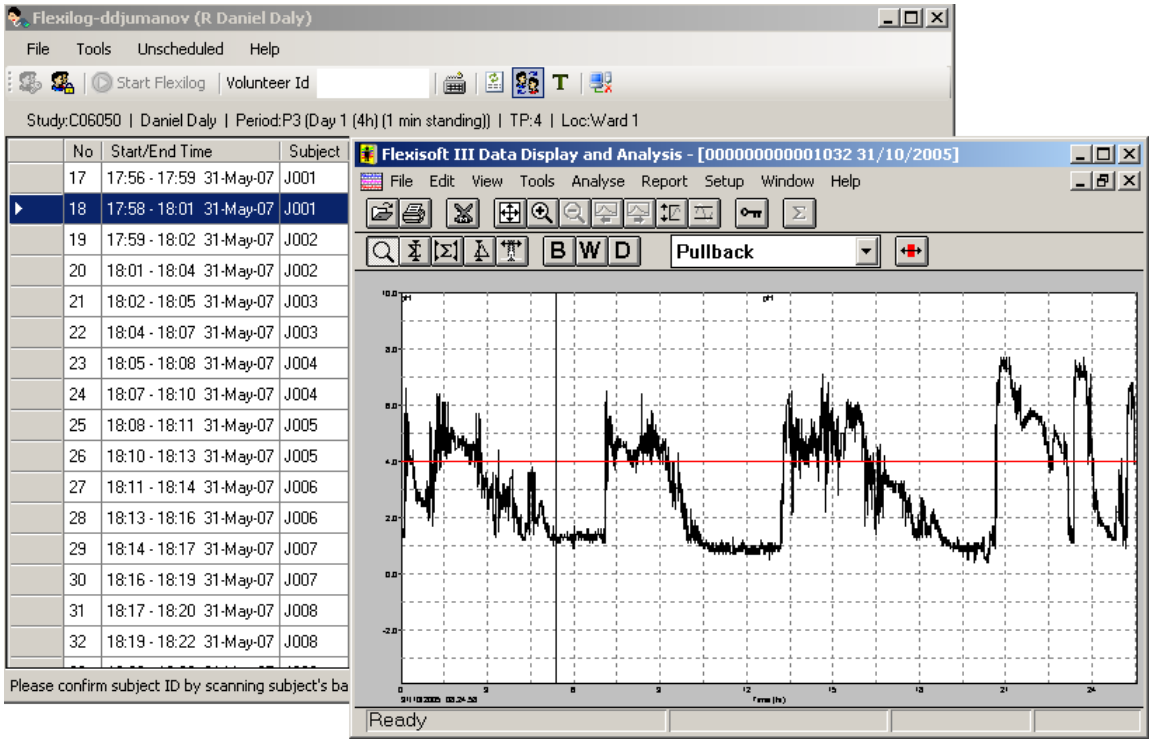


Figure 2.23. Screenshots of Flexilog and Flexisoft programs.

2.7 Administrative tools

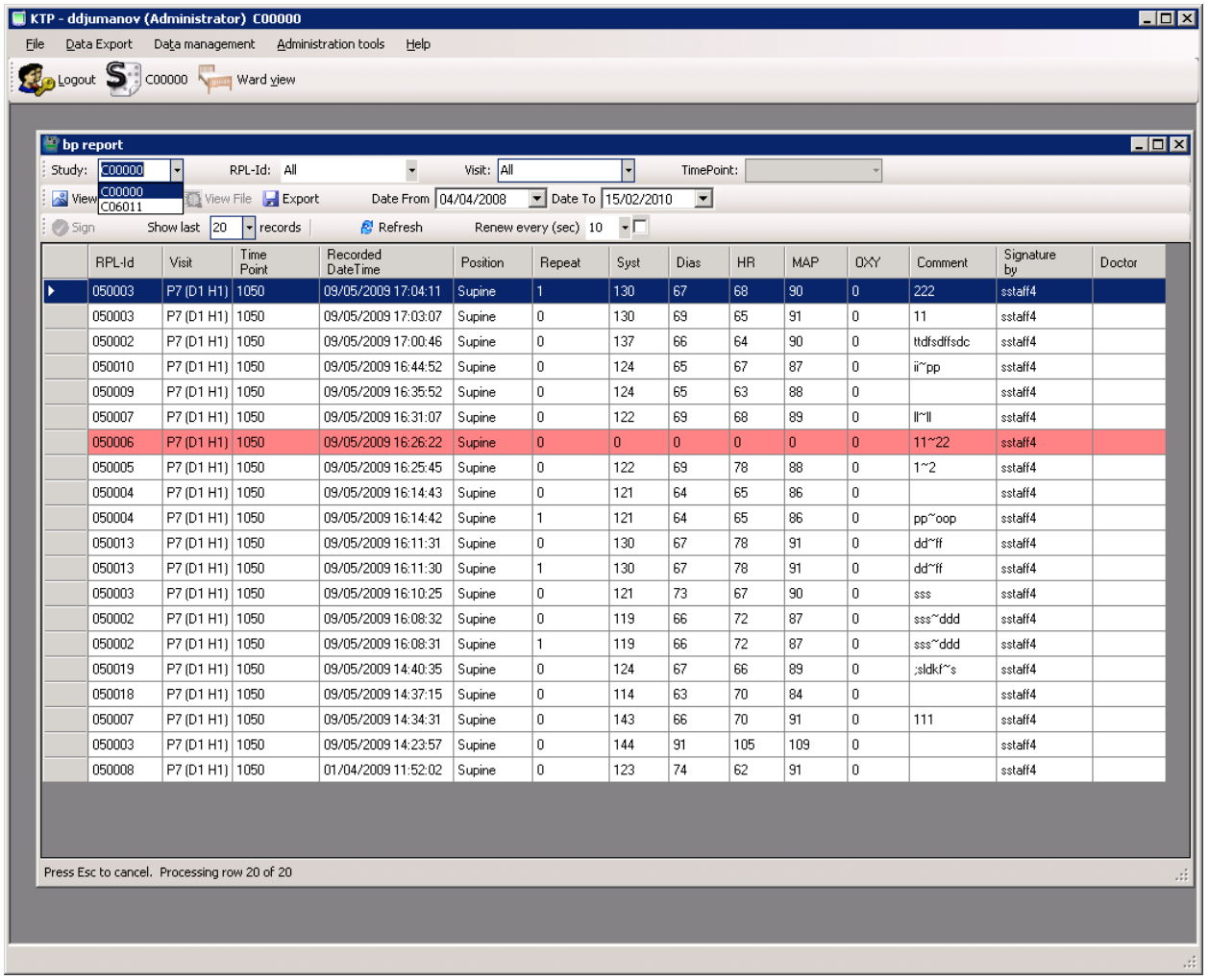
The Administrative module was developed to combine all the modules into one system. It is a customizable module with a set of additional tools is at user's disposal. This module is developed for processing, monitoring and controlling the data produced by the different devices. A manager can monitor all the processes and measurements taking place in any ward remotely even from a different hospital. The two main different types of reports are pre-programmed including table view and a ward view.

Table view represents a grid with downloaded data being refreshed at regular time intervals. The data may belong to any of the devices once the user chooses which fields to monitor. There is a set of filtering options available for a user as demonstrated in Figure 2.24 below. All displayed measurements are sorted in descending order - most recent measurements at the top of the result table. Users are able to display and hide monitored fields and data renewal frequency. If threshold values are set for a study, the measurements outside the threshold values are highlighted in red. This is particularly convenient for research physicians where they can request a repeat of seemingly abnormal measurements.

The ward view demonstrates graphically the ward layout where measurements are taking place. Since early stage clinical trials are conducted within a relatively short period of time each bed is assigned to a volunteer, to enable a study manager to monitor a study conduct having a ward layout on the screen. This is of even higher importance considering that are frequently simultaneous studies in the same ward. Figure 2.25 shows the dialog box for opening a ward view window which represents an interactive window with animations for realistic experience. The animations were created using an Adobe Flash animations integrated into C# desktop application. First, two hospital sites are displayed on a map, selection of a hospital displays a second level menu outlining ward locations. Once ward is selected it is displayed on a separate window with a layout of beds. The user has an option of changing the layout of beds and redesigning the ward using custom designing tools. Figure 2.26 demonstrates the ward design process. At the initial stage of a ward design each bed is assigned to a patient and each patient to a study. Designing a ward is very similar to most graphical applications, where general controlling rules and techniques apply. Objects such as walls and beds can be added, removed, dragged and rotated. Positions of beds are interchangeable and can be relocated as needed.

The screenshot of the software in Figure 2.27 shows the layout of a ward. After loading a ward, the study manager can pinpoint the location of each patient and identify their association to a particular study. Last 10 data readings, for example, blood pressure for a patient can be observed by simply selecting a particular bed. As every study has thresholds for the selected measurements, any readings out of these limits are highlighted with a different background colour. This allows monitoring and controlling of blood pressure readings and performing additional measurements if needed.

Study managers responsible for a particular study are solely allowed access to the data from this study. Remaining beds are deactivated (visualised as a faded image) if they belong to a different study.



RPL-Id	Visit	Time Point	Recorded DateTime	Position	Repeat	Syst	Dias	HR	MAP	OXY	Comment	Signature by	Doctor
050003	P7 (D1 H1)	1050	09/05/2009 17:04:11	Supine	1	130	67	68	90	0	222	sstaff4	
050003	P7 (D1 H1)	1050	09/05/2009 17:03:07	Supine	0	130	69	65	91	0	11	sstaff4	
050002	P7 (D1 H1)	1050	09/05/2009 17:00:46	Supine	0	137	66	64	90	0	ttdfsdffsdc	sstaff4	
050010	P7 (D1 H1)	1050	09/05/2009 16:44:52	Supine	0	124	65	67	87	0	ii~pp	sstaff4	
050009	P7 (D1 H1)	1050	09/05/2009 16:35:52	Supine	0	124	65	63	88	0		sstaff4	
050007	P7 (D1 H1)	1050	09/05/2009 16:31:07	Supine	0	122	69	68	89	0	ll~ll	sstaff4	
050006	P7 (D1 H1)	1050	09/05/2009 16:26:22	Supine	0	0	0	0	0	0	11~22	sstaff4	
050005	P7 (D1 H1)	1050	09/05/2009 16:25:45	Supine	0	122	69	78	88	0	1~2	sstaff4	
050004	P7 (D1 H1)	1050	09/05/2009 16:14:43	Supine	0	121	64	65	86	0		sstaff4	
050004	P7 (D1 H1)	1050	09/05/2009 16:14:42	Supine	1	121	64	65	86	0	pp~oop	sstaff4	
050013	P7 (D1 H1)	1050	09/05/2009 16:11:31	Supine	0	130	67	78	91	0	dd~ff	sstaff4	
050013	P7 (D1 H1)	1050	09/05/2009 16:11:30	Supine	1	130	67	78	91	0	dd~ff	sstaff4	
050003	P7 (D1 H1)	1050	09/05/2009 16:10:25	Supine	0	121	73	67	90	0	sss	sstaff4	
050002	P7 (D1 H1)	1050	09/05/2009 16:08:32	Supine	0	119	66	72	87	0	sss~ddd	sstaff4	
050002	P7 (D1 H1)	1050	09/05/2009 16:08:31	Supine	1	119	66	72	87	0	sss~ddd	sstaff4	
050019	P7 (D1 H1)	1050	09/05/2009 14:40:35	Supine	0	124	67	66	89	0	;sldkf~s	sstaff4	
050018	P7 (D1 H1)	1050	09/05/2009 14:37:15	Supine	0	114	63	70	84	0		sstaff4	
050007	P7 (D1 H1)	1050	09/05/2009 14:34:31	Supine	0	143	66	70	91	0	111	sstaff4	
050003	P7 (D1 H1)	1050	09/05/2009 14:23:57	Supine	0	144	91	105	109	0		sstaff4	
050008	P7 (D1 H1)	1050	01/04/2009 11:52:02	Supine	0	123	74	62	91	0		sstaff4	

Figure 2.24. Table view of a data refreshed at regular time intervals

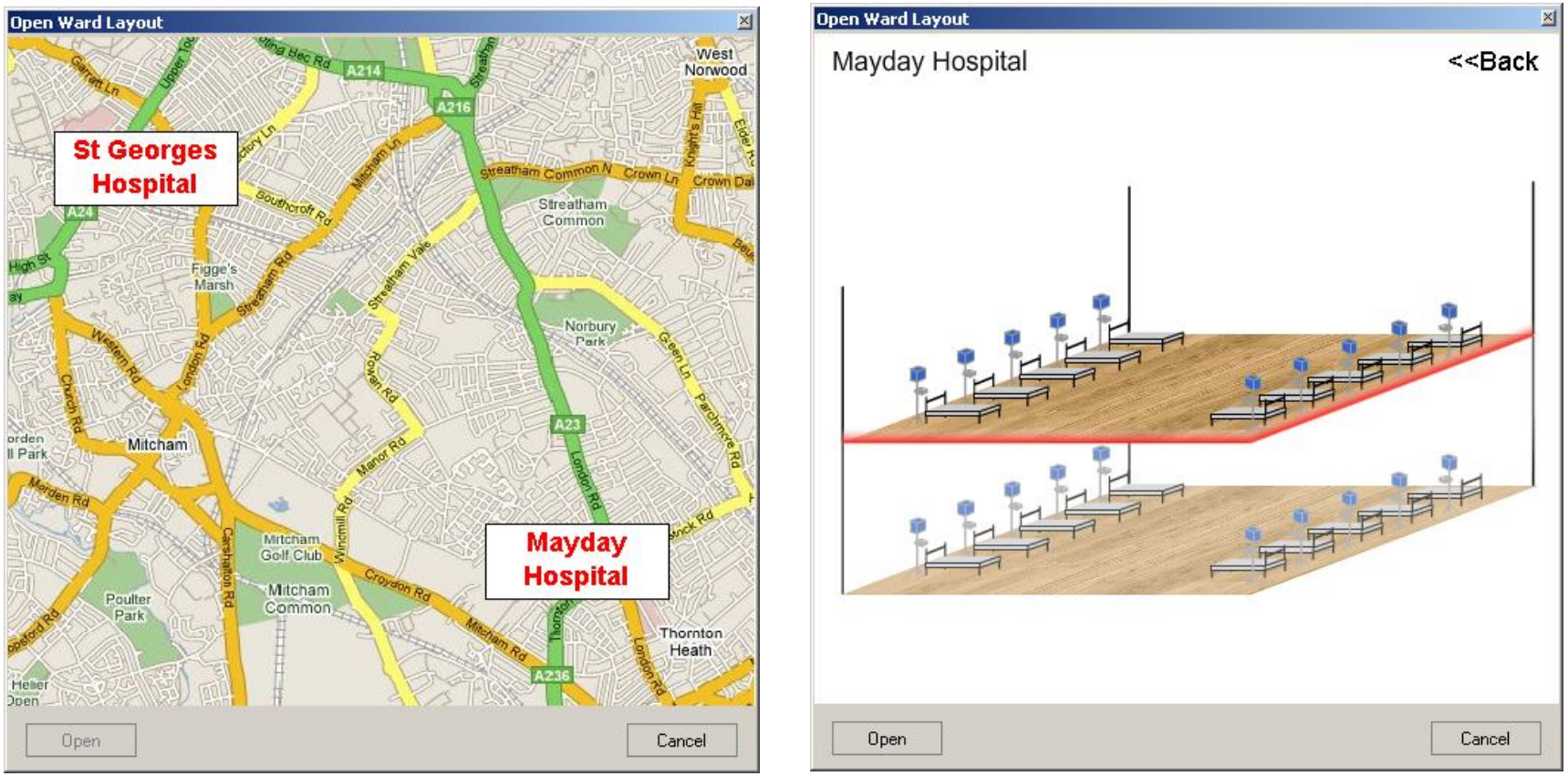


Figure 2.25. Animated graphical window for opening the ward for monitoring.

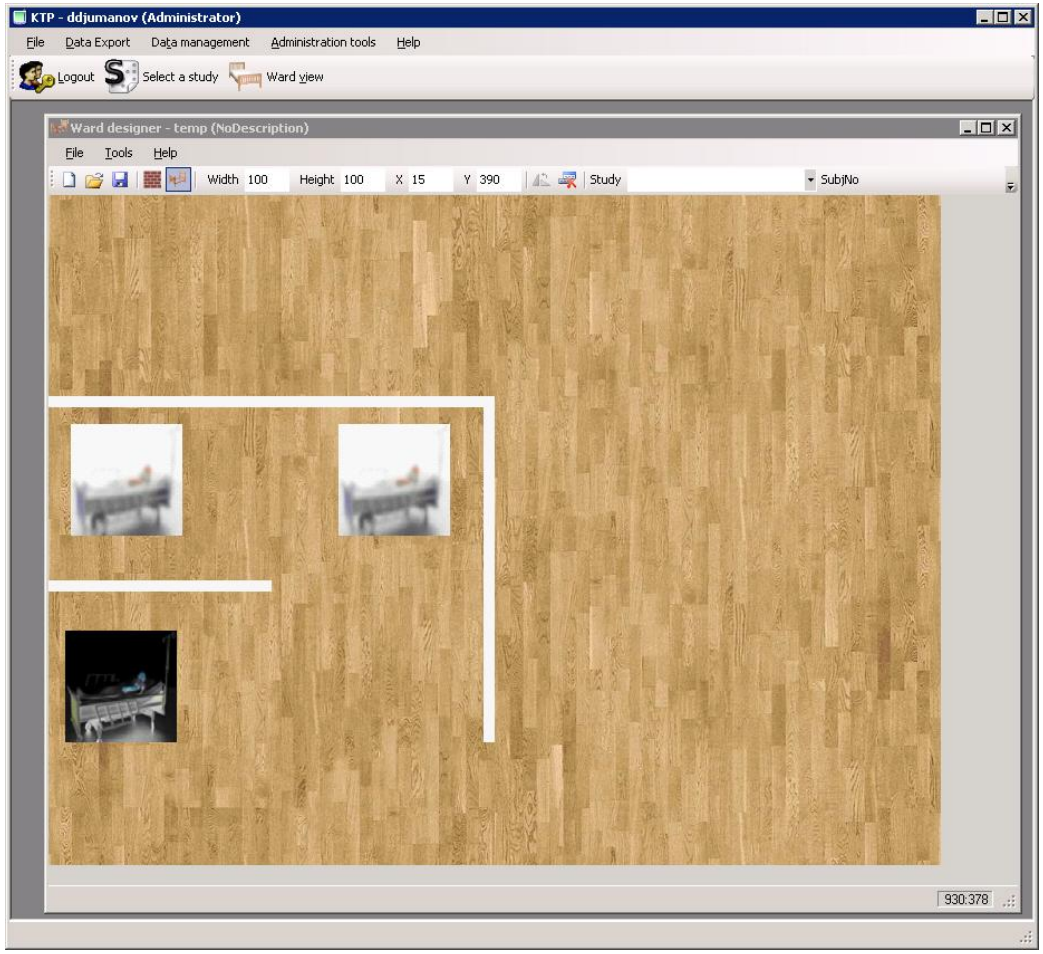


Figure 2.26. Ward design window.

