COOP-CT-2003-508154

HAEMOSCAN

Development of a Technology to measure body fluid distribution in patients to improve dialysis treatment efficiency and patient comfort

Specific Research Project for SMEs (CRAFT)

PUBLISHABLE FINAL ACTIVITY REPORT

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PURPOSE

This document contains the Publishable Final Activity Report, as part of the contract's Final Report.

It is therefore one element of deliverable D11, as defined in the Annex I – "Description of the Work" in contract [AD 1].

SCOPE

This document provides a summary of the project activities and the results obtained. Reporting is done following the guidelines and recommendations established in [RD 2].

APPLICABLE AND REFERENCE DOCUMENTS

Applicable Documents

[AD 1] EC Contract N. COOP-CT-2003-508154-HAEMOSCAN for the implementation of the "*Development of a Technology to measure body fluid distribution in patients to improve dialysis treatment efficiency and patient comfort*" project, plus

Amendment Nº. 1 to Contract COOP-CT-2003-508154-HAEMOSCAN, dated 11/08/06, granting a 6.month extension of the contract.

Reference Documents

[RD 1] NTE Fax Ref. F-122-02-04/JM, dated 18/11/04

[RD 2] Project Reporting in FP6. *Guidance notes for Integrated Projects, Networks of Excellence, Specific Targeted Research or Innovation Projects, Coordination Actions, Specific Support Actions, Co-operative Research Projects and Collective Research Projects.* October 2004.

1. PROJECT EXECUTION

1.1 Project objectives

The HAEMOSCAN project pursues the solution of a clinically relevant problem. Currently, about 25% of all patients requiring haemodialysis treatment suffer from complications derived from haemodynamic instability during the haemodialysis sessions due to symptomatic hypotension. These instabilities cause discomfort to the patients suffering fainting, vomits and requiring relative long recovery periods. In addition to the associated morbidity, derived psychological problems affecting these patients are also important.

The referred instabilities are partly due to inadequate fluid amongst the various compartments in the body, as shown in several publications and studies performed in the last years. Therefore, an accurate estimation of the fluid distribution in the patient during the haemodialysis sessions could help defining the measures to maintain the proper fluid balance thus preventing the raise of such crisis.

Up to date there are no suitable methods to measure on line this distribution with enough accuracy. The HAEMOSCAN project proposes the use of a non-invasive method that, by means of segmental, multifrequency bioimpedance measurements, would allow to measure on line the haemodynamic behaviour in patients undergoing haemodialysis treatment. This can be achieved by developing a non-invasive electronic medical device able to perform local bioimpedance measurements from the body tissues. Conveniently treated, the obtained bioimpedance signals can deliver useful information on body fluid balance.

The HAEMOSCAN system is composed of the following elements:

- The HAEMOSCAN medical device. It is a lightweight sensor that can be attached to the patient while undergoing haemodialysis. This device is connected to the patient through four electrodes. When in measurement mode the sensor injects a small current and detects the voltage drop thus measuring the bioimpedance of the tissues
- A central PC, connected to several HAEMOSCAN sensors, each corresponding to one patient. The PC controls the activity of these sensors and also processes the bioimpedance raw data measurements. Data process is performed through built-in estimators that convert the row engineering values into meaningful clinical information

Therefore, the ultimate goal of the HAEMOSCAN project is the design, development and empirical (clinical) verification of a measurement system based on a medical device using electrical impedance spectroscopy technology that allows the determination of body fluid distribution in patients requiring haemodialysis treatment, to improve its efficiency and patient comfort by early detection and prevention of the symptomatic hypotension crisis that affect about 25% of the total population requiring chronic haemodialysis treatment.

1.2 Project consortium

A Consortium integrated by the following contractors developed the HAEMOSCAN project:

1. IBP Instruments GmbH (D), SME

2. *MSV Mediinzinische Systeme GmbH* (D), SME
3. *AKERN Srl* (I), SME
4. NTE SA (E), acting as coordinator and RTD Performer
5. *Universitat Politècnica de Catalunya, UPC,* (E), RTD Performer
6. *Technische Universität Graz, TUG,* (A), RTD Performer

The RTD performers (NTE, UPC and TUG) have a wide experience in developing systems based on biompedance technology in medical applications but also in other applications like biotechnology or food industry. Some of these developments are under European patents.