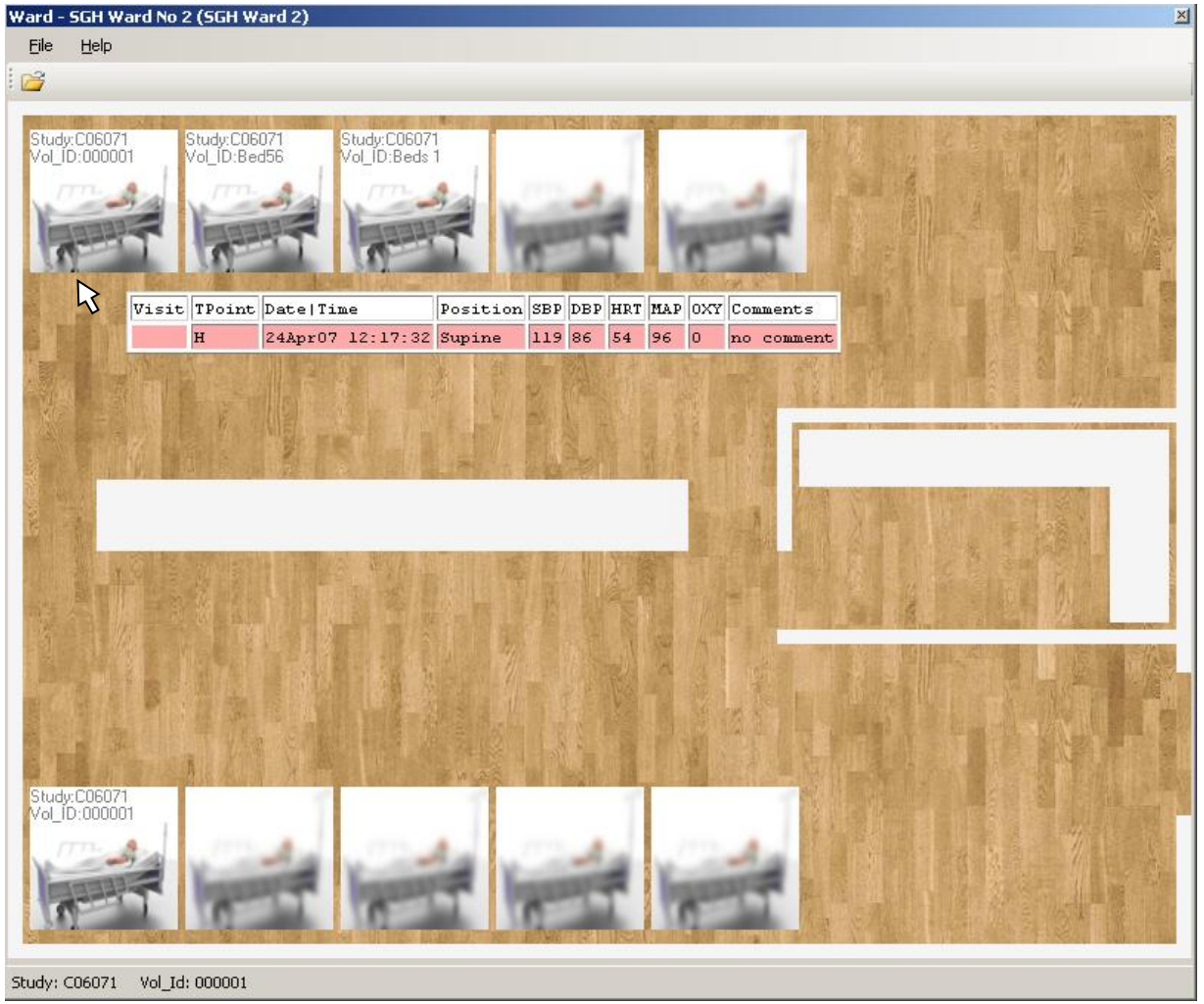


Figure 2.27. Interactive view of a ward for monitoring patient's vital signs.

2.8 Field test results

The system was tested in 2 stages for technical problems and usability features. The test procedure described below represents the test preformed for checking the parallel recording to a database from different devices at the same time.

System testing procedure (04.04.2008)

1. Study design – 2 groups of 10 subjects each.
2. Devices used:
    a. Group-1 (Dinamap, Spirometer)
    b. Group-2 (Dinamap, Spirometer, Finometer)
3. Number of CTAs: 5 (2 for Group-1 and 3 for Group-2).
4. Procedure:
    a. All CTAs are assigned mock usernames from Scheduler.
    b. Volunteers are assigned mock RPL-IDs 5 min prior test.
    c. CTAs are logging in 3 min before test and start-up software.
    d. Tests are performed according to a preliminary prepared schedule.
    e. Test measurements are recorded in parallel to CRFs by CTAs.
    f. In Group-1 two subjects are misplaced to check the stability of the system.
    g. In Group-2 a barcode-reader is switched off mocking an accident to test the stability of the system.
    h. Logging in with wrong Username is performed at the end of the test.
    i. Group-1 is allocated to assigned beds.
    j. Group-2 performs rounds from one device to another.
    k. After completion all CRFs are collected and entered into Excel sheet.
5. Electronically captured data is compared against CRF data.

All measurements are scheduled as rounds for 20 subjects and the requirements for the measurements are as follows:

- Measurement to be performed on time, within the minute it was scheduled;
- Each volunteer ID to be confirmed against scheduled task using barcode;
- Measurement will be recorded electronically automatically and values also to be recorded into CRF correctly and immediately.

Schedule is created in order to match real study procedures where 1 round represents performing of a task on a group of patients. Table below represents an example of a schedule where one row represents a clinical round with 2 min round interval. Each round contains information about a location, task, time and subject information. Assigned column indicates the staff responsible for the clinical round.

Generated Master Treatment Schedule (0000, P7, G2)

Location	Protocol Time	Task	Start/End Date	Assigned	bed01	bed02	bed03	bed04
Ward 1	D1 H1	Dosing	01-Jan-2000 16:30 - 16:50	Dr HK	16:30	16:32	16:34	16:36
Ward 1	D1 H1	Vital signs	01-Jan-2000 17:30 - 17:50	DW	17:30	17:32	17:34	17:36
Ward 1	D1 H1	Spirometer	01-Jan-2000 17:32 - 17:52	DD	17:32	17:34	17:36	17:38
Ward 1	D1 H1	Finometer	01-Jan-2000 17:34 - 17:54	LB	17:34	17:36	17:38	17:40
Ward 1	D1 H1	Data download	01-Jan-2000 17:40 - 18:00	HB	17:40	17:42	17:44	17:46

The two tables below represent results from mock field tests. Table 1 represents a comparison of electronic records against CRF paper records for the Spirometer device. Paper records were entered manually and QC-ed. Highlighted values on the right hand side of the table represent mistakes or typos of paper records. As it can be seen, in four cases the data either has been recorded incorrectly or has not been recorded at all due to time constraints. Having 22 measurements (110 fields) error rate in this case averaged 7.3%. The error rate is considered high, having in mind that in Clinical research the acceptable error rate is 0.05%. In addition the time difference is not taken into account since this falls into another category of discrepancies and in most studies time window for scheduled measurements is ±10%.

Table 2 represents the comparison table of electronic and paper records for Dinamap device (blood pressure readings). Highlighted values represent mistakes or typos of paper records. All discrepancies have been verified with source documents and confirmed their validity. As it can be seen, 2 out of 34 records (136 fields) have error values representing 1.5% of the data.

Electronic Data					CRF records				
ID	**Time**	**FEV1**	**FVC**	**PEF**	**RPL ID**	**Time**	**FEV1**	**FVC**	**PEF**
050001	10:04	211	271	264	50001	10:04	211	271	**261**
050002	10:06	446	539	496	50002	10:06	446	539	496
050003	10:10	267	354	464	50003	10:09	267	354	464
050004	10:13	170	172	542	50004	10:12	170	172	542
050005	10:15	187	188	524	50005	10:15	187	188	524
050006	10:18	311	312	778	50006	10:18	311	312	778
050007	10:23	102	102	202	50007	10:21	102	102	202
050007	-	237	241	450	50007	10:22	237	241	451
050008	10:25	198	242	531	50008	10:24	198	242	531
050009	10:27	306	394	452	50009	**not recorded**			
050010	10:31	209	292	317	50010	**not recorded**			
050011	10:06	464	464	1032	50011		464	464	1032
050012	10:08	238	274	320	50012	10:17	238	274	320
050013	10:10	509	533	1065	50013	10:09	509	533	1065
050014	10:13	308	372	618	50014	10:17	308	372	618
050015	10:15	335	355	799	50015	10:14	335	355	799
050016	10:19	479	603	824	50016	10:18	479	603	824
050016	-	475	617	807	50016	10:19	**479**	617	807
050017	10:22	248	316	372	50017	10:21	248	316	372
050018	10:27	239	248	570	50018	10:25	239	248	570
050019	10:28	485	485	1126	50019	10:27	485	485	1126
050020	10:31	299	390	468	50020	10:30	299	390	468

Table 1. Comparison of electronic and paper records for the Spirometer device.

Electronic Data				CRF records			
ID	**Sys**	**Dias**	**HR**	**ID**	**Sys**	**Dias**	**HR**
50001	128	77	91	50001	128	77	91
50001	111	68	79	50001	111	68	79
50002	144	93	70	50002	144	93	70
50002	144	96	67	50002	144	96	67
50003	116	78	88	50003	116	78	88
50003	106	76	88	50003	106	76	88
50004	110	67	69	50004	110	67	69
50004	118	69	80	50004	118	69	80
50005	125	76	83	50005	125	76	83
50006	124	66	60	50006	124	66	**66**
50006	119	64	65	50006	119	64	65
50007	104	63	71	50007	104	63	71
50007	100	63	78	50007	100	63	78
50008	140	80	62	50008	140	80	62
50008	135	79	67	50008	135	79	67
50009	108	60	50	50009	108	60	50
50009	99	64	51	50009	99	64	51
50010	107	73	39	50010	107	73	39
50010	105	69	73	50010	105	69	73
50011	128	62	95	50011	128	62	95
50012	113	62	76	50012	113	62	76
50013	132	86	75	50013	132	86	75
50014	125	77	95	50014	125	77	95
50015	144	96	94	50015	144	96	94
50015	159	94	96	50015	159	94	96
50016	146	97	73	50016	146	97	73
50016	143	92	78	50016	143	92	78
50017	107	68	87	50017	107	68	87
50017	95	74	86	50017	95	74	86
50018	107	76	82	50018	107	76	82
50018	103	73	78	50018	103	73	78
50019	119	85	81	50019	119	85	81
50020	100	71	86	50020	100	71	86
50020	96	65	87	50020	96	**69**	87

Table 2. Comparison table of electronic and paper records for Dinamap device (blood pressure reading).

Electronic data capture has a definite advantage over the traditional methods which have been proven by the number of field tests. The error rate of an EDC system is virtually zero proven by numerous data collection sessions when two observers confirmed that accurate values were recorded.

In summary the data stability tests, "idiot proof" tests and mock data gathering showed that:

1. Device measurements are correctly picked up by the PC application

2. Without exception during the numerous trials they were correctly recorded to the DB.

3. All records were properly updated and consistent, i.e. no blank fields or erroneous data were found.

2.9 Technical test

To ensure that patient records are correctly retrieved from a device and appropriately recorded to a database another set of tests have been performed. For this purpose Blood pressure device has been selected and 154 measurements made while recording manually as well as saving electronic data directly to a database.

An excel spread-sheet has been created with manual records and all automatic records have been matched (Appendix 4). Data have been electronically compared and the following observed:

- Three MAP (Mean Arterial Pressure) values have not been recorded on the manual sheet.
- There have been 2 typos while recording MAP and a HR (Heart Rate) on the manual sheet.
- Since first 18 records have been created in addition with oxygen saturation there were 16 errors in MAP and HR values on the manual sheet. This is due to MAP and HR values being changed while recording other parameters. Due to this reason oxygen saturation sensor was removed after the 19^{th} record.

Comparison of the spread-sheets shows that all values were picked up by the software and correctly recorded in the database.

To test that records are maintained and consistent the test was performed in two days. At the end of the first day all 68 measurement electronic records were retrieved and saved in a separate spread-sheet. On the second day 86 new measurements were performed and saved to the database in the same manner. Measurement records created on the first day were re-retrieved again and compared against the spread-sheet created

earlier which showed no difference between records. After 30 days since above 68 records have been created, the same records have been re-retrieved again and compared to ensure that records are maintained. This demonstrates that records are kept unaffected and sustained over the period of time and while the database has been in use.

2.10 Further development of tools

The Laboratory Management System (LMS) module was developed as an addition to the system. The LMS module is intended to assist laboratory assistants in managing blood and other sample tubes. To integrate further with RPL internal functions and consistently with the other modules described, the application incorporates the Scheduler Database.

Laboratory manager creates custom matrices for processing laboratory samples, monitors and controls on-going laboratory processes. The Schedule module is offered as optional third party software. To be compliant with changing clinical software security requirements, a card login system is used together with barcode readers. The system is self-prompting – advising end-users of the sequence of actions necessary to complete a laboratory task matrices once they logged in. Users are allocated to specific groups such as “Lab Manager” and “Lab technician” with internal group structure. Lab technician user is responsible for creating and printing lab matrices only. Lab Manager have the same access level as technician and is also responsible for managing system users and have access to a wider range of settings.

The application consists of:

- Barcode label printing module.
- Blood Sample collection unit combined with Scheduler database.
- Laboratory Matrix Management module for managing tasks within the matrices.
- Post Processing module (for managing and sending samples to analytical labs).

The system meets the common audit requirements for clinical trials:

- Compliant to CFR 21 part 11 of the Code of Federal Regulations which deals with the FDA (Food and Drug Administration) guidelines on electronic records and electronic signatures (Appendix 3).
- All task completion confirmations are performed while logged in with password identified as an electronic signature.
- A full audit trail of all entries and changes made to date are available to nominated users.
- Appropriate reports are provided to authorised users for each relevant section of the system.

- The system provides colour coding of a scheduled sample collection task. The Laboratory Manager (LM) is able to set up different colour codes for different types of Blood Samples in a schedule.

2.11 Discussion

Data acquisition and recording are critical steps in clinical trials. The automatic data acquisition system presented in this chapter addresses the issues of virtually error-free data.

The presented Automatic Electronic Data Acquisition system was developed for clinical research. A more viable solution for automation of health care processes in terms of medical applications and introducing automated technologies by utilizing the existing medical devices is presented. The development and testing stages of this project were completed and validations of the software applications have been finalized. The number of field tests has shown the advantage of the system compared to existing techniques. Field Test Results demonstrated that 6 out of 56 records, comparing to electronic records, were either not recorded due to lack of time or recorded incorrectly. Comparisons of the results identified no errors and shows that the system is reliable. Furthermore, the Technical test showed that device measurements were correctly recorded by the relevant applications and all records were properly updated and maintained during a period of time.

Reliability of the systems as well as recoded data was increased by utilizing the double check of recorded data against measurements. An audit trail of the database was introduced allowing rolling back the actions performed at any point. All software solutions were developed in strict compliance with FDA (Food and Drug Administration) Clinical Software requirements Title 21 Code of Federal Regulations (21 CFR Part 11) such as: All task completion confirmations are performed while logged in with password identified as an electronic signature; A full audit trail of all entries and changes made to date are saved.

Flexible architecture of the software allowed the inclusion of additional devices together with post processing modules when needed. Since the software platform is Windows based the direction it to work towards web based systems to expand the area of system use and shift the focus on outpatients.

The development described above is based on utilising existing devices to keep the cost of Data Acquisition Systems down. However with existing technology we might be limited to features which might be required to perform more refined analysis. Research of existing and development of a new device for assessment of neurological diseases using Stroop test is performed which described in the next chapter.

3 Stroop test for Multiple Sclerosis

Multiple Sclerosis mostly affects brain cores leading to muscle deficiency. There have been several algorithms for identifying the stage of the disease that use ordinary PC with a keyboard as a diagnostic tool - Stroop test. The aim of this chapter is to describe the process of replicating the keyboard version of the Stroop test and development of a more accurate data collection device similar to a keyboard. The device utilizes Hall sensors and significantly increases data accuracy by more frequent data exchange and more precise key pressure detection. The Stroop test software can be also customized for use in other diseases affecting Central Nervous System such as Parkinson's disease.

3.1 MS background

Multiple sclerosis (MS) is an inflammatory demyelinating predominantly autoimmune disease of the Central Nervous System (CNS). MS affects mostly white matter tracts of the CNS and is characterized by rising MS lesions surrounded by perivascular infiltration of monocytes and lymphocytes. MS is a dynamic disease, with almost constant lesion formation and a progressive clinical course leading to physical disability and cognitive decline. Despite intensive efforts for finding the source of the disease, no specific etiologic agent has been identified. Genetic and environmental factors are known to contribute to MS but a specific cause for this disease is still unknown.

The frequency of MS varies depending on population characteristics and geographic location. MS is most prevalent in the white population of northern European descent and in populations living in temperate climates. The existing research suggests that both genetic and environmental factors influence the frequency of MS. The highest prevalence of MS occurs in the Orkney Islands of Scotland at a rate of 250 cases per 100,000 population [24]. A rate of only 2 cases per 100,000 population is observed in Japan and MS is exceedingly rare in Africa. MS affects females more than males (≈2:1), but the underlying reasons for this difference are unknown.

MS is the leading cause of neurologic disability in early-to-middle adulthood. Practically any neurologic function can be affected during the course of MS. People with MS usually die of complications rather than of MS itself, including recurrent infections (especially in bedridden patients). Patients with MS are thought to have 7 years shorter life expectancy than the general population.

Pathophysiology of the disease is similar to other autoimmune conditions. In patients with MS, the immune trigger is unknown, but the targets are myelinated CNS tracts.

The clinical course of MS can follow different patterns, and this observation has led to the classification of distinct types of MS. The disease can present in primary progressive, relapsing remitting, relapsing progressive and secondary progressive phenotypes.

Although most patients have a wide range of symptoms from lesions in different areas of the brain and spinal cord, others may present with predominantly visual, cognitive, or cerebellar symptoms. Some patients have a predominance of cognitive changes, while others present with prominent ataxia (inability to coordinate the movements of muscles), hemiparesis (weakness on one side of the body) or paraparesis (partial paralysis of the lower limbs), depression, or visual symptoms. Bipolar disorder and frank dementia may appear late in the disease course, but sometimes are found at the time of initial diagnosis. Optic neuritis presents clinically as orbital pain at rest or during eye movement and loss of vision. Patients may complain of "patchy loss of vision", and upon examination, a cecocentral scotoma and an afferent pupillary defect may be found. Patients may experience colour desaturation even with normal visual acuity, usually manifested as the perception of red colour as different shades of orange or grey. Commonly, patients complain of numbness or tingling in one or more limbs, variable weakness, or sensory level-related symptoms. Some have difficulty describing weakness or numbness, as these symptoms are obscured by incapacitating fatigue [25, 26].

Studies shown that people suffering from MS have attention problems or in other words slower cognitive process [35]. Cognitive process is a psychological process involved in acquisition and understanding of knowledge, decision making and problem solving which is distinct from emotional and volitional processes. As an example, multiple sclerosis patients have been found to be slower in their response on a Stroop test [35-37] compared to control patients. The results presented in [35] are replicating the previous findings [36-37] suggesting that the MS patients may have a specific impairment in selective attention. The extent to which multiple sclerosis slows cognitive processes has been reviewed in [38] where speeded tasks were administered to 22 participants with and without MS. On all tasks, patients with MS responded more slowly than comparison subjects.

3.2 Stroop Test

Cognitive impairments in information processing, attention and executive functioning are widely reported in patients with MS [27]. In the Table 3, if naming (ignoring the meaning of the words) the first group of colours is easier and quicker than the second, then the performance demonstrates the Stroop effect.

Test 1	Test 2
Green, Red, Blue, Green, Blue, Red	Green, Red, Blue, Green, Blue, Red

Table 3 Stroop test effect

In psychology, the Stroop effect is a demonstration of interference in the reaction time of a task. When a word such as blue, green, red, etc. is printed in a colour differing from the colour expressed by the word's semantic meaning (e.g. the word "red" printed in blue ink), a delay occurs in the processing of the word's colour, leading to slower test reaction times and an increase in mistakes. The effect is named after John Ridley Stroop who first published in English in 1935 [28]. The effect had previously been published in 1929, but only in German. The original paper is one of the most cited papers in the history of experimental psychology, leading to over 710 replications [29, 30].

3.2.1 Original experiment

J. Ridley Stroop, in his experiment, administered several variations of two main tests. Stroop referred to his tests as RCN, to stand for "Reading Colour Names", where participants were required to repeat the written meaning of words with differing coloured fonts, and NCW, to stand for "Naming Coloured Words", in which participants were asked to orally identify the colour of each printed colour name. Additionally Stroop tested his participants at different stages of practice with each task, to account for the effects of association [28].

Stroop identified a large increase on the time taken by participants to complete the NCW (Naming Coloured Words) tasks, an effect still pronounced despite continued practice at each task. This interference was explained by the automation of reading, where the mind automatically determines the semantic meaning of the word, and then must override this first impression with the identification of the colour of the word, a process which is not automated.

3.2.2 Clinical use

The Stroop test has been utilized to investigate the aspects of such varied psychological disorders as Attention Deficit Hyperactivity Disorder, Schizophrenia, and Anorexia. EEG and fMRI studies of the Stroop effect have revealed selective activation of the anterior cingulate cortex during a Stroop task, a prefrontal structure in the brain which is hypothesized to be responsible for conflict monitoring. According to Kujala et al, cognitive functioning evolves over time in patients with MS [31]. The Stroop test can be used to analyse the current state of such patients in addition to other cognitive tests [32] since, progressive cognitive deterioration should be considered as one of the characteristics of multiple sclerosis.

3.2.3 Further development and usage

Edith Kaplan's group (developer of the Delis-Kaplan neuropsychological test battery) developed the task further by separating the task into four different stages: naming colour fields, congruent colour words, incongruent colour words, and combined. The additional strain on the executive function of the brain allows for a more precise diagnosis [33].

The Stroop task is also employed to study frontal function and attention in brain imaging studies. Speaking is not possible in the scanner because it moves the head, so a number theme is often used instead. For instance, three words may be displayed that read "two" and the participant must press three on their button box.

The test has additionally been modified to include other sensory modalities and variables, to study the effect of bilingualism, or to investigate the effect of emotions on interference. A similar effect has also been observed in individuals with grapheme-colour synaesthesia - people who perceive colours when seeing certain numbers and letters. If a number or letter is presented to such an individual in a colour other than what they would perceive, there is a delay in determining what colour the character actually is.

3.3 Software design using a keyboard

As a result of research, the Stroop test software has been developed utilizing ordinary computer keyboard. The system was built with three tier architecture separating logical layer from storage. Three different Stroop tests were pre-programmed allowing comparison of results between their outcomes.

Test 1. Three equidistant keyboard keys are marked with stickers:

Key "1" = Red

Key "6" = Green

Key "-" = Blue

For Test 1, Black & White text is used for a random flash of a series of three words Red, Green and Blue once a Space key is pressed. The flashing of a word on a screen is a stimulus to react to. The time that it takes from the stimulus to lift a finger from the Space key to hitting the appropriate target key is measured.

Test 2 differs from Test 1 by using coloured words which represents the word meaning i.e. word Red is displayed in red colour and word Blue is displayed in blue colour. The same parameters and variables are measured during the test.

In Test 3, the above mentioned words are displayed in random colours. The user has to ignore the printed word and respond to the colour of the word, which involves a cognitive task. Similar to the previous tests the reaction times are measured.

Use Case Diagram for the software application is shown in picture *Figure* 3.1.

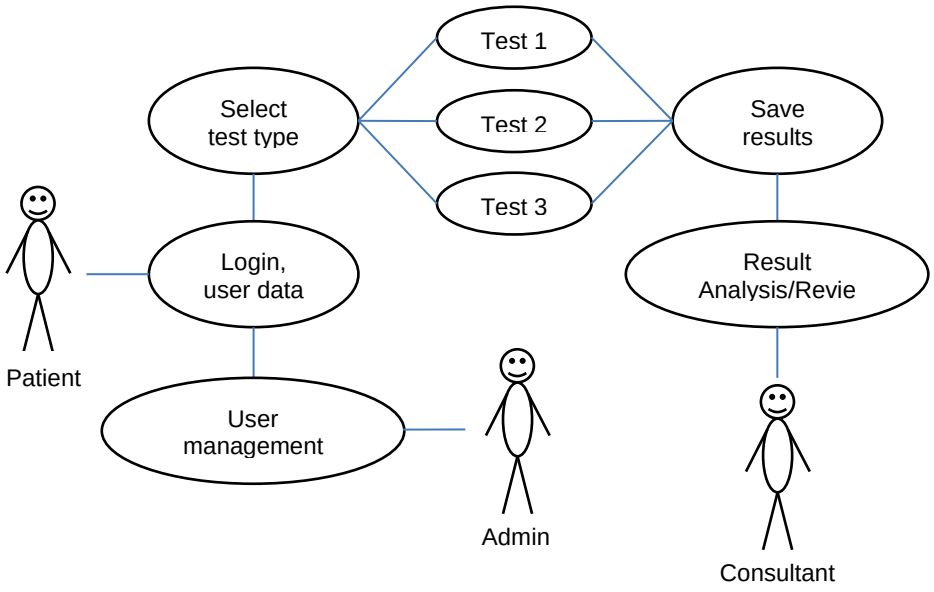


Figure 3.1. Use Case Diagram for Stroop test software (keyboard version).

There are 5 indicators for each test step:

1. Finger on the Space bar
2. Random time (0.5 to 4 sec)
3. Visual stimulus
4. Release of space bar
5. Target key hit

A further 4 parameters are calculated as following:

Time difference between 4 and 3 is a Central reaction time.

Time difference between 5 and 4 is a Peripheral reaction time.

Time difference between 5 and 3 is a Total reaction time.

Accuracy is the number of correct keys hit during each test.

Using the above described requirements, software was developed allowing the performance of measurements of different reaction times with a precision of up to 60msec. Figure 3.2 represents a block diagram of the software.

The application was build using .NET technology with a dedicated storage server for use from any location with internet access. A login system was implemented to prevent unauthorized access. After the application is started a password prompt window is displayed. Two types of users are defined: admin and ordinary user. An admin user has access to all features of the software as well as the user management window.

Once the correct username and password combinations are provided then the test number can be selected. Currently 3 different tests have been developed. In the first test the colour word is displayed in black and white and the user has to react to the meaning of the word, by pressing the appropriate coloured key on a keyboard. In the second test the colour words are displayed in different colours and the user has to react to the meaning of the word rather to its colour. In the third test the colour words are displayed in random ink colour and the user reacts to the colour of the word ignoring the meaning. Figure 3.3 below represents a screenshot of the window while Test 1 is being performed. The user can decide the repeat number and then clicks the “Start test” button where instructions are displayed along with the test. ‘Press the SPACE’ message is displayed on the screen. Once pressed, after 0.5-4 seconds a colour word is displayed.

From the point of the time when the word is displayed, the application starts counting the time until the correct key is pressed.

The results of each test can be reviewed using the Results window. It contains several filters such as test date, test type and displayed values. One can monitor the progression of tests observing several calculated parameters: Central reaction time, Peripheral reaction time, Total reaction time and Accuracy (Figure 3.4 below).

The screenshot of the second test is displayed in Figure 3.5 below. Compared to Test 1 it is slightly more complex to accomplish as words are displayed in random ink colour and the user should react to the meaning of the words only. The results of each test vary depending on personal abilities of a user. The second test results are displayed in Figure 3.6. It can be seen that the user achieved better performance towards the end of the test.

The third type of test window and associated results are displayed respectively in Figure 3.7 and Figure 3.8 below. In this test the user should react to the colour of the word while ignoring its meaning. When the word “Brown” is displayed in yellow colour, the user should press the yellow key rather than the brown key. When the number of set repeats is achieved the software saves all data into a database on an external server. This is to avoid data loss due to unstable connection that occurs when data is sent in packets. Every single key-pressing is recorded and confirmed once recorded. If connection is lost a local copy of the data is created, and sent to the server when connection to the internet is restored.

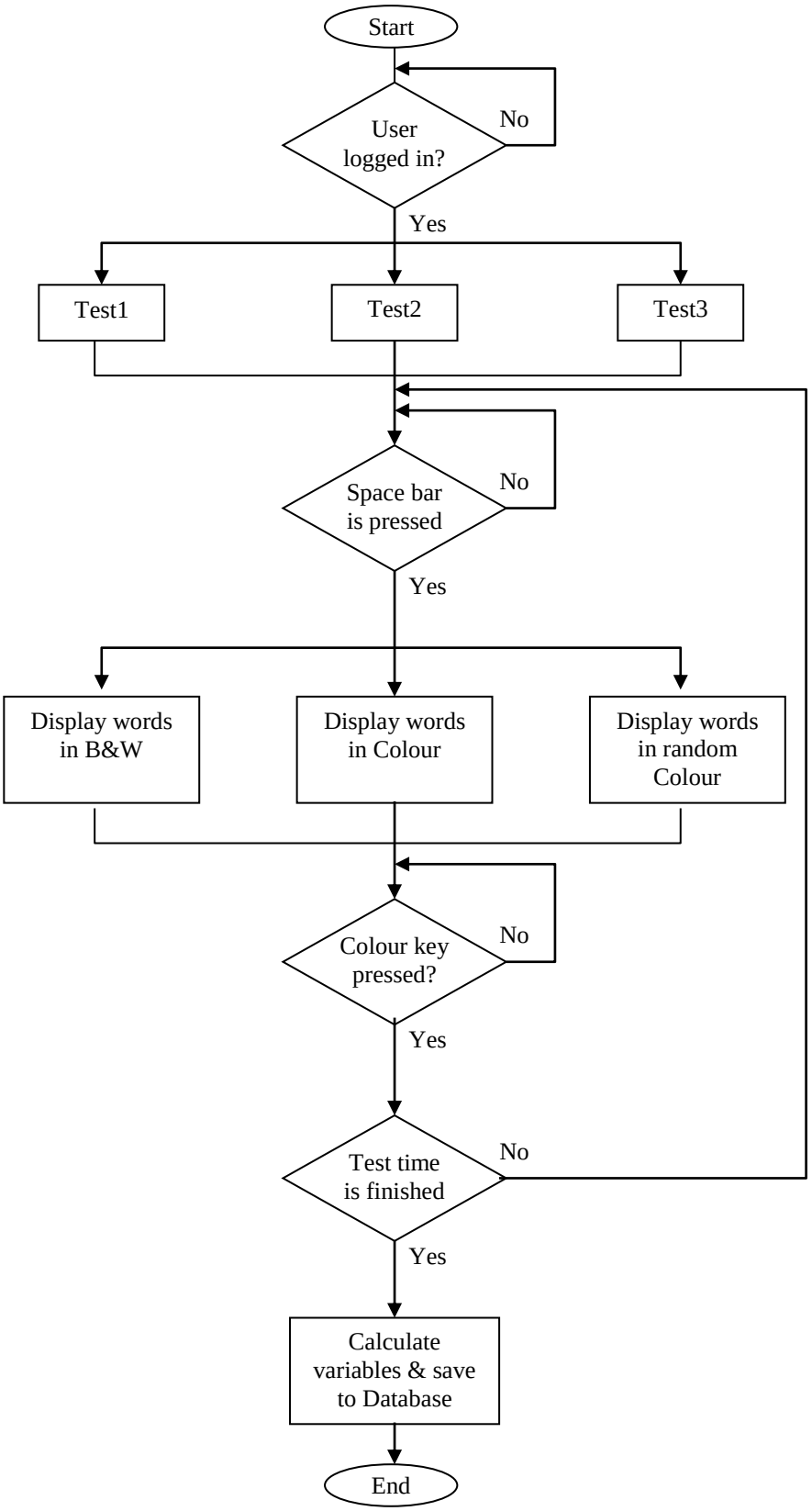


Figure 3.2. Block diagram of the Stroop test software using Keyboard.

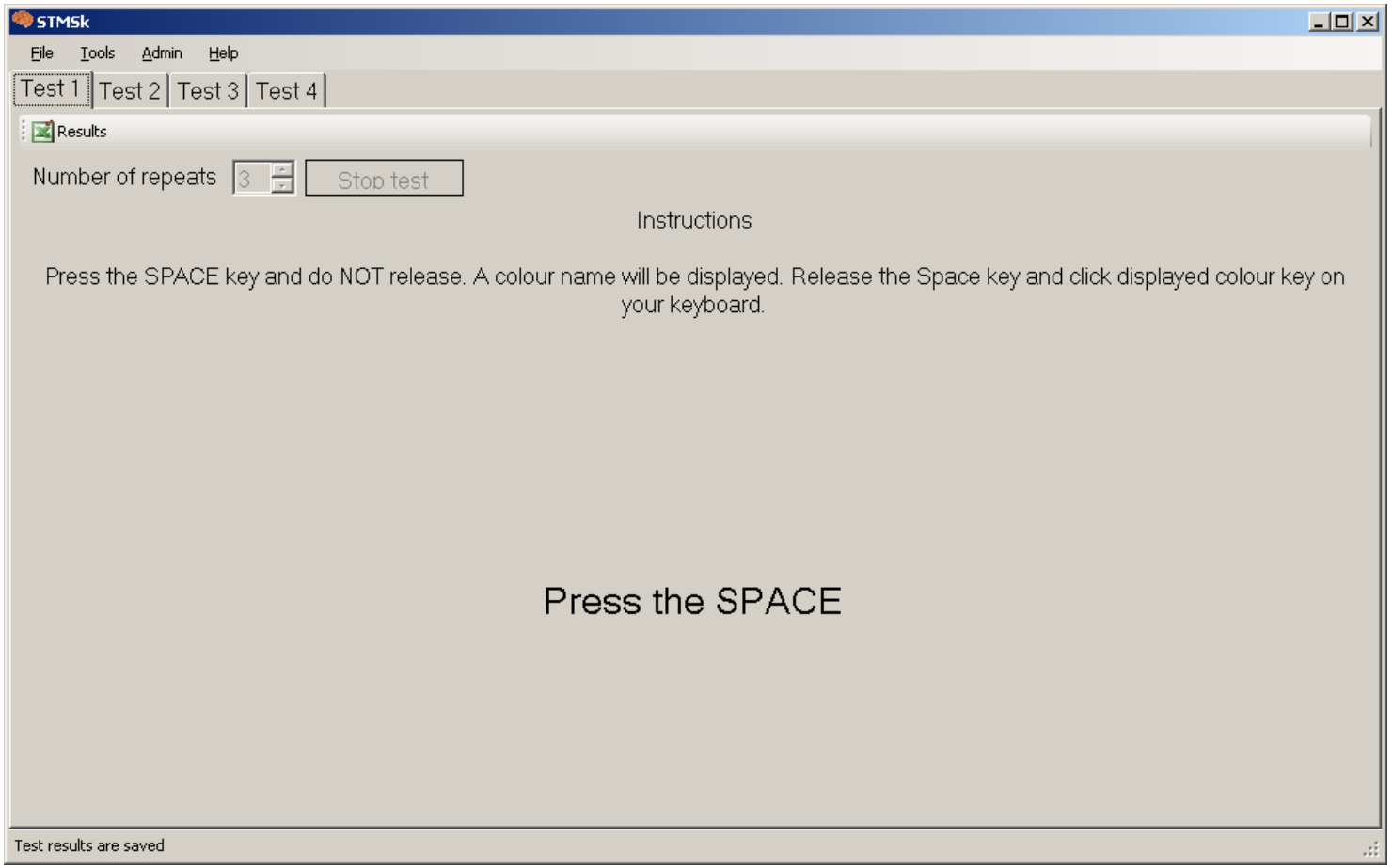


Figure 3.3. Software for a Stroop test software using Keyboard (Test1).

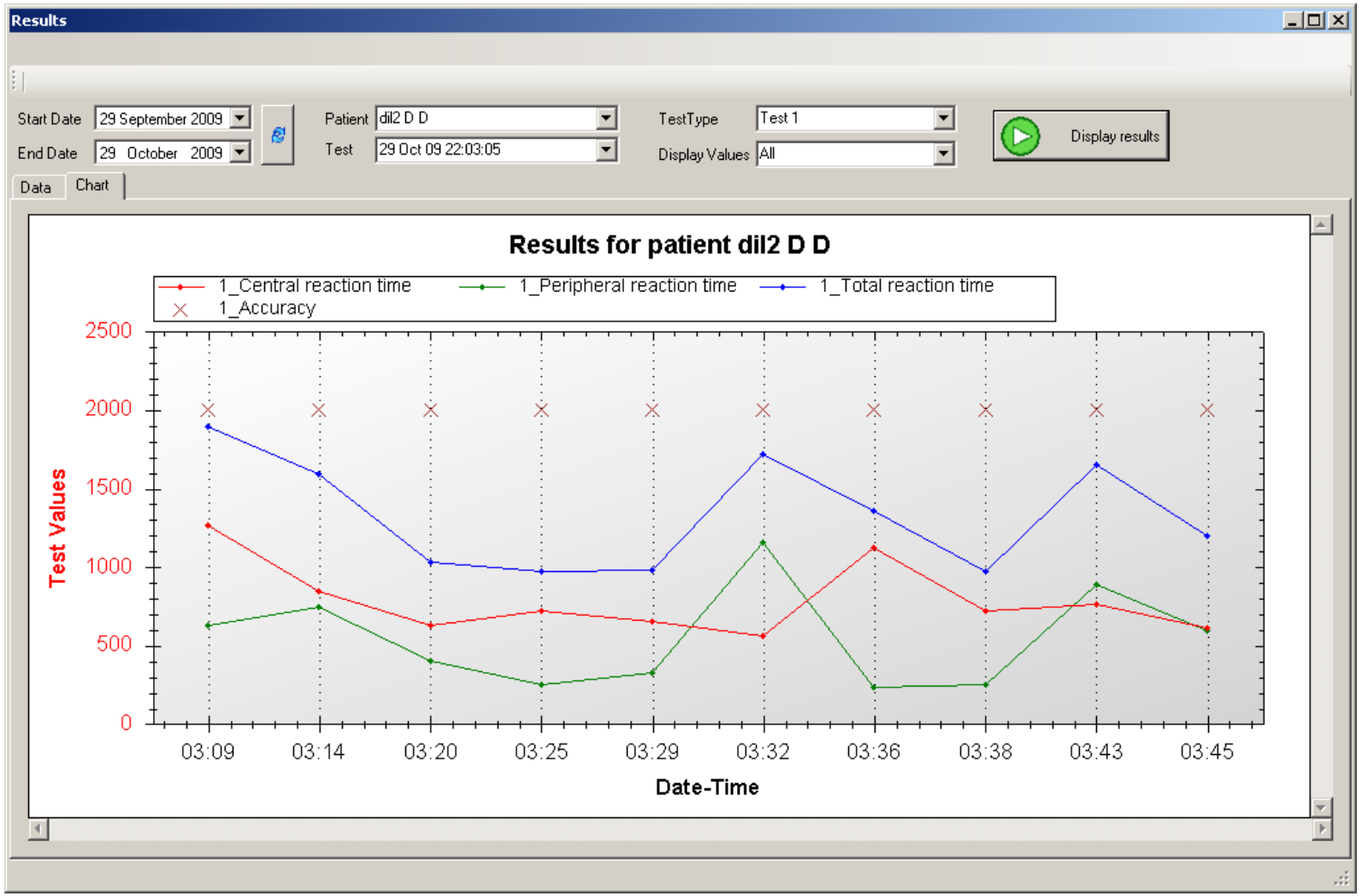


Figure 3.4. Software results for a Stroop test software using Keyboard (Test1).

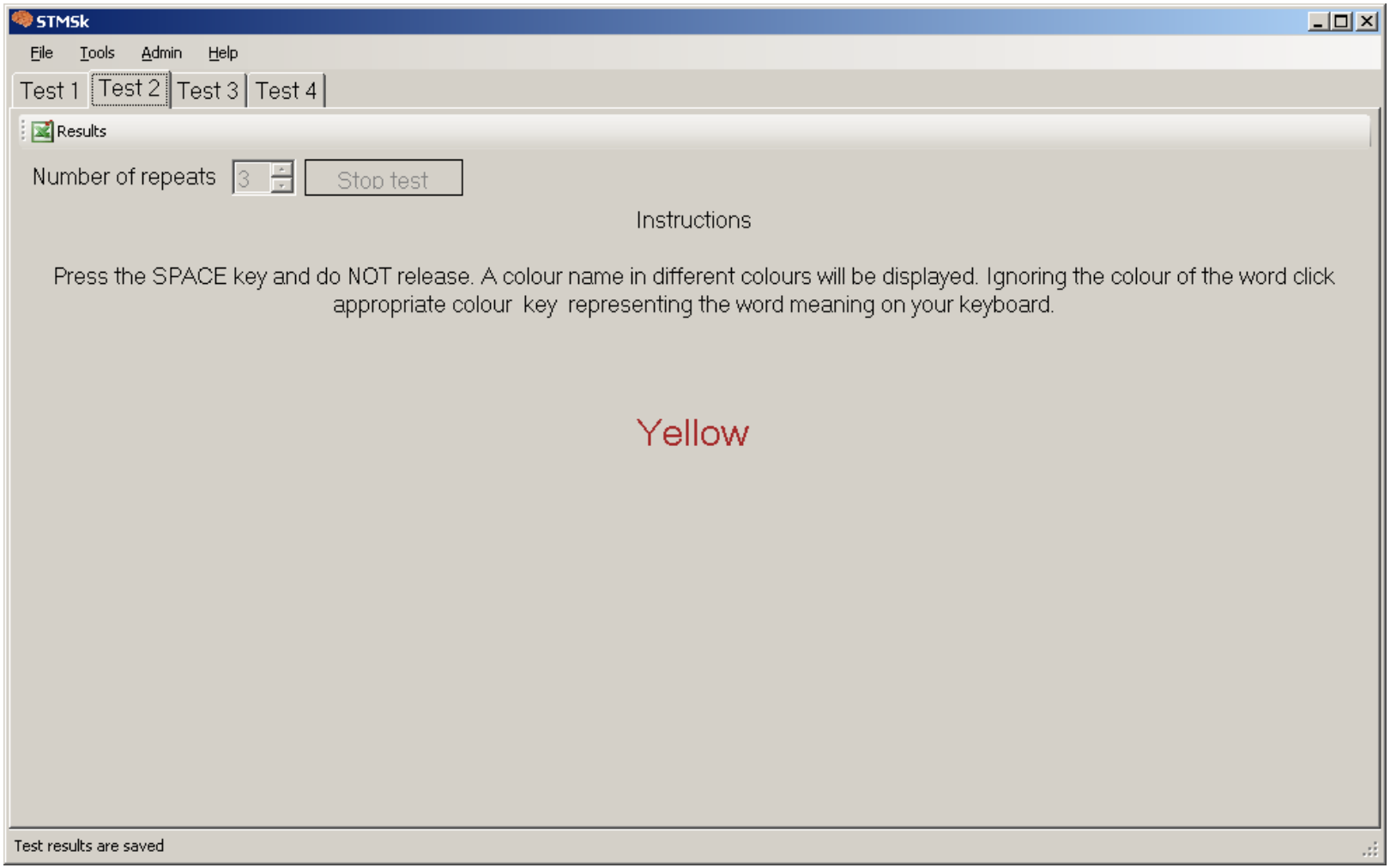


Figure 3.5. Software for a Stroop test software using Keyboard (Test2).