The sector of instrumentation companies for dialysis applications is mostly concentrated in large multinationals, usually based in the United States. These companies focus their activities on treatment-based instrumentation (filtration systems with control strategies). Some small companies are also active in the dialysis instrumentation field, few of them located in Europe, but their activity fields are somehow limited by the multinational's dominant position. Nevertheless, the development of dialysis related products such as the HAEMOSCAN sensor is regarded as an interesting market opportunity. For this reason three European SMEs are participating in the project.

IBP Instruments GmbH and MSV GmbH, from Germany, and AKERN Srl, from Italy, are highly interested in evaluating the feasibility of the proposed technology in order to start product development activities after the finalisation of the project. These companies are already working either exclusively (IBP and MSV) or partly (AKERN) in the dialysis market and are very active in sales throughout Europe and in the United States.

1.2.1 Coordinator contact

The project's Coordinator details are the followings:

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1.3 Work performed

During the HAEMOSCAN project there has been a definition phase focussing on the conceptual design of the HAEMOSCAN bioimpedance sensor for haemodialysis applications, the implementation of a functional validation prototype to perform pre-clinical, engineering verifications, the conduction of clinical tests (split in an initial Clinical Investigation phase followed by a multicentric Clinical Trial), the data processing and

statistical and clinical analysis of the obtained results and finally the improvement of the prototype design aiming at future industrialization and commercialization. These issues are developed in the following paragraphs.

1.3.1 Specification phase

The specification of the product consisted of defining the set of technical requirements that must be met by the HAEMOSCAN system and sensor. A Specifications Document was compiled covering mechanical, performance, interface, SW and operational requirements. Relevant standards in the medical devices domain followed in the specification of the sensor were:

- Council Directive 93/42/EEC of 14 June 1993 concerning Medical Devices
- Medical Devices. General Requirements for Safety. Standard IEC 60601-1
- Medical Devices. Electromagnetic Compatibility – Requirements and Tests, Standard IEC 60601-1-2
- Medical Devices, part 1: General requirements for Safety, IEC 60601-1

1.3.2 Design phase

The electrical design of the sensor was produced. The conceptual block diagram is shown in Figure 1. The design features an analog front end module in charge of injecting currents and detecting voltage drops, an analog to digital conversion module and a digital module in charge of synthesising signals at different frequencies. There is also a communications module that permits establishing a communication link with the central PC. At prototype level this is implemented as a serial interface link but the final design could feature a wireless communication system. The sensor is controlled by a microprocessor with a dedicated built-in SW and is battery-powered.

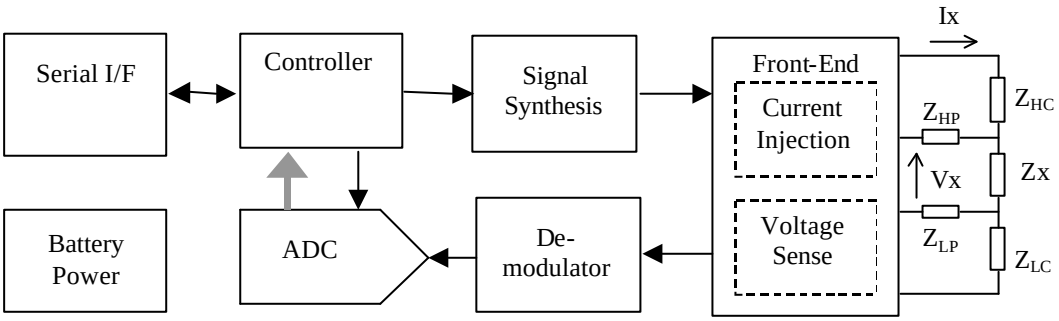

Figure 1: HAEMOSCAN sensor block diagram

In addition, as safety is a key element, a risk analysis was conducted based on the standard ISO 14971, 1.0, Application of Risk Management to Medical Devices.