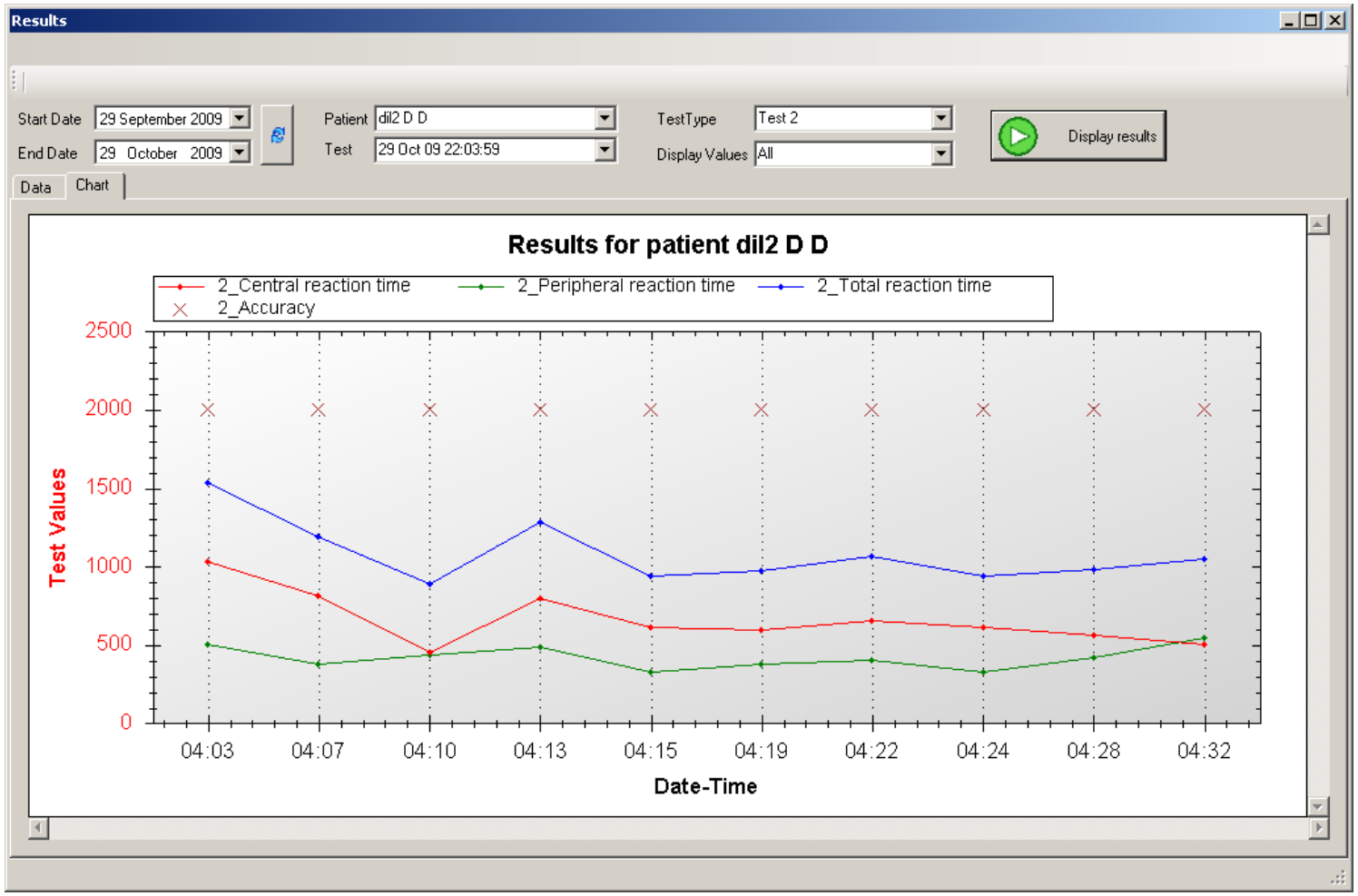


Figure 3.6. Software results for a Stroop test software using Keyboard (Test2).

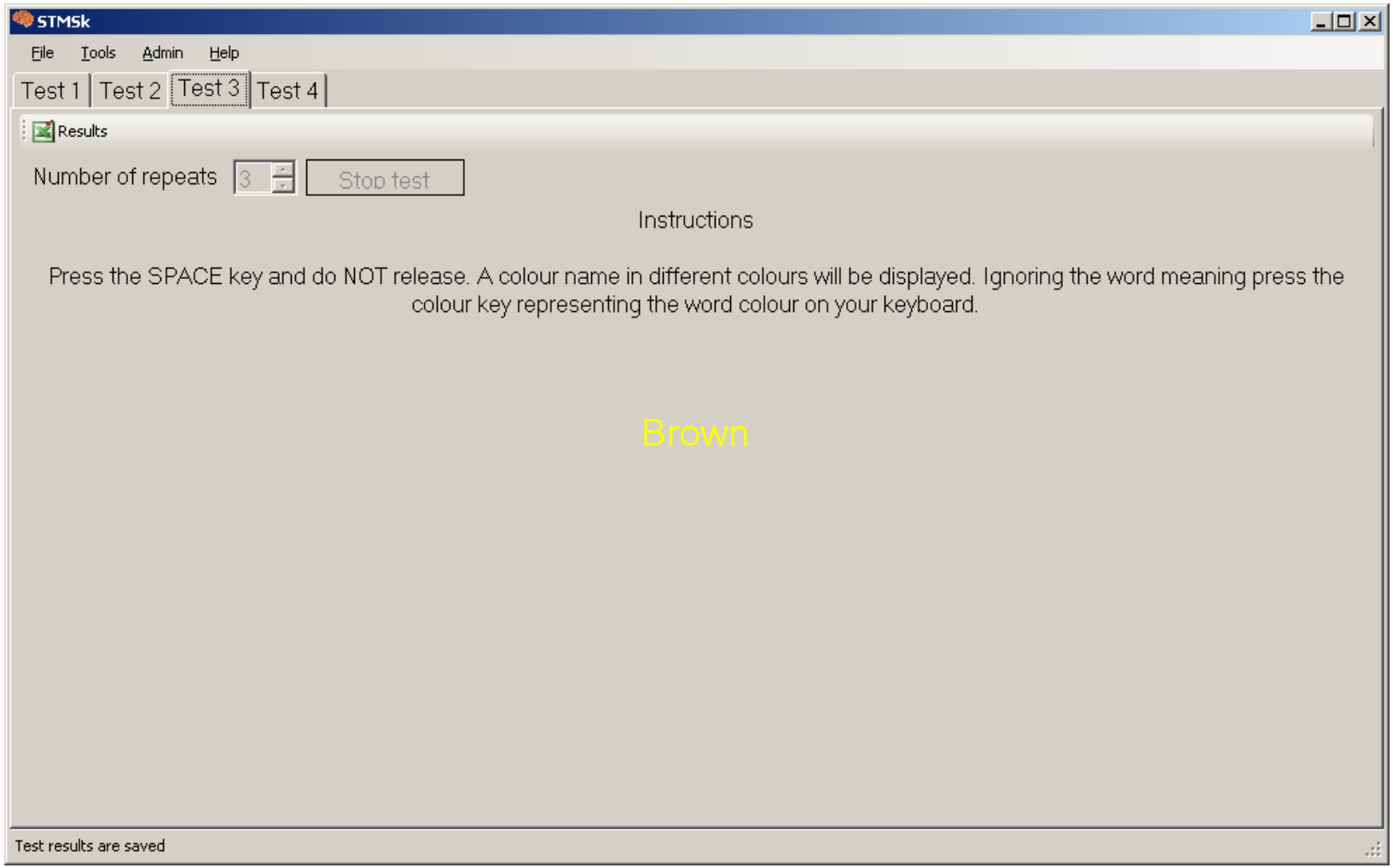


Figure 3.7. Software for a Stroop test software using Keyboard (Test3).

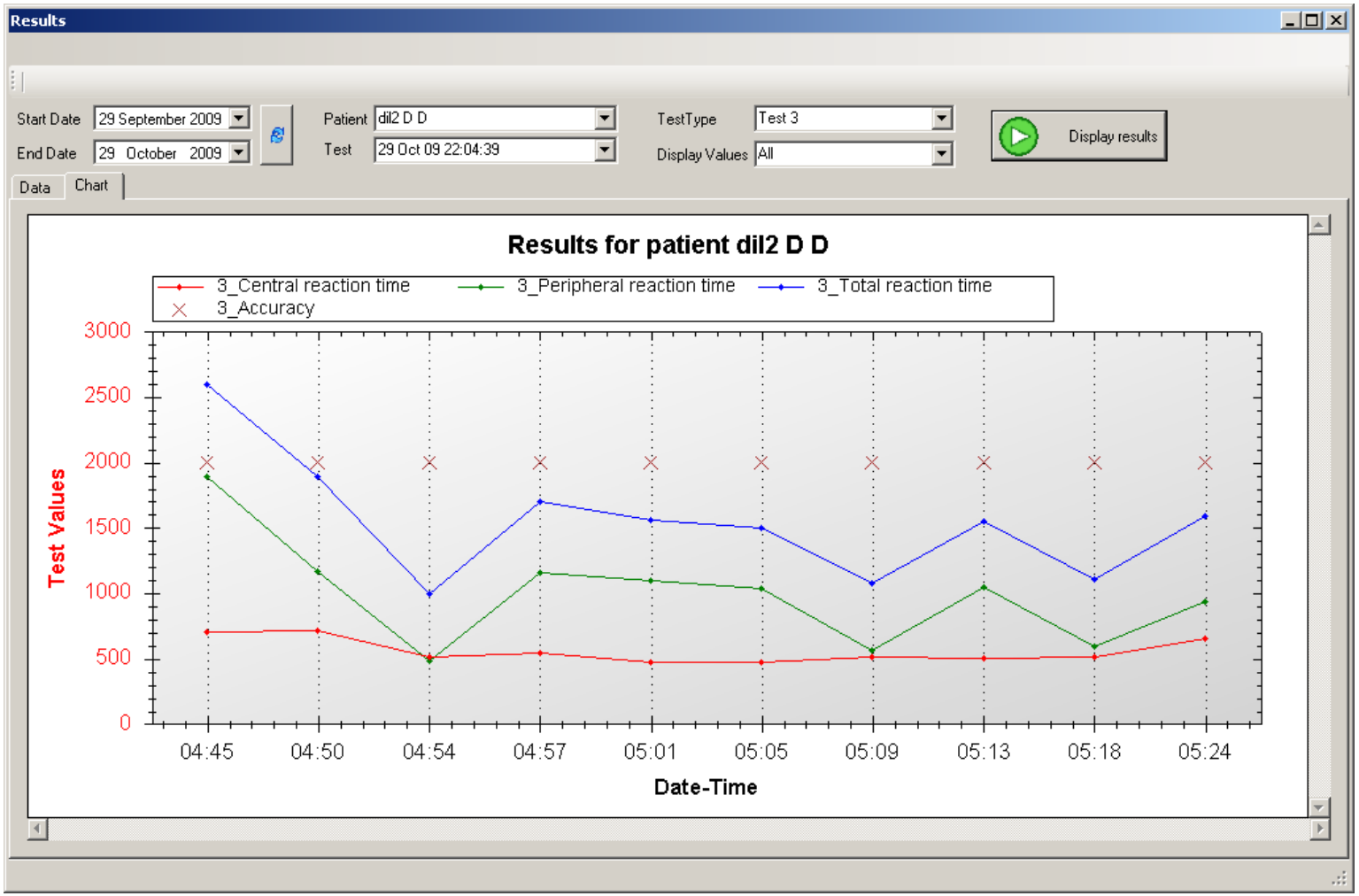


Figure 3.8. Software results for a Stroop test software using Keyboard (Test3).

In order to identify disorders in the rate and accuracy of upper limb movement a fourth test was developed. It involves consecutive taping of two keys located at about 15 cm from each other. The test is performed first with the right hand for 60 seconds then repeated with the left hand which is adapted for diagnosis of Parkinson Disease (PD).

The test starts with the text displayed in Figure 3.9 below. Figure 3.10 shows a window when the first part of the test has been completed. The user is looking at the keyboard while performing the test and meanwhile a series of red flashing screens are displayed.

Six parameters are calculated after the test including total number of keys, the number of keys pressed correctly, Kinesia Score - the number of keystrokes in 60 seconds, Akinesia Time - cumulative time that keys are pressed, Dysmetria score - a weighted index calculated using the number of incorrectly hit keys corrected for speed and Arrhythmia score - a measure of rhythmicity which corresponds to the variance of the time interval between keystrokes. These parameters correspond to disease severity. Since the values of different parameters vary substantially, scaling is introduced while drawing results. Each parameter can be scaled or un-scaled to match to the rest of the graph lines. Users can perform custom calculations by using raw data in the Data tab.

Welcome to the Bradykinesia Akinesia Incoordination (BRAIN©) Test.

This is a short, simple, software-based medical device that is used to pick up disorders in the rate and accuracy of upper limb movement.

Now that you have successfully downloaded and installed the test to your computer, you should read the instructions below. The data collected from this test will be uploaded to a secure online database and analysed by experts in the nervous system and movement disorders. The full patient information sheet is available on the Predict PD Website, and should be read before agreeing to undertake this test.

At the bottom of this window you will see two boxes: agree and disagree. If you wish to undertake this short test, having read the patient information sheet, please click on ‘agree’. If you do not wish to take the test, click ‘disagree’. If you click ‘agree’, you will pass to the next window, which requests a unique username and password. You should use the username and password allocated to you on registering with the Predict PD website.

In the interests of ensuring best-quality data, try to do the following:

- Sit comfortably directly in front of your computer.
- Place a single red sticker (provided) on both the 'S' key and the ';' key. These are approximately 15cm apart on a standard desktop keyboard.
- Adjust the seat/computer height (if possible) to ensure that your arms are just above the keyboard when your elbows are flexed to 90 degrees.
- When the timer starts, use your index finger of your right hand to alternatively strike the two keys marked with a red dot.
- Do this as fast and accurately as you can.
- The test will last for 60 seconds.
- Repeat the test for the left hand, again using the index finger.

Figure 3.9. Software for a Stroop test software using Keyboard (Test4).

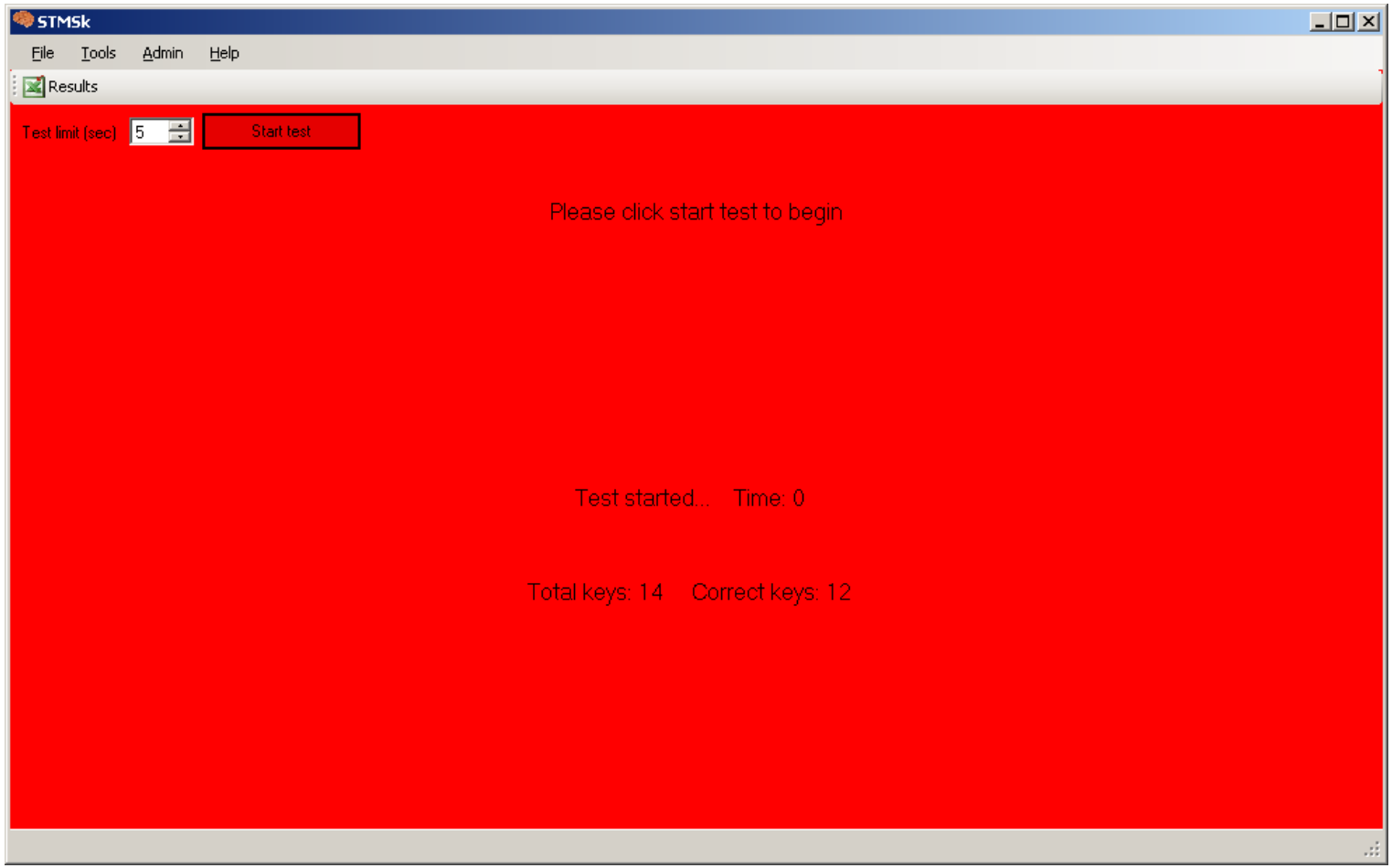


Figure 3.10. Software for a Stroop test software using Keyboard (Test4).

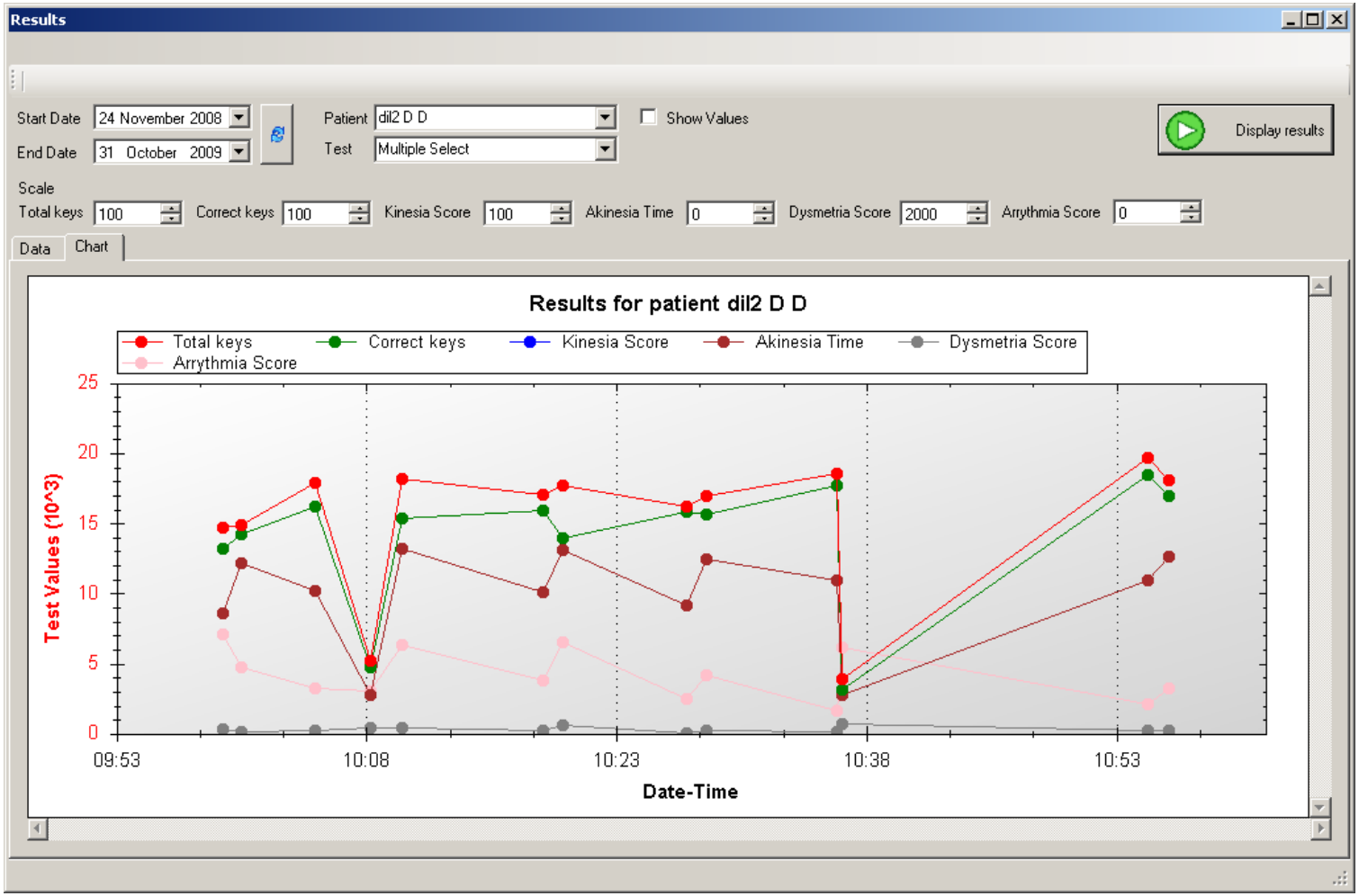
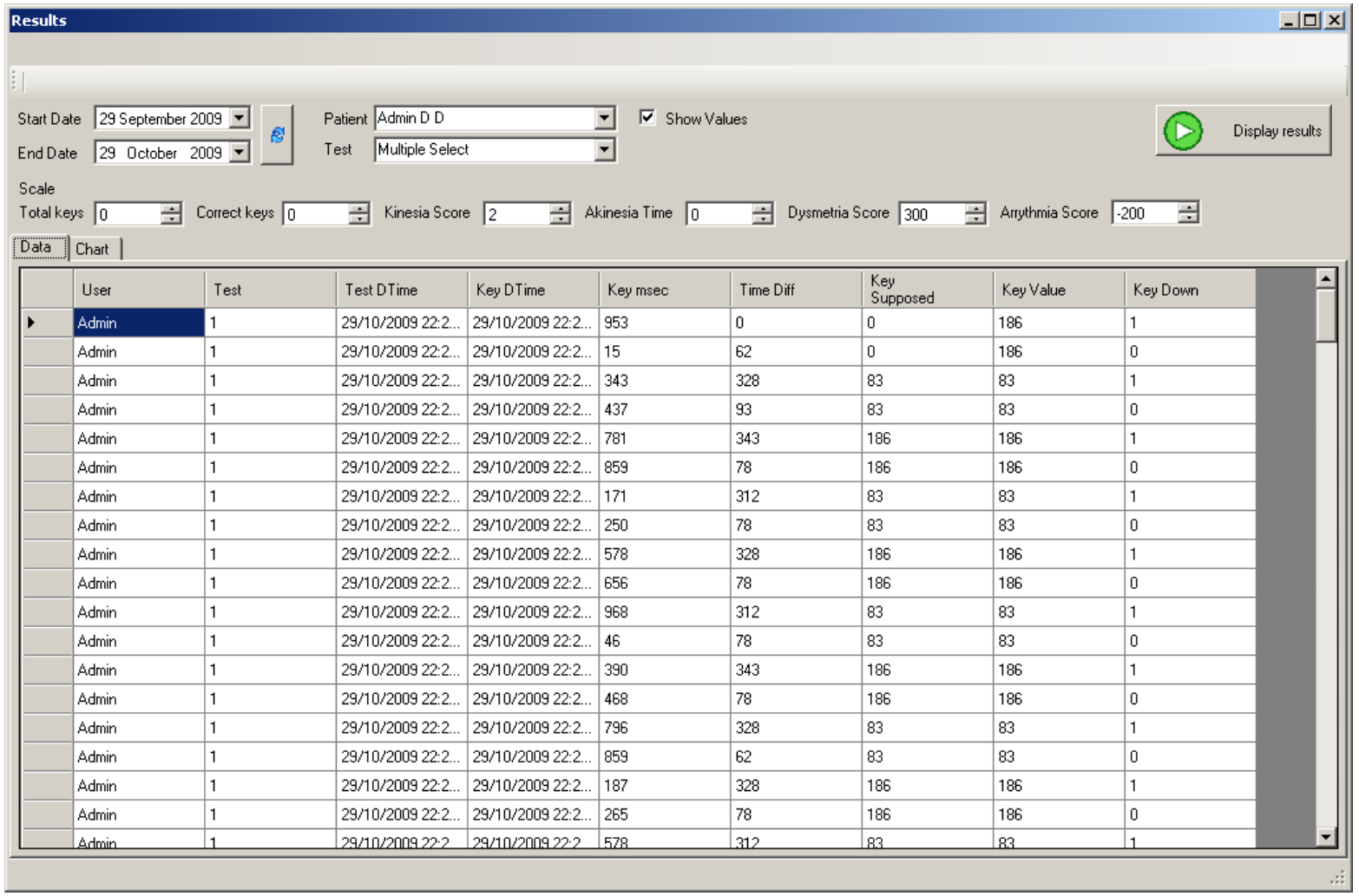


Figure 3.11. Software results for a Stroop test software using Keyboard (Test4).



	User	Test	Test DTime	Key DTime	Key msec	Time Diff	Key Supposed	Key Value	Key Down
▶	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	953	0	0	186	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	15	62	0	186	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	343	328	83	83	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	437	93	83	83	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	781	343	186	186	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	859	78	186	186	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	171	312	83	83	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	250	78	83	83	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	578	328	186	186	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	656	78	186	186	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	968	312	83	83	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	46	78	83	83	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	390	343	186	186	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	468	78	186	186	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	796	328	83	83	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	859	62	83	83	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	187	328	186	186	1
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	265	78	186	186	0
	Admin	1	29/10/2009 22:2...	29/10/2009 22:2...	578	312	83	83	1

Figure 3.12. Software results for a Stroop test software using Keyboard (Test4).

3.4 Specialized device development

Although the keyboard device is suitable for certain tests such as measuring the speed, frequency and correctness of key pressings, it cannot be used to subtly analyse key press actions i.e. how hard it was pressed and is limited due to size and speed of response. A device similar to a keyboard was designed and developed to fulfil the requirements for testing reaction times and other parameters of MS patients.

Piezoelectric and Hall sensors were tested using a mini prototype of the device. Due to Hall sensors performing better than Piezoelectric for particular application the first was used to create full scale prototype.

At the initial stage 2 design concepts were proposed for the device (Figure 3.13):

a) A device consisting of 2 similar parts with 64 keys each. Hall sensors are used to emulate keys for the device and to measure the key pressure value and reduce the response. Each key can be lit by 3 different colours: red, green and blue. Two parts of the device will slide to increase or decrease the distance between keys while being used for Test 4.

b) A device consisting of 2 similar parts with four spots of sensors with 11 sensors each on the left part of the device, and one spot of sensors with 11 sensors each on the right part of the device. As with the concept "a" Hall sensors is used to create keys for the device. Two parts of the device slide apart to increase or decrease the distance between keys while being used for Test 4.

Considering all the pros and cons of each concept and due to the fact that the second concept limits users for the number of tests, the first concept has been used to develop a device, although it requires more processor time to process all 128 key values. The final design and technical specification of the device is shown in the Figure 3.14.

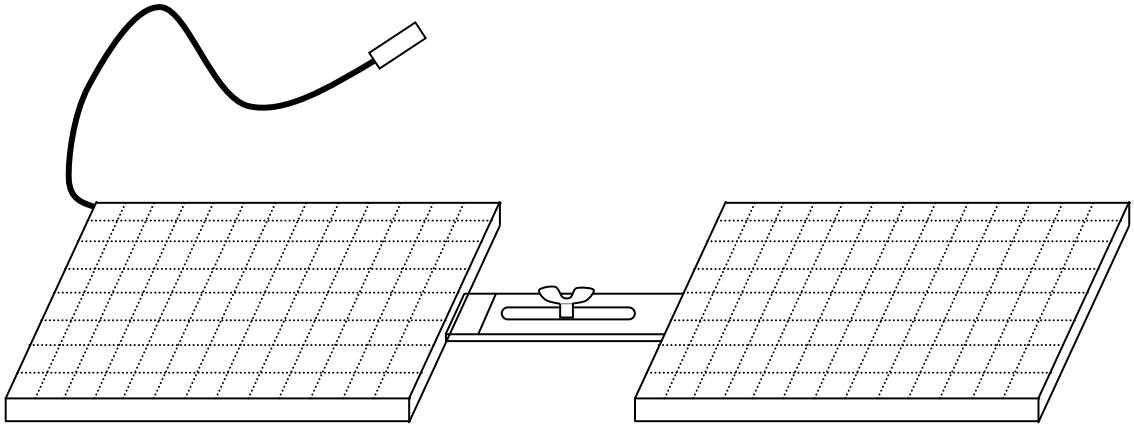
Figure 3.15 and Figure 3.16 illustrate the designing of the device prototype. The device can be connected via Serial port for data exchange while using an external power source. Each button contains three LED lights and can be switched on and off individually. The communication protocol description for data exchange between PC and a device is described in Appendix 1.

The first prototype of the device is illustrated in Figure 3.17 and Figure 3.18. To test the data exchange between the PC and the device, software has been developed which is described in Appendix 2. The testing software allows for each cell of the device to be independently switched on and off using communication protocol.

Testing the software also allowed evaluation of each cell pressure value and the effects on adjacent cells. While testing the device, several improvements had been made to the communication protocol and the device functioning which reduced the number of unnecessary data flow between the device and PC and increases the response time of the device. This was achieved by being able to disable some cells. As an example, the previously described test has been considered where the user would press 2 keys located within 15cm from each other. The main 2 cells of the device were set as 49 and 56. Since adjacent cells may be pressed by accident an additional 5 cells for each main cell (41,42,50,57,58 and 48,47,55,63,64) have been monitored leaving us with 52 disabled cells. The device allowed us to measure how precise the pressed points were and how hard the key-cells were pressed.

All software tests were adjusted to be used with the specialized device and have proven to deliver much more reliable and only the necessary data for analysis compared to the ordinary keyboard.

a) Concept 1



b) Concept 2 (dots indicate sensor positions)

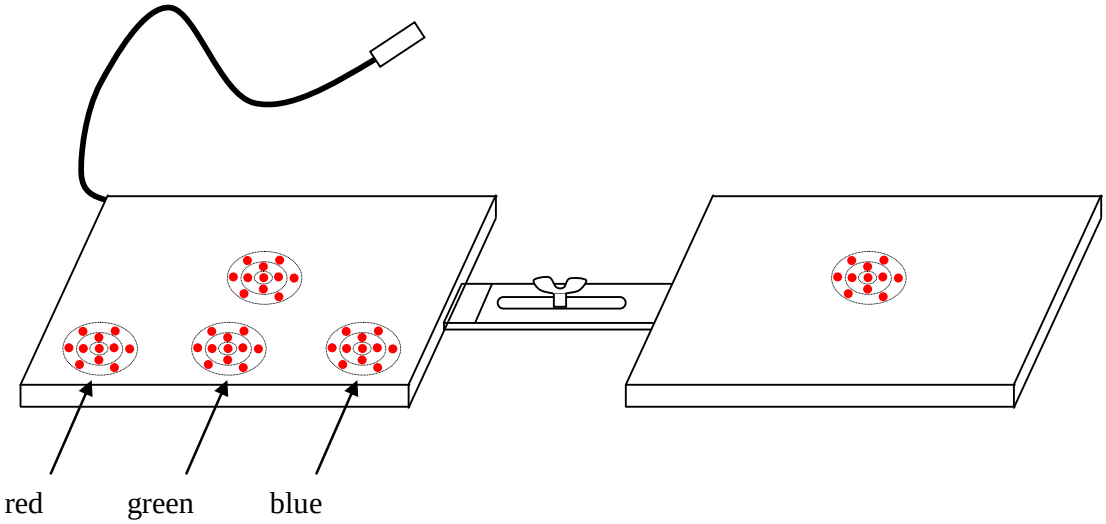


Figure 3.13. Design concept of Stroop test device

1. Every cell will have 2 number address;
2. Every cell will have a sensor and 3 colour led (Red, Green and Blue) to highlight the cell e.g. mark cells to be pressed.
3. Device is split into 2 sections, with adjustable length to allow changing the distance between sensors located in separate sections.
4. Signals under X mV and over Y mV are ignored.
5. X and Y values are changeable (calibration).
6. Calibration method can be set by manufacturer, by specific command sent to the device (i.e. MIN100 and MAX600 will set min and max values to 100 and 600, respectively).
7. Each side of the keyboard has 8x8 cells = 64x2 = 128 cells in total
8. Cells are square 20mm x 20mm.
9. Cell addressing format is XX by YY. Where XX is horizontal line from left to right (01,02,…,15,16); and YY is vertical line from top to bottom (01,02,…,07,08);.
10. Signal, sent from the device (according to 4) consists of XXYYVVV. Where XX is x coordinate of the cell; YY is a y coordinate of the cell; VVV is the value of pressure in mV.
11. Signal, from the device, is sent every 2msec.
12. Signal, sent from PC to device consists of XXYYCC. Where XX is x coordinate of the cell; YY is a y coordinate of the cell; CC is the value for color (00-Off, 01-Red, 02-Green, 03-Blue).
13. If signal to set the colour is set as 000000 it means that all cells should be off; 000001- all cells led Red, etc.

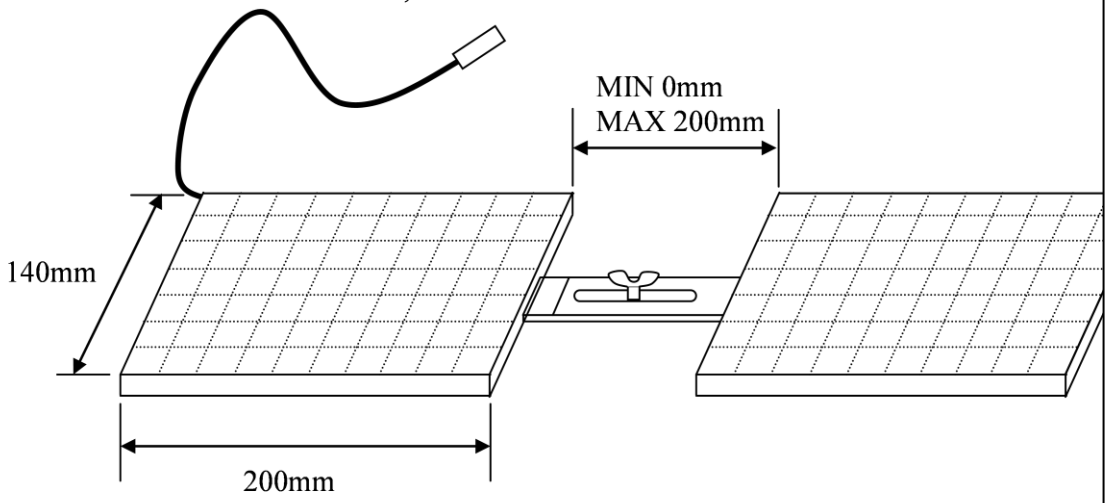


Figure 3.14. Final design and technical specification

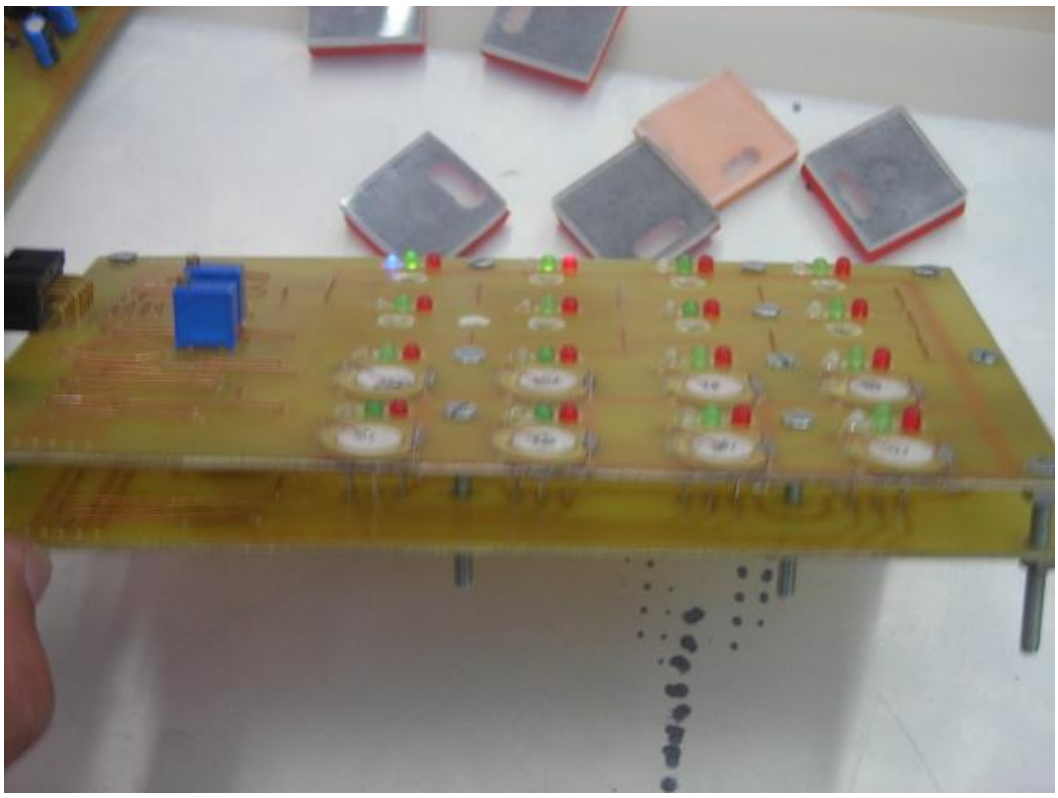


Figure 3.15. Specific device for Stroop test software (board).

Figure 3.16. Specific device for Stroop test software (LED design).

Figure 3.17. Specific device for Stroop test software (PC connection).