A Quality Management procedure was established at this phase for the building-up of the HAEMOSCAN product file for future registration (e.g. CE marking) and commercialisation activities.

1.3.3 Prototype

An initial prototype sensor was built, as shown in Figure 2. This prototype has been used for several purposes:

- Proof of design and final design tuning
- Test object for pre-clinical tests, namely Safety, Electromagnetic Compatibility and Functional performance
- Test object for clinical investigations

Figure 2: HAEMOSCAN prototype

1.3.4 Conduction of Clinical Tests

1.3.4.1 Regulatory affairs

Regulatory affairs plays an important role as one of the core activities within the project is the conduction of Clinical Investigations and Trials using HAEMOSCAN medical devices with humans. The following EU and national (Spanish in that case as the medical trials were performed in Spanish hospitals) regulations have been followed in the authorisation request process in front of the *Agencia Española del Medicamento y Productos Sanitarios* (AEMPS, Spanish Agency for Drugs and Medical Devices):

- EU directives and international standards:
  - Council Directive 93/42/EEC of 14 June 1993 concerning Medical Devices
  - Clinical Investigations of Medical Devices for Human Subjects, ISO 14155–1:2003, Part 1: General Requirements
  - Clinical investigations of Medical devices for Human Subjects, ISO 14155–2:2003, Part 2: Clinical Research Plans
- Spanish directives:
  - *Real Decreto 223/2004, 06/02 aplicable a las investigaciones clínicas con productos sanitarios*
  - *Circular nº 07/2004 relativa a Investigaciones Clínicas con Productos Sanitarios*

The project followed the above listed procedures in order to:

- Document the medical trials by means of specific protocols
- Document the medical device by means of a specific dossier
- Satisfy the ethical requirements imposed by the hospitals' ethical committees (patients' informed consent, contracting an insurance for civil liability coverage, etc.)

In the course of the project this activity has to be performed twice. Firstly, in request for the authorisation of the Clinical Investigation, which was foreseen as a unicentric trial in one single hospital (date of request 09/11/05, authorisation granted on 20/01/06). Secondly, in request for the Clinical Trial, which was foreseen as a multicentric (three hospitals) trial (date of request 18/12/06, authorisation granted on 06/02/07).

1.3.4.2 Production of medical devices for research use

The clinical investigations and clinical trials require the inclusion of a certain number of patients suffering from chronic renal insufficiency that must undergo through haemodialysis (HD) treatment. During the trials patients are monitored with the HAEMOSCAN devices, which quasi-continuously record bioimpedance signals from the patients through the course of the HD session.

Patients were monitored in three different locations (arm, leg and abdomen) during the Clinical investigation phase, and were monitored in the leg during the Clinical Trial phase. Thus, enough number of devices had to be manufactured in order to allow the completion of the referred tests. In view of the characteristics of the Clinical Investigations and Trials it was needed to produce ten units for the Clinical Investigation phase and twelve for the trial phase.

These devices were considered prototypes, therefore were manufactured, assembled, tested and calibrated manually.

1.3.4.3 Clinical Investigation

The Clinical Investigation was a unicentric essay completed at Hospital *Corporació Sanitària Parc Taulí*, located in Sabadell (Spain) during the period March to June 2006. The objectives of this trial were the functional verification of the HAEMOSCAN bioimpedance sensor in realistic hospital conditions and the preliminary identification of correlations between the measured bioimpedance data and fluid shifts between body's compartments from the estimation of the variation in intracellular water (ICW) and extracellular water (ECW).

For that purpose 10 stable patients (i.e. patients that do not suffer from symptomatic hypotension crisis during haemodialysis) were selected and monitored through six consecutive sessions thus yielding a total of 60 observations. This number of patients and monitored sessions was considered enough representative for the purpose of the investigation.

Two patients were monitored simultaneously with a set-up as shown in Figure 1. Bioimpedance sensors were connected in three body locations, namely leg, arm and abdomen, as shown in Figures 2 to 4. A large number of variables were recorded per each patient, per each sensor position and per each session. Data was processed off-line and plotted in figures like Figure 5 and further, several correlations amongst various parameters were computed.