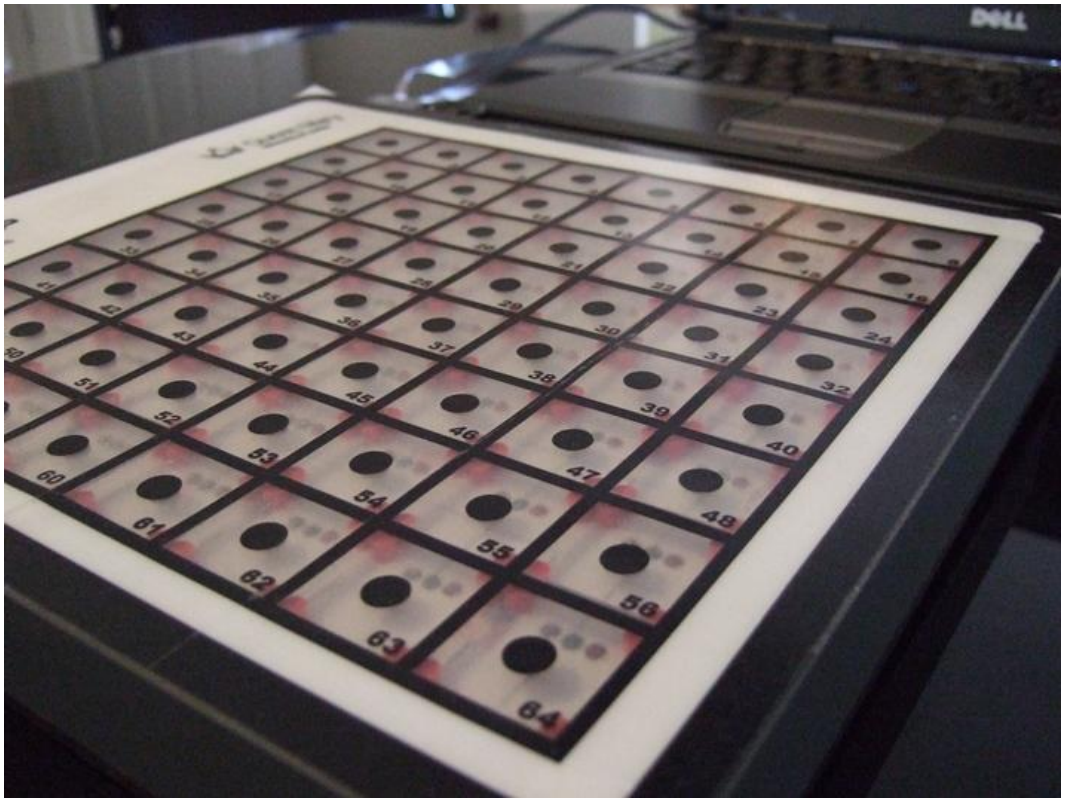


Figure 3.18. Specific device for Stroop test software (keys layout).

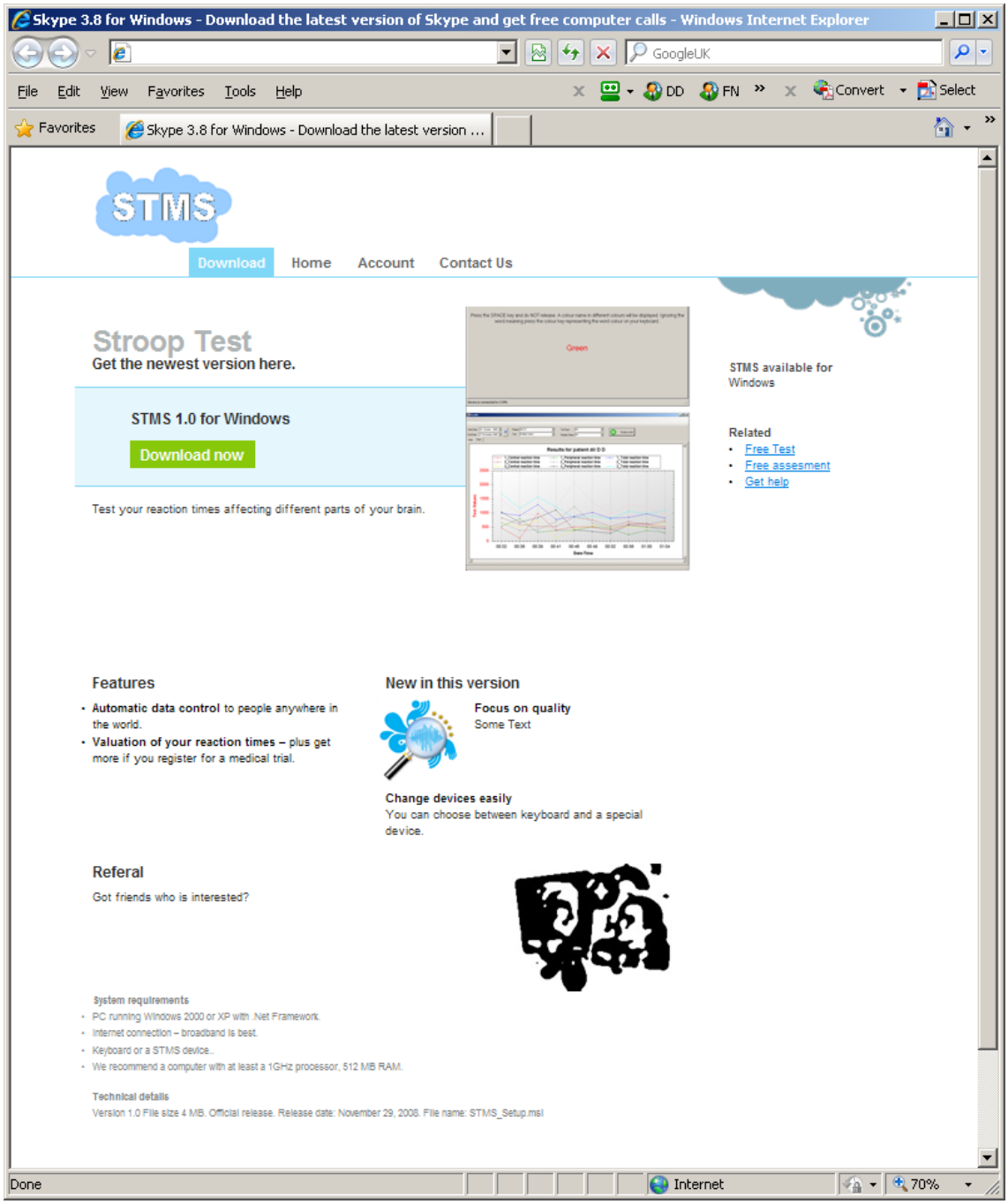


Figure 3.19. Web portal design for Stroop test software distribution.

3.5 Web portal deployment

A web portal is being developed allowing users to register and download the application for installation. The portal incorporates several pages including a user forum for discussions. The sketch of the web portal is displayed in Figure 3.19 above. Web based software distribution was made available only for a keyboard based Stroop test software at this initial stage. Users can download and install the application similar to other software such as Skype or Firefox browser. In order to use the software, users are required to register, after which username and a password is provided. Using a dedicated website allows faster distribution of the software.

3.6 Assessment process and proposed actions

Assessment of the current state of MS patients and healthy population can be performed using the reporting module of the software which provides preliminary data for analysis. It is not currently pre-programmed but can be setup for the system to monitor progress through its testing features and inform health professionals if certain parameters are likely to go beyond threshold values. These could be caused by regression in the test results or a sudden drop in result parameters. Having sufficient data for analysis the software can provide advice on the state of the MS patient allowing appropriate action to be taken in improving or at least stabilizing patient's status.

The Stroop test software can be customized for use in other diseases affecting Central Nervous System such as Parkinson's disease - progressive neurological condition affecting movements such as walking, talking, writing and exhibiting following symptoms:

1. Tremor - which usually begins in one hand. This is the first symptom for 70% of people with Parkinson's
2. Slowness of movement (bradykinesia) - people with Parkinson's may find that they have difficulty initiating movements or that performing movements takes longer.
3. Stiffness or rigidity of muscles - problems with activities such as standing up from a chair or rolling over in bed may be experienced.

These symptoms can be identified using the specialized device relatively easily with Test 4 as described earlier.

3.7 Discussion

The presented software application can potentially become a valuable diagnostic tool, in conjunction with other tests, in identifying patients with neurological diseases such as MS and PD, using Stroop test analysis. As a result a keyboard based Stroop test software was developed including reporting tools for analysis. Four types of tests have been pre-programmed with different applied techniques. The software will be freely distributed by the use of a web portal with registration capabilities. Due to the keyboard limitations a specialized device was designed and manufactured for which patent is currently pending. The device consists of 64 cells equipped with Hall sensors, which can identify the speed and the pressure applied to each cell. The precision of applied pressure can be identified much more precisely hence the analysis of error rates is more accurate. This will allow performing a more accurate and refined analysis compared to the data produced by the keyboard version.

Although the Stroop test software and device are in the development stage it can prove to be useful in identifying a disease at early stages or provide continuous monitoring of MS patient's health state. The Stroop test can be part of assessments when identifying some other neurological diseases affecting cognitive functions. It could become a key tool in the first step of patient diagnosis before referring to more advanced tests for further investigation. This might reduce the number of unnecessary tests which uses invasive techniques and other tests which are more expensive such as MRI and CT scans.

3.8 Conclusion

Automation of healthcare processes by introducing intelligent technologies require appropriate data which can be reliable and consistent. Eradication of erroneous data can save time and improve the quality of patients care. This dissertation describes the development of an EDC (Electronic Data Capture) system incorporating a set of other applications in order to achieve minimise and when possible eradicate manual interference. The devised software solutions and protocols ensure correctness of results by having reliable data. A set of security measures are used to ensure that communicated data is transmitted reliably enabling consistent diagnosis. An audit trail feature is integrated into the software applications as a standard safety measure. The developed EDC system equipped with intelligent features allows the prevention of errors and inconsistency in collected data. The system has been used in a clinical trial

environment, after conducting thorough validation procedures, and has been consistently shown to be fully accurate in data collection processes and valuable in providing ongoing data monitoring and study management. Another advantage of the system is the introduction of automated technologies by utilizing the existing medical devices, cutting the costs to a minimum. The EDC system has been tested against conventional procedures and showed the advantages of the system compared to existing techniques. Comparisons of the results proved the system reliability and advantage in data collection. All software solutions have been developed to be compliant to the FDA requirements. The system architecture is flexible allowing the inclusion of additional devices together with post processing modules.

Development of data acquisition systems using existing devices showed was satisfactory, however we were limited by technical possibilities of devices in some instances. Therefore, new type of input device has been development for building a Data Acquisition System for analysis and monitoring patients with neurological diseases. Hardware is designed with proprietary communication protocol and set of applications were developed for MS and PD patients allowing the use of Stroop test techniques. Initially, a keyboard based software for testing cognitive and muscular impairments as a result of diseases affecting Central Nervous System such as MS and PD was developed. The keyboard based application includes 4 varieties of tests which use similar techniques but with a different level of complexity. A web portal will be used for distributing and marketing the software. The specialized peripheral device has been designed and manufactured consisting of 64 cells equipped with Hall sensors, which can identify the speed (up to 2msec) and the pressure applied to each cell with more precision for which Patent is currently pending. The device can identify the precision of applied pressure much more accurately making possible deeper analysis. Using the software together with the specialized device can be potentially valuable in identifying diseases at an early stage, saving patients from invasive diagnosis techniques and may reduce the number of unnecessary tests. The application calculates 6 parameters that correspond to disease severity: total number of keys, the number of keys pressed correctly, Kinesia Score - the number of keystrokes in 60 seconds, Akinesia Time - cumulative time that keys are depressed, Dysmetria score - a weighted index calculated using the number of incorrectly hit keys corrected for speed and Arrhythmia score - a measure of rhythmicity which corresponds to the variance of the time interval between keystrokes. A custom set of statistical analysis can be performed

by using raw data provided by the software. The Stroop test software cannot fully ensure the diagnosis of MS or PD but can make significant contribution in the process of diagnosis and monitoring.

3.9 Future work

Electronic Data Capture system can be developed as a web based system allowing the performance of measurements without local network connection. An internet connection is sufficient for data exchange. One of the advantages is when conducting multi-site trials a web based EDC system can be used much more efficiently rather than a desktop based version.

The Stroop test application can be expanded by including additional tests. New patterns of results can be identified by specialists for easier monitoring of the state of patients. Disease progression can be monitored automatically by the software and a consultant notified only in case of emergencies.

An improvement can be made to a database structure by placing tables with personal information into a separate database such as names would be saved in another database and data would be recognised by Name-IDs only. The same approach can be used for Audit trail tables by placing them separately where even application database owner will not be able to access audit trail data.

4 Literature

1. “Introduction to the special issue on intelligent technologies in medicine and bioinformatics”, G.Magoulasa, G.Douniasb, Computers in Biology and Medicine, Volume 36, Issue 10 , October 2006, Pages 1155-1184.
2. “Smart technology”, S.Dillon, J.Blower, Building Engineer -London- Association Of Building Engineers, 2006, Vol 81; No 7, Pages 16-17.
3. “A Proposal for a Home-Based Health Monitoring System for the Elderly or Disabled”, K.H.Jun J.Bart, R.D.Hyun, Lecture Notes in Computer Science, Springer Berlin / Heidelberg, Computer Science, Volume 4061/2006, Pages 473-479.
4. “Intelligent monitoring system of bedridden elderly”, Y.Wei et al, Proceedings of SPIE, Volume 6040, ICMIT 2005: Mechatronics, MEMS, and Smart Materials.
5. “Medical data acquisition system for telemedicine applications”, M.F.A.Karim, R.Muhamad, Faculty of Engineering and Technology (FET), Multimedia University, Malaysia. WSEAS Transactions on Systems, Issue 11, Volume 5, 2006, Page 2588.
6. “Old Age, New Technology, and, Future Innovations in Disease Management and Home Health Care”, J.F.Coughlin, J.E.Pope, B.R.Leedle, Home Health Care Management & Practice, April 2006, Volume 18, Number 3, 2006 Sage Publications, Pages 196-207.
7. “Asynchronous Web-Based Patient-Centered, Home Telemedicine System”, C.Lau, R.S.Churchill, J.Kim, F.A.Matsen, Y.Kim, Transactions on Biomedical Engineering, Vol 49, No 12, 2002, Page 1452.
8. “Applying telecommunication technology to health-care delivery.” J.C.Lin, EECS and Bioengineering Departments, University of Illinois at Chicago. IEEE Engineering in Medicine and Biology, July/Aug 1999, Pages 28-31.
9. “An Intelligent Remote Monitoring System for Artificial Heart”, J.Choi, J.W.Park, J.Chung, B.G.Min, IEEE Transactions on Information Technology in Biomedicine, Vol. 9, No. 4, Dec 2005, Pages 564-573.
10. “Integrated design of the intelligent web-based Chinese Medical Diagnostic System (CMDS) – Systematic development for digestive health”, M.J.Huanga, M.Y.Chenb, Expert Systems with Applications, Volume 32, Issue 2, February 2007, Pages 658-673.

11. “Guardian: An Intelligent Autonomous Agent for Medical Monitoring and Diagnosis”, J.E.Larsson, B.Hayes-Roth, IEEE Intelligent Systems, 1998, Pages 58-64.
12. “Accuracy of intelligent medical systems”, P.Povalej, M.Lenin, M.Zorman, P.Kokol, D.Dinevski, Computer Methods and Programs in Biomedicine, Vol.80, Dec 2005, Pages S95-S105.
13. “Trends extraction and analysis for complex system monitoring and decision support”, S. Charbonnier, C. Garcia-Beltan, C. Cadet and S. Gentil, Engineering Applications of Artificial Intelligence, Volume 18, Issue 1, February 2005, Pages 21-36.
14. “Fuzzy logic in a patient supervision system”, S.Barroa, R.Marínb, F.Palaciosc, and R.Ruizd, Artificial Intelligence in Medicine, Volume 21, Issues 1-3 , January-March 2001, Pages 193-199.
15. “Design and validation of an intelligent patient monitoring and alarm system based on a fuzzy logic process model”. K.Beckera, B.Thulla, H.Käsmacher-Leidingerb, J.Stemmerb, G.Raua, G.Kalffb and H.J.Zimmermannc. Artificial Intelligence in Medicine, Volume 11, Issue 1 , September 1997, Pages 33-53.
16. “A study towards fuzzy logic-based assessment of nasal harmony of rhinoplasty patients”, T.Ozkul, M.H.Ozkul, Journal of the Franklin Institute, Volume 343, Issues 4-5, July-August 2006, Pages 329-339.
17. “A Decision Support System for Rheumatic Evaluation and Treatment in Oriental Medicine Using Fuzzy Logic and Neural Network”, C.Thang, E.W.Cooper, Y.Hoshino, K.Kamei, Modeling Decisions for Artificial Intelligence, Lecture Notes in Computer Science, 2005, Volume 3558/2005, Pages 399-409.
18. “MEDADVIS: A Medical Advisory System”, R.Khosla et al., KES 2005, LNAI 3682, Springer-Verlag Berlin, 2005, Pages 789-795.
19. “An Annotated Data Collection System to Support Intelligent Analysis of Intensive Care Unit Data”, X.Liu, P.Cohen, M.Berthold, Advances in Intelligent Data Analysis, Springer-Verlag Berlin Heidelberg, 1997, Pages111-121.

20. “Disease Diagnosis Support System Using Rules, Neural Network and Fuzzy Logic”, M.Gh.Negoita et al., KES 2004, LNAI 3214, 2004, Springer-Verlag Berlin Heidelberg, Pages 1114–1120.
21. “Intuitionistic Fuzzy Sets in Intelligent Data Analysis for Medical Diagnosis”, V.N.Alexandrov et al. ICCS 2001, LNCS 2074, Springer-Verlag Berlin Heidelberg, 2001, Pages 263-271.
22. “Self-Learning Fuzzy Logic Control in Medicine”, D.G.Mason, D.A.Linkens, N.D.Edwards, Lecture Notes In Computer Science; Vol. 1211, Proceedings of the 6th Conference on Artificial Intelligence in Medicine in Europe, 1997, Pages 300-303.
23. “Neural Based CAD and CAP Agent System Framework for High Risk Patients in Ubiquitous Environment”, L.Wang et al., Springer-Verlag Berlin Heidelberg, 2006, Pages 1054 – 1057.
24. “Multiple sclerosis and other demyelinating diseases”, S.L.Hauser et al., Harrison’s Principles of Internal Medicine. New York: McGraw-Hill; 1994. Pages 2287–2295.
25. “Oxford handbook of Clinical Medicine” M.Longmore et al, Seventh Edition, Oxford University Press, 2007.
26. "Multiple sclerosis", A.Compston, A.Coles, Lancet, 2008, 372(9648):1502-17.
27. “Stroop performance in multiple sclerosis: Information processing, selective attention, or executive functioning?” J.A.B. Macniven et al. Journal of the International Neuropsychological Society, Cambridge University Press, 2008.
28. "Studies of interference in serial verbal reactions", J.R. Stroop, Journal of Experimental Psychology, 1935.
29. "The Stroop colour-word test: a review", Jensen AR, 1966, Pages 36–93.
30. "Half a century of research on the Stroop effect: an integrative review", C.M.MacLeod, Psychological bulletin 109 (2), March 1991,Pages 163–203.
31. “The progress of cognitive decline in multiple sclerosis. A controlled 3-year follow-up”, P.Kujala, R.Portin and J.Ruutiainen, 1997, Pages, 289–297.
32. “Executive function in multiple sclerosis. The role of frontal lobe pathology”, J. Foong et al., Brain, 1997, Pages 15–26.

33. “Serendipity in science: A personal account” Kaplan, E. et al., Pathways to prominence in neuropsychology: Reflections of twentieth century pioneers. New York: Psychology Press, 2002.
34. “Experiments with a new boosting algorithm”, Y.Freund, R.E.Schapire, Proc. 13th Int. Conf. on Machine Learning, Morgan Kaufmann, San Francisco, CA, 1996, Pages 148-156.
35. “Stroop interference and negative priming in patients with multiple sclerosis”, M.Vitkovitch et al, Scopus, Neuropsychologia, Volume 40, Issue 9, 2002, Pages 1570-1576.
36. “Attention related performance in two cognitively different subgroups of patients with multiple sclerosis”, P. Kujala et al, Journal of Neurology, Neurosurgery & Psychiatry, 1995, Pages 77–82.
37. “Cognitive dysfunction in multiple sclerosis: I. Frequency, patterns, and prediction”, Rao, Stephen M. etal, Unverzagt, Frederick, Neurology, Vol 41(5), May 1991, Pages 685-691.
38. “Speed of information processing in patients with multiple sclerosis”, R.Kail, Journal of Clinical and Experimental Neuropsychology, Volume 20, Issue 1, 1998, Pages 98-106.

Appendix 1

Stroop test device communication protocol

REFLEX CONTROL COMMANDS

GENERAL CONSIDERATIONS

-- The matrix keys consist in 2 parts of 64 keys each area. (128 keys)

-- The control plots are composed of stream of three fields, this provides the system flexibility, open to future enlargements.

-- The keys are sized 20x20mm

-- Each key incorporates 3 RGB LEDs

-- The position of each key word is defined by an 8bit word (0-128)

-- The sensors give us a value between 0-255. (8bit resolution)

-- Communications 115200 bauds

With quotation marks:

"@" = (64 decimal)

"R" = (82 decimal)

"W" = (87 d)

"L" = (76 d)

Without quotation marks:

decimal 10 = 10

COMMANDS

The communication with the PC is master slave mode.

Master : PC

Slave : Matrix

1 º Command Field one character length

2 º Operation Field (0-255) one character length

3 º Data Field variable length

READ

Field 1 : "R" (82 decimal) read command

Field 2 : "@" (64 decimal) The mat Transmit to the PC a stream with 2*128 bytes of the position & value of each sensor [(position1, value1)(position2,value2)…(position n, value n)]

Example: PC transmits: "R" "@"

The mat returns: VX1 VX2 ….. VX128

(VX1….VX128 is a stream with the value of each cell, 128 data)

TRIGGER

Field 1 "T": Command Level

Field 2 Trigger Level

Example: PC Transmit "T" 50

The mat working in "S" 1 mode will transmit only the sensors above 50

OPERATION

Field 1 "S" Start / Stop : Start: continuous TX

Field 2 0 = Stop transmission

Field 2 1 = Start transmitting only the sensors above predefined trigger level (continuously mode)

WRITE

Scripture commands are used to turn on / off the LEDs

Field 1 º "W": (decimal 87): Writing

Field 2 "R" (decimal 82): network is the 3 rd field position led

Field 2 "G" (decimal 71): green field is the 3 rd position led

Field 2 "B" (decimal 66): blue field is the 3 rd position led

Field 3 255 : All Leds ON

Field 3 0 : All Leds OFF

Field 3 Position Led

(Field 4)* Flag On/Off Led: If previously led ON□now led OFF and vice versa

Examples:

"W" "R" 74 1 decimal stream 87 82 74 1 : Puts ON the Red led the of the cell 74

"W" "B" 75 1 decimal stream 87 82 75 0 : Puts OFF the Blue led the of the cell 75

"W " 255 decimal stream 87 255 All Leds ON

"W " 0 decimal stream 87 0 All Leds OFF

SPECIAL COMMANDS

C This command is only to test the communications and only contains one field

The PC send "C"

The mat returns "C"

Appendix 2

Stroop test device communication protocol testing

REFLEX USER'S INTERFACE

Once program is started, the following screen appears. Cells will show the value of sensors. Each value is represented in the corresponding position. At this time only 16 sensors are enabled (1) controlled by command buttons (2).

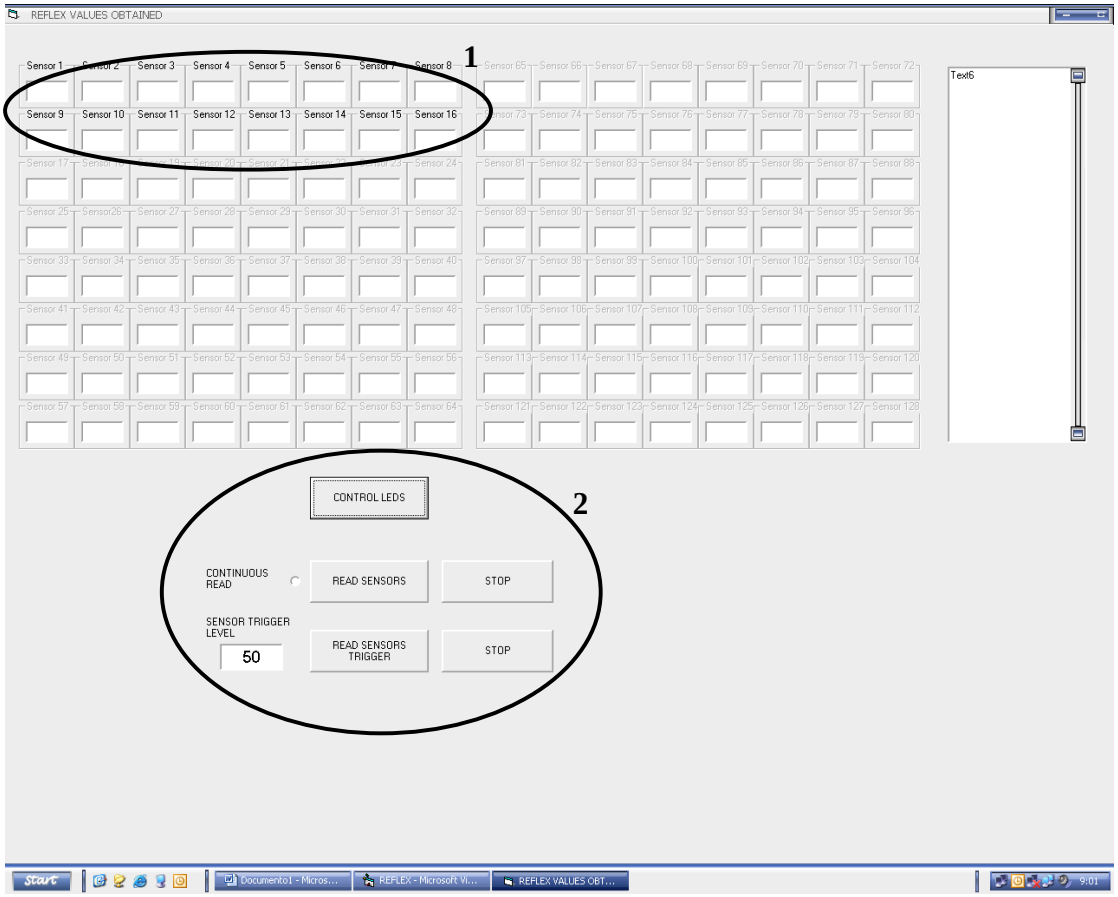


Figure 1

COMMAND BUTTONS

READ SENSOR

If option Continuous Read is not activated, program reads and represents value of 16 sensors only once. Otherwise, if option is ON, values are represented continuously, until we press STOP (Figure 2).

READ SENSORS TRIGGER

When the button is pressed, display shows (continuously) sensors above trigger level. Trigger level is indicated (and it can be modified) in the text box allocated in left side of button. In the text box on the right side of screen sensors and values will be shown above trigger level (Figure 3). When we want to stop this operation, we must

press the STOP button. When we press this button, a new window will open up with the option save file (Figure 4).

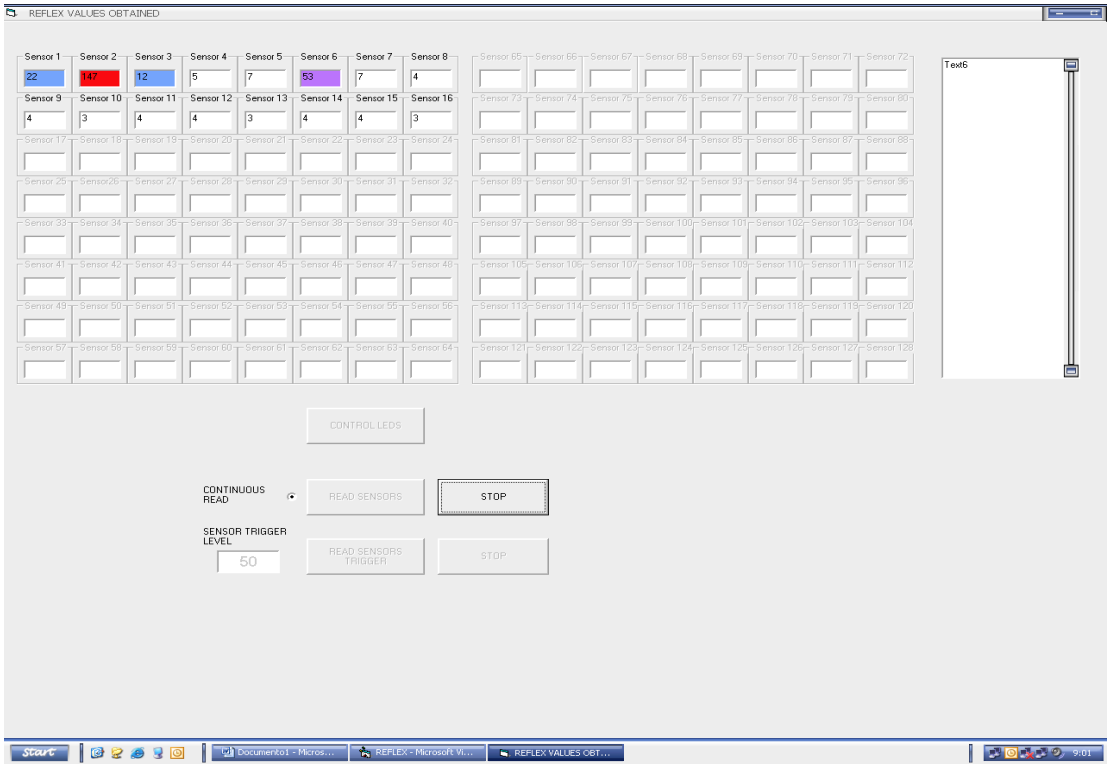


Figure 2

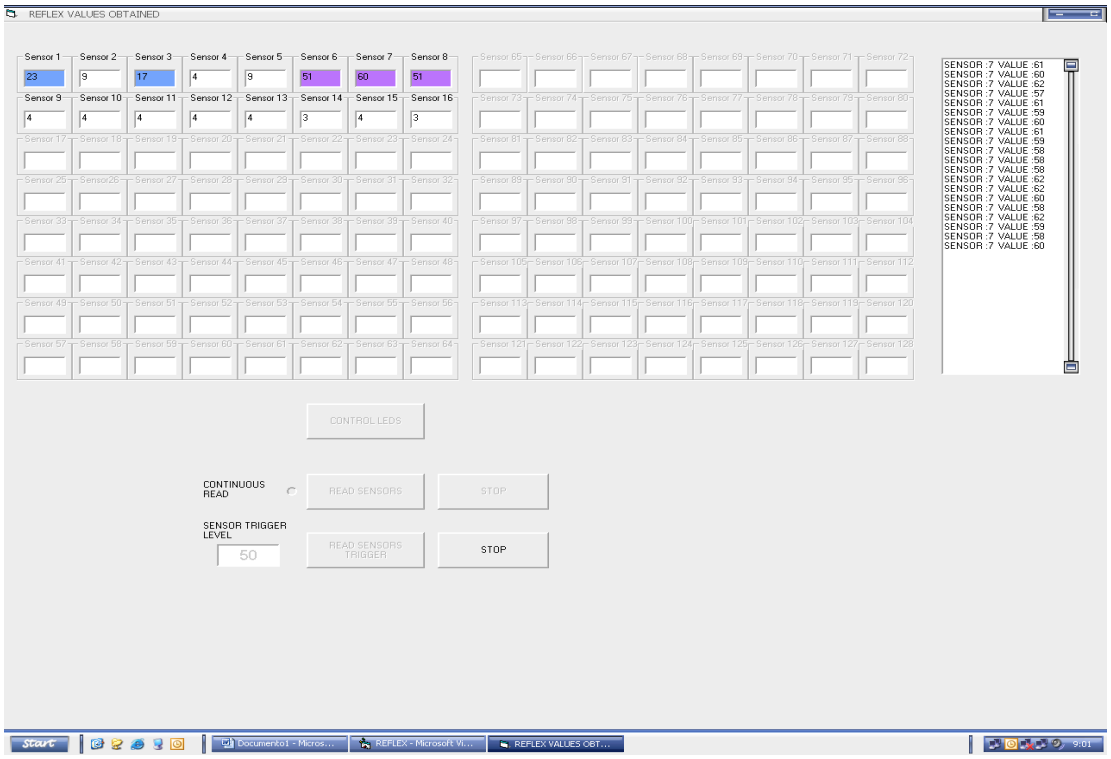


Figure 3

CONTROL LEDS: Once this button is pressed, led control screen will be displayed (Figure 5).

In this new screen we'll find 3 command buttons:

- ALL LEDs OFF
- ALL LEDs ON
- SENSOR VALUES: Returns to the previous screen.

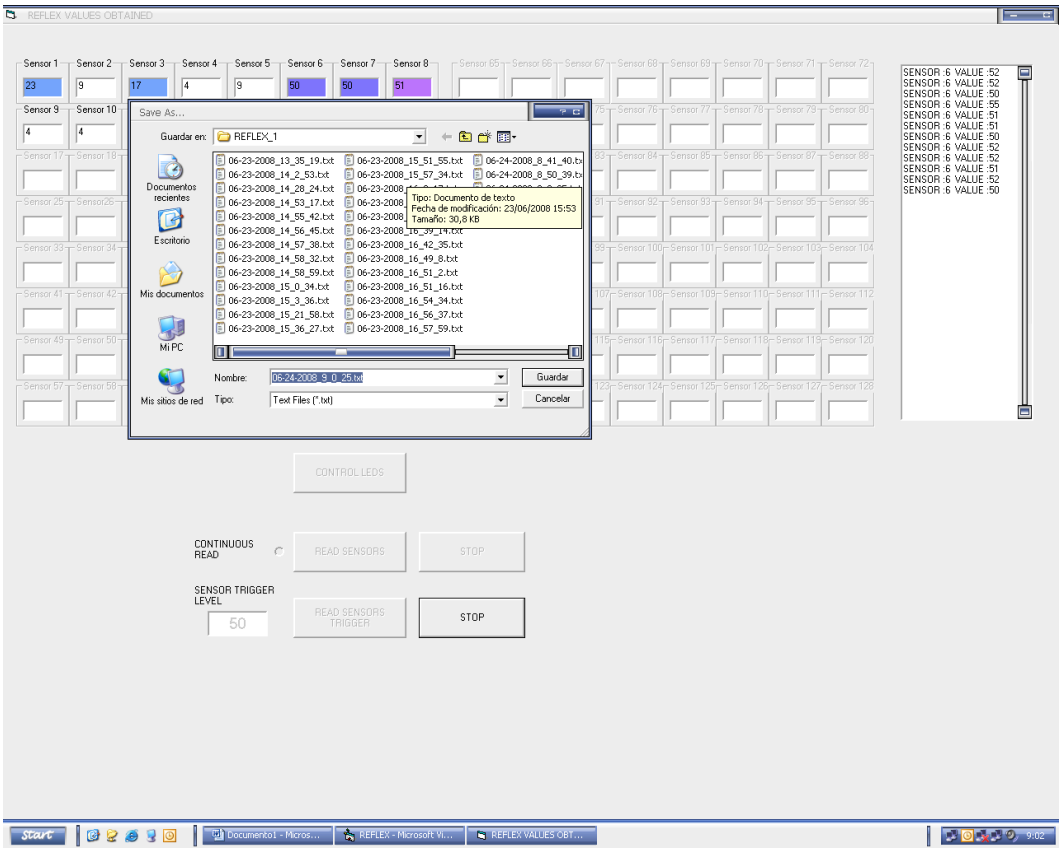


Figure 4

In control leds screen we can control each LED individually, pressing in each symbol, see Figure 6.

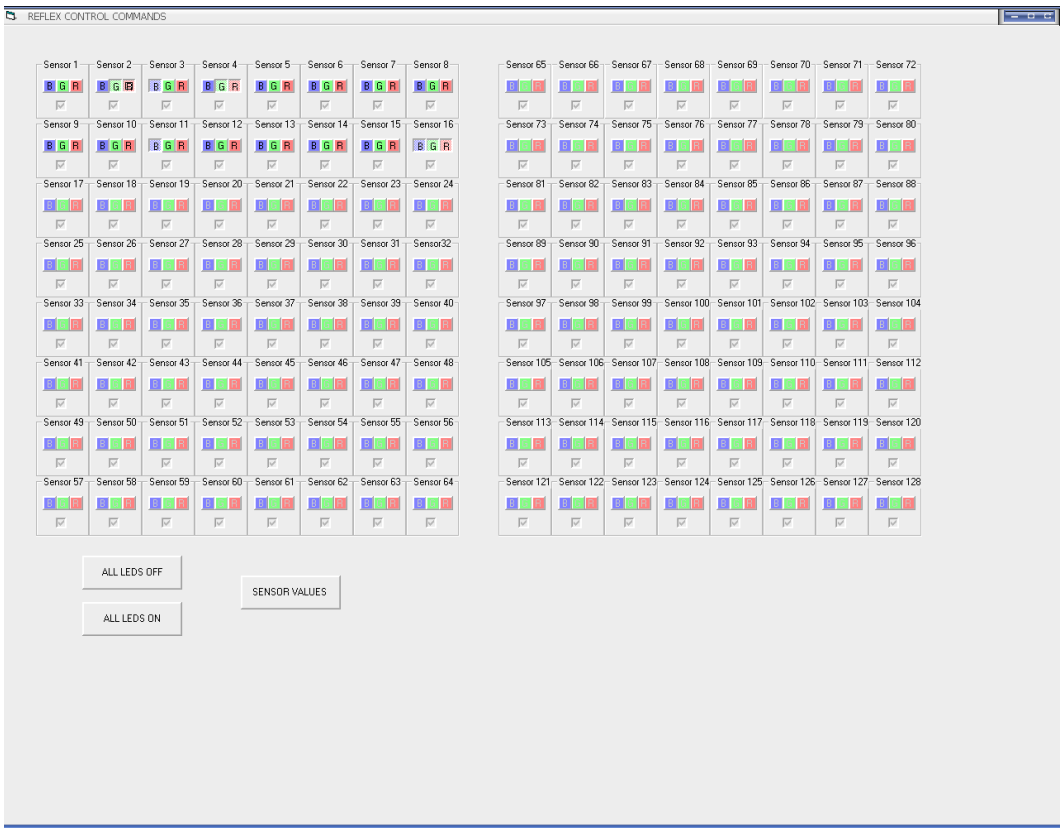


Figure 5

Figure 6

Appendix 3

[Code of Federal Regulations]
[Title 21, Volume 1]
[Revised as of April 1, 2010]
[CITE: 21CFR11]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 11 ELECTRONIC RECORDS;
ELECTRONIC SIGNATURES

Subpart A--General Provisions

Sec. 11.1 Scope.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.
(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.
(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.
(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with 11.2, unless paper records are specifically required.
(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.
(f) This part does not apply to records required to be established or maintained by 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.
[62 FR 13464, Mar. 20, 1997, as amended at 69 FR 71655, Dec. 9, 2004]

Sec. 11.2 Implementation.

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional

signatures, in whole or in part, provided that the requirements of this part are met.
(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:
(1) The requirements of this part are met; and
(2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Sec. 11.3 Definitions.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.
(b) The following definitions of terms also apply to this part:
(1)*Act* means the Federal Food, Drug, and Cosmetic Act (secs. 201-903 (21 U.S.C. 321-393)).
(2)*Agency* means the Food and Drug Administration.
(3)*Biometrics* means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.
(4)*Closed system* means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.
(5)*Digital signature* means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.
(6)*Electronic record* means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
(7)*Electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.
(8)*Handwritten signature* means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture

the name or mark.
(9)*Open system* means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B--Electronic Records

Sec. 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:
(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.
(d) Limiting system access to authorized individuals.
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.
(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.
(k) Use of appropriate controls over systems documentation including:
(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Sec. 11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Sec. 11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
(1) The printed name of the signer;
(2) The date and time when the signature was executed; and
(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.
(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Sec. 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C--Electronic Signatures

Sec. 11.100 General requirements.

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.
(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
(1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.
(2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Sec. 11.200 Electronic signature components and controls.

(a) Electronic signatures that are not based upon biometrics shall:
(1) Employ at least two distinct identification components such as an identification code and password.
(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.
(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.
(2) Be used only by their genuine owners; and
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.
(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Sec. 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:
(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.
(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).
(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.
(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.
(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

Authority: 21 U.S.C. 321-393; 42 U.S.C. 262.
Source: 62 FR 13464, Mar. 20, 1997, unless otherwise noted.

Appendix 4

Automatic and manual record comparison

RPL-Id	Recorded DateTime	Syst	Dias	HR	MAP	OXY	RPL-Id	DateTime	Syst	Dias	HR	MAP	Oxy
50001	06/03/2010 13:46:21	119	70	66	91	0	50001	06/03/2010 13:46:00	119	70	66	91	0
50011	06/03/2010 13:59:16	115	74	72	88	100	50011	06/03/2010 13:59:00	115	74	72	88	100
50012	06/03/2010 14:02:48	107	68	69	80	100	50012	06/03/2010 14:03:00	107	68	70	72	100
50013	06/03/2010 14:04:45	112	66	77	87	100	50013	06/03/2010 14:04:00	112	66	72	77	100
50014	06/03/2010 14:06:34	107	68	71	82	100	50014	06/03/2010 14:06:00	107	68	68	82	100
50015	06/03/2010 14:08:20	112	70	75	81	100	50015	06/03/2010 14:08:00	112	70	73	81	100
50016	06/03/2010 14:09:57	110	73	70	82	100	50016	06/03/2010 14:09:00	110	73	67	82	100
50017	06/03/2010 14:11:15	114	68	72	79	100	50017	06/03/2010 14:11:00	114	68	72	79	100
50018	06/03/2010 14:18:50	116	68	81	92	100	50018	06/03/2010 14:18:00	116	68	86	82	100
50019	06/03/2010 14:20:30	119	69	79	86	100	50019	06/03/2010 14:20:00	119	69	81	86	100
50020	06/03/2010 14:22:27	112	67	70	85	100	50020	06/03/2010 14:22:00	112	67	70	85	100
50011	06/03/2010 15:11:25	117	68	94	83	100	50011	06/03/2010 15:11:00	117	68	88	83	100
50012	06/03/2010 15:13:38	117	70	92	87	100	50012	06/03/2010 15:13:00	117	70	89	87	100
50013	06/03/2010 15:14:45	109	67	85	85	100	50013	06/03/2010 15:14:00	109	67	85	85	100
50014	06/03/2010 15:17:02	110	65	83	84	100	50014	06/03/2010 15:16:00	110	65	84	84	100
50015	06/03/2010 15:19:25	108	63	90	81	100	50015	06/03/2010 15:19:00	108	63	89	81	100
50016	06/03/2010 15:20:47	108	68	86	92	100	50016	06/03/2010 15:20:00	108	68	89	92	100
50017	06/03/2010 15:22:48	115	69	93	85	100	50017	06/03/2010 15:22:00	115	69	91	85	100
50011	06/03/2010 18:42:34	100	71	75	86	0	50011	06/03/2010 18:42:00	100	71	75	:	0
50012	06/03/2010 18:44:54	105	71	75	82	0	50012	06/03/2010 18:45:00	105	71	75	82	0
50013	06/03/2010 18:49:17	126	76	62	89	0	50013	06/03/2010 18:49:00	126	76	62	89	0
50014	06/03/2010 18:50:28	123	77	67	96	0	50014	06/03/2010 18:50:00	123	77	67	96	0
50015	06/03/2010 18:51:53	128	80	71	105	0	50015	06/03/2010 18:52:00	128	80	71	105	0
50016	06/03/2010 18:54:46	127	64	64	94	0	50016	06/03/2010 18:54:00	127	64	64	94	0
50016	06/03/2010 18:59:35	124	66	64	92	0	50016	06/03/2010 00:00:00	124	66	64		0
50017	06/03/2010 19:06:14	109	69	61	88	0	50017	06/03/2010 19:06:00	109	69	61	86	0
50018	06/03/2010 19:07:21	119	77	65	95	0	50018	06/03/2010 19:07:00	119	77	65	95	0

RPL-Id	Recorded DateTime	Syst	Dias	HR	MAP	OXY	RPL-Id	DateTime	Syst	Dias	HR	MAP	Oxy
50019	06/03/2010 19:08:39	111	72	65	86	0	50019	06/03/2010 19:08:00	111	72	65	86	0
50020	06/03/2010 19:09:55	114	69	63	83	0	50020	06/03/2010 19:10:00	114	69	63	83	0
50011	06/03/2010 20:23:16	108	76	69	90	0	50011	06/03/2010 20:23:00	108	76	69	90	0
50012	06/03/2010 20:24:54	119	73	73	90	0	50012	06/03/2010 20:25:00	119	73	73	90	0
50014	06/03/2010 20:30:33	126	78	82	100	0	50014	06/03/2010 20:30:00	126	78	82	100	0
50015	06/03/2010 20:31:47	137	74	78	88	0	50015	06/03/2010 20:31:00	137	74	78	88	0
50016	06/03/2010 20:34:01	133	70	80	91	0	50016	06/03/2010 20:33:00	133	70	80	91	0
50017	06/03/2010 20:35:38	135	81	76	92	0	50017	06/03/2010 20:35:00	135	81	76	92	0
50018	06/03/2010 20:38:09	133	76	79	96	0	50018	06/03/2010 20:37:00	133	76	79	96	0
50019	06/03/2010 20:39:14	129	72	84	89	0	50019	06/03/2010 20:38:00	129	72	84	89	0
50020	06/03/2010 20:41:52	133	76	74	94	0	50020	06/03/2010 20:41:00	133	76	74	94	0
50011	06/03/2010 20:46:43	141	63	90	88	0	50011	06/03/2010 20:46:00	141	63	90	88	0
50012	06/03/2010 20:47:48	127	89	79	102	0	50012	06/03/2010 20:47:00	127	89	79	102	0
50013	06/03/2010 20:48:50	123	73	84	88	0	50013	06/03/2010 20:48:00	123	73	84	88	0
50014	06/03/2010 20:49:52	121	74	82	93	0	50014	06/03/2010 20:49:00	121	74	82	93	0
50015	06/03/2010 20:52:37	119	73	86	91	0	50015	06/03/2010 20:51:00	119	73	86	91	0
50016	06/03/2010 20:53:47	118	87	80	97	0	50016	06/03/2010 20:53:00	118	87	80	97	0
50017	06/03/2010 20:56:26	121	93	86	104	0	50017	06/03/2010 20:55:00	121	93	86	104	0
50018	06/03/2010 20:59:01	122	89	52	102	0	50018	06/03/2010 20:58:00	122	89	52	102	0
50019	06/03/2010 21:01:05	124	87	84	98	0	50019	06/03/2010 21:00:00	124	87	84	98	0
50020	06/03/2010 21:03:14	124	81	79	103	0	50020	06/03/2010 21:02:00	124	81	79	103	0
50011	06/03/2010 22:32:26	129	80	68	96	0	50011	06/03/2010 22:31:00	129	80	68	96	0
50012	06/03/2010 22:34:15	122	63	68	88	0	50012	06/03/2010 22:33:00	122	63	68	88	0
50013	06/03/2010 22:36:00	121	77	65	90	0	50013	06/03/2010 22:35:00	121	77	65	90	0
50014	06/03/2010 22:37:52	134	76	74	96	0	50014	06/03/2010 22:37:00	134	76	74	96	0
50015	06/03/2010 22:39:49	117	72	67	94	0	50015	06/03/2010 22:39:00	117	72	67	94	0
50016	06/03/2010 22:41:35	118	73	70	88	0	50016	06/03/2010 22:40:00	118	73	70	88	0
50017	06/03/2010 22:42:47	122	77	63	91	0	50017	06/03/2010 22:42:00	122	77	63	91	0
50018	06/03/2010 22:44:59	124	73	69	92	0	50018	06/03/2010 22:44:00	124	73	69	92	0
50019	06/03/2010 22:47:14	125	69	68	89	0	50019	06/03/2010 22:46:00	125	69	68	89	0

RPL-Id	Recorded DateTime	Syst	Dias	HR	MAP	OXY	RPL-Id	DateTime	Syst	Dias	HR	MAP	Oxy
50020	06/03/2010 22:48:45	119	74	66	89	0	50020	06/03/2010 22:48:00	119	74	66	89	0
50011	06/03/2010 23:28:34	119	81	69	96	0	50011	06/03/2010 23:28:00	119	81	69	96	0
50012	06/03/2010 23:31:54	112	75	72	87	0	50012	06/03/2010 23:31:00	112	75	72	87	0
50013	06/03/2010 23:35:57	115	75	66	89	0	50013	06/03/2010 23:35:00	115	75	66	89	0
50014	06/03/2010 23:37:43	110	69	80	84	0	50014	06/03/2010 23:37:00	110	69	80	84	0
50015	06/03/2010 23:40:42	114	72	67	91	0	50015	06/03/2010 23:40:00	114	72	67	91	0
50016	06/03/2010 23:42:36	119	71	68	92	0	50016	06/03/2010 23:42:00	119	71	68	92	0
50017	06/03/2010 23:44:23	113	77	70	90	0	50017	06/03/2010 23:44:00	113	77	70	90	0
50018	06/03/2010 23:45:47	113	74	65	88	0	50018	06/03/2010 23:45:00	113	74	65	88	0
50019	06/03/2010 23:46:57	116	76	67	90	0	50019	06/03/2010 23:46:00	116	76	67	90	0
50020	06/03/2010 23:48:29	116	69	70	84	0	50020	06/03/2010 23:48:00	116	69	70	84	0
50011	07/03/2010 06:16:56	128	69	70	87	0	50011	07/03/2010 06:16:00	128	69	70	87	0
50012	07/03/2010 06:18:16	115	77	76	94	0	50012	07/03/2010 06:17:00	115	77	76	94	0
50013	07/03/2010 06:19:51	127	77	67	92	0	50013	07/03/2010 06:19:00	127	77	67	92	0
50014	07/03/2010 06:21:10	118	75	67	97	0	50014	07/03/2010 06:20:00	118	75	67	97	0
50015	07/03/2010 06:22:32	115	80	79	95	0	50015	07/03/2010 06:21:00	115	80	79	95	0
50016	07/03/2010 06:24:45	117	70	59	87	0	50016	07/03/2010 06:24:00	117	70	59	87	0
50017	07/03/2010 06:27:10	130	74	74	108	0	50017	07/03/2010 06:26:00	130	74	74	108	0
50018	07/03/2010 06:28:55	119	70	81	91	0	50018	07/03/2010 06:28:00	119	70	81	91	0
50019	07/03/2010 06:30:13	111	71	78	90	0	50019	07/03/2010 06:29:00	111	71	78	90	0
50020	07/03/2010 06:31:21	115	73	63	87	0	50020	07/03/2010 06:30:00	115	73	63	87	0
50011	07/03/2010 06:35:00	111	65	80	86	0	50011	07/03/2010 06:34:00	111	65	80	86	0
50012	07/03/2010 06:37:35	95	72	68	84	0	50012	07/03/2010 06:37:00	95	72	68	84	0
50013	07/03/2010 06:38:38	122	76	61	91	0	50013	07/03/2010 06:38:00	122	76	61	91	0
50014	07/03/2010 06:39:44	109	76	69	89	0	50014	07/03/2010 06:39:00	109	76	69	89	0
50015	07/03/2010 06:40:45	125	76	72	95	0	50015	07/03/2010 06:40:00	125	76	72	95	0
50016	07/03/2010 06:41:53	123	74	62	92	0	50016	07/03/2010 06:41:00	123	74	62	92	0
50017	07/03/2010 06:42:59	117	76	65	89	0	50017	07/03/2010 06:42:00	117	76	65	89	0
50018	07/03/2010 06:45:16	105	80	81	93	0	50018	07/03/2010 06:44:00	105	80	81	93	0
50019	07/03/2010 06:46:20	121	69	72	97	0	50019	07/03/2010 06:45:00	121	69	72	97	0

RPL-Id	Recorded DateTime	Syst	Dias	HR	MAP	OXY	RPL-Id	DateTime	Syst	Dias	HR	MAP	Oxy
50020	07/03/2010 06:48:27	122	69	73	93	0	50020	07/03/2010 06:47:00	122	69	73	93	0
50011	07/03/2010 07:02:17	123	75	62	102	0	50011	07/03/2010 07:01:00	123	75	62	102	0
50012	07/03/2010 07:08:00	119	74	74	94	0	50012	07/03/2010 07:07:00	119	74	74	94	0
50013	07/03/2010 07:09:11	132	72	72	89	0	50013	07/03/2010 07:08:00	132	72	72	89	0
50014	07/03/2010 07:10:24	111	65	61	76	0	50014	07/03/2010 07:09:00	111	65	61	76	0
50015	07/03/2010 07:11:45	107	77	74	87	0	50015	07/03/2010 07:10:00	107	77	74	87	0
50016	07/03/2010 07:12:48	113	79	73	94	0	50016	07/03/2010 07:12:00	113	79	73	94	0
50017	07/03/2010 07:22:31	116	76	93	93	0	50017	07/03/2010 07:21:00	116	76	93	93	0
50018	07/03/2010 07:25:37	109	70	72	93	0	50018	07/03/2010 07:24:00	109	70	72	93	0
50019	07/03/2010 07:28:16	115	83	77	97	0	50019	07/03/2010 07:27:00	115	83	77	97	0
50020	07/03/2010 07:29:22	126	70	72	91	0	50020	07/03/2010 07:28:00	126	70	72	91	0
50012	07/03/2010 10:07:23	112	74	78	84	0	50012	07/03/2010 10:07:00	112	74	78	84	0
50013	07/03/2010 10:08:48	102	72	78	86	0	50013	07/03/2010 10:08:00	102	72	78	86	0
50014	07/03/2010 10:10:11	99	72	78	81	0	50014	07/03/2010 10:09:00	99	72	78	81	0
50015	07/03/2010 10:11:14	101	74	81	84	0	50015	07/03/2010 10:11:00	101	74	81	84	0
50016	07/03/2010 10:12:21	103	69	79	90	0	50016	07/03/2010 10:12:00	103	69	79	90	0
50017	07/03/2010 10:13:28	105	71	74	81	0	50017	07/03/2010 10:13:00	105	71	74	81	0
50018	07/03/2010 10:14:44	93	63	79	76	0	50018	07/03/2010 10:14:00	93	63	79	76	0
50019	07/03/2010 10:15:54	110	68	78	75	0	50019	07/03/2010 10:15:00	110	68	78	75	0
50020	07/03/2010 10:17:11	104	64	80	81	0	50020	07/03/2010 10:16:00	104	64	80	81	0
50012	07/03/2010 10:47:16	99	68	74	80	0	50012	07/03/2010 10:46:00	99	68	74	80	0
50013	07/03/2010 10:48:17	97	65	78	77	0	50013	07/03/2010 10:47:00	97	65	78	77	0
50014	07/03/2010 10:49:18	98	70	72	79	0	50014	07/03/2010 10:48:00	98	70	72	79	0
50015	07/03/2010 10:50:22	102	68	77	77	0	50015	07/03/2010 10:49:00	102	68	77	77	0
50017	07/03/2010 10:52:47	102	67	79	81	0	50017	07/03/2010 10:52:00	102	67	78	81	0
50018	07/03/2010 10:54:05	99	62	73	77	0	50018	07/03/2010 10:54:00	99	62	73	77	0
50019	07/03/2010 10:55:21	95	68	83	77	0	50019	07/03/2010 10:54:00	95	68	83	77	0
50020	07/03/2010 10:56:20	101	70	76	81	0	50020	07/03/2010 10:55:00	101	70	76	81	0
50011	07/03/2010 10:59:12	101	67	80	88	0	50011	07/03/2010 10:58:00	101	67	80	88	0
50012	07/03/2010 11:00:15	96	70	77	82	0	50012	07/03/2010 11:00:00	96	70	77	82	0

RPL-Id	Recorded DateTime	Syst	Dias	HR	MAP	OXY	RPL-Id	DateTime	Syst	Dias	HR	MAP	Oxy
50013	07/03/2010 11:01:21	100	70	80	82	0	50013	07/03/2010 11:01:00	100	70	80	82	0
50014	07/03/2010 11:02:24	94	62	78	72	0	50014	07/03/2010 11:02:00	94	62	78	72	0
50015	07/03/2010 11:03:26	96	68	77	78	0	50015	07/03/2010 11:03:00	96	68	77	78	0
50017	07/03/2010 11:05:50	88	69	80	74	0	50017	07/03/2010 11:05:00	88	69	80	74	0
50018	07/03/2010 11:06:57	97	65	73	73	0	50018	07/03/2010 11:06:00	97	65	73	73	0
50020	07/03/2010 11:09:37	103	69	75	79	0	50020	07/03/2010 11:09:00	103	69	75	79	0
50016	07/03/2010 11:11:54	91	68	79	75	0	50016	07/03/2010 11:12:00	91	68	79	75	0
50011	07/03/2010 11:22:33	116	63	63	79	0	50011	07/03/2010 11:22:00	116	63	63	79	0
50012	07/03/2010 11:24:52	124	56	67	83	0	50012	07/03/2010 11:24:00	124	56	67	83	0
50012	07/03/2010 11:27:21	110	59	59	78	0	50012	07/03/2010 11:27:00	110	59	59	:	0
50013	07/03/2010 11:32:08	121	55	65	77	0	50013	07/03/2010 11:32:00	121	55	65	77	0
50014	07/03/2010 11:33:35	118	55	71	80	0	50014	07/03/2010 11:33:00	118	55	71	80	0
50015	07/03/2010 11:35:15	112	62	61	80	0	50015	07/03/2010 11:34:00	112	62	61	80	0
50016	07/03/2010 11:36:55	108	59	70	78	0	50016	07/03/2010 11:36:00	108	59	70	78	0
50017	07/03/2010 11:38:32	107	63	65	78	0	50017	07/03/2010 11:38:00	107	63	65	78	0
50018	07/03/2010 11:40:07	111	61	63	79	0	50018	07/03/2010 11:39:00	111	61	63	79	0
50019	07/03/2010 11:41:28	118	58	59	82	0	50019	07/03/2010 11:40:00	118	58	59	82	0
50020	07/03/2010 11:43:12	111	57	63	81	0	50020	07/03/2010 11:42:00	111	57	63	81	0
50011	07/03/2010 11:48:37	109	58	66	76	0	50011	07/03/2010 11:47:00	109	58	66	76	0
50012	07/03/2010 11:57:14	115	56	58	74	0	50012	07/03/2010 11:56:00	115	56	58	74	0
50013	07/03/2010 11:58:32	111	58	60	80	0	50013	07/03/2010 11:57:00	111	58	60	80	0
50014	07/03/2010 11:59:39	110	60	62	84	0	50014	07/03/2010 11:59:00	110	60	62	84	0
50015	07/03/2010 12:02:20	111	50	66	83	0	50015	07/03/2010 12:01:00	111	50	66	83	0
50016	07/03/2010 12:03:49	113	61	61	77	0	50016	07/03/2010 12:03:00	113	61	61	77	0
50017	07/03/2010 12:07:12	121	61	64	85	0	50017	07/03/2010 12:05:00	121	61	64	85	0
50018	07/03/2010 12:10:22	110	55	67	75	0	50018	07/03/2010 12:09:00	110	55	67	75	0
50019	07/03/2010 12:12:26	102	58	63	80	0	50019	07/03/2010 12:11:00	102	58	63	80	0
50020	07/03/2010 12:13:36	109	71	63	83	0	50020	07/03/2010 12:13:00	109	71	63	83	0
50011	07/03/2010 12:24:06	108	56	62	81	0	50011	07/03/2010 12:22:00	108	56	62	81	0
50012	07/03/2010 12:25:43	118	58	59	88	0	50012	07/03/2010 12:25:00	118	58	59	88	0

RPL-Id	Recorded DateTime	Syst	Dias	HR	MAP	OXY	RPL-Id	DateTime	Syst	Dias	HR	MAP	Oxy
50013	07/03/2010 12:27:15	112	59	57	86	0	50013	07/03/2010 12:26:00	112	59	57	86	0
50014	07/03/2010 12:30:10	115	59	60	81	0	50014	07/03/2010 12:29:00	115	59	60	81	0
50015	07/03/2010 12:31:15	109	62	56	80	0	50015	07/03/2010 12:30:00	109	62	56	80	0
50017	07/03/2010 12:33:55	111	58	60	79	0	50017	07/03/2010 12:33:00	111	58	60	79	0
50018	07/03/2010 12:39:12	107	59	56	81	0	50018	07/03/2010 12:38:00	107	59	56	81	0
50019	07/03/2010 12:40:40	111	60	54	82	0	50019	07/03/2010 12:40:00	111	60	54	82	0
50020	07/03/2010 12:43:48	118	54	66	80	0	50020	07/03/2010 12:43:00	118	54	66	80	0