After the thorough analysis of the data it was concluded that:

- The HAEMOSCAN device was measuring the bioimpedance signals properly through the course of the HD sessions and, therefore, was delivering good bioimpedance data in terms of phase and module
- The leg location presents the highest correlation between body fluid shift estimators derived from the measured bioimpedance data and fluid shift values measured from independent sources.

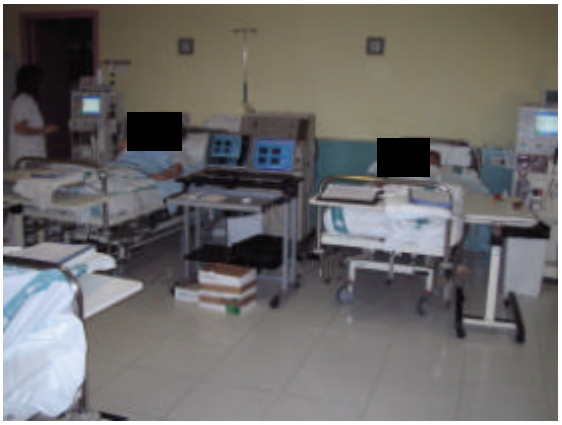

Figure 3: Clinical Investigation at CSPT

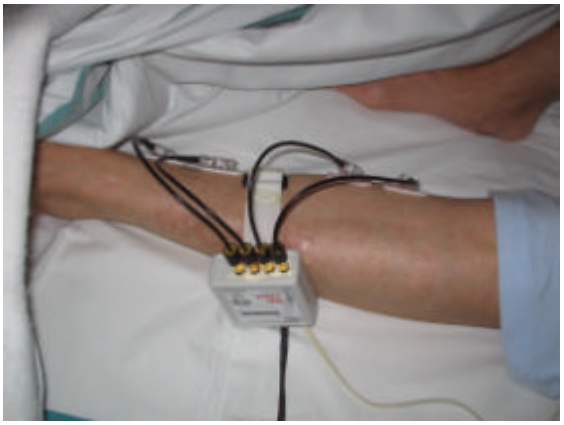

Figure 4: Clinical Investigation at CSPT

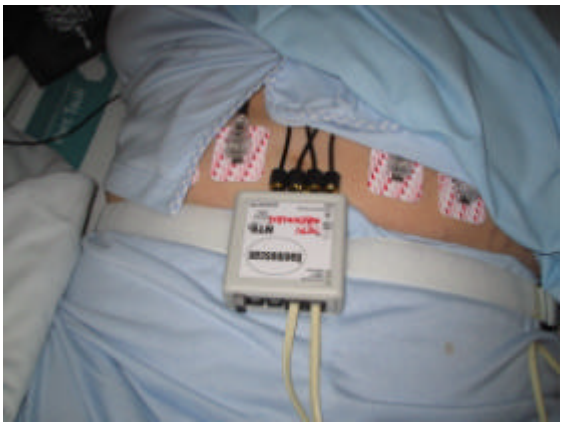

Figure 5: HAEMOSCAN sensor in abdominal position

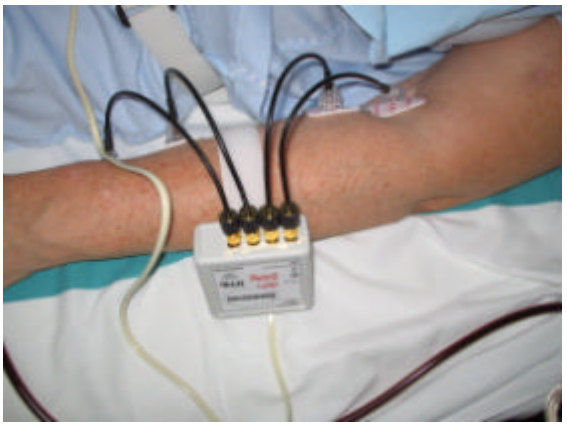

Figure 6: HAEMOSCAN sensor in arm position

1.3.4.4 Clinical Trial

Following the confirmation of results regarding the potential use of the HAEMOSCAN medical device in the haemodialysis context obtained from the Clinical Investigation conclusions, a Clinical Trial was undertaken.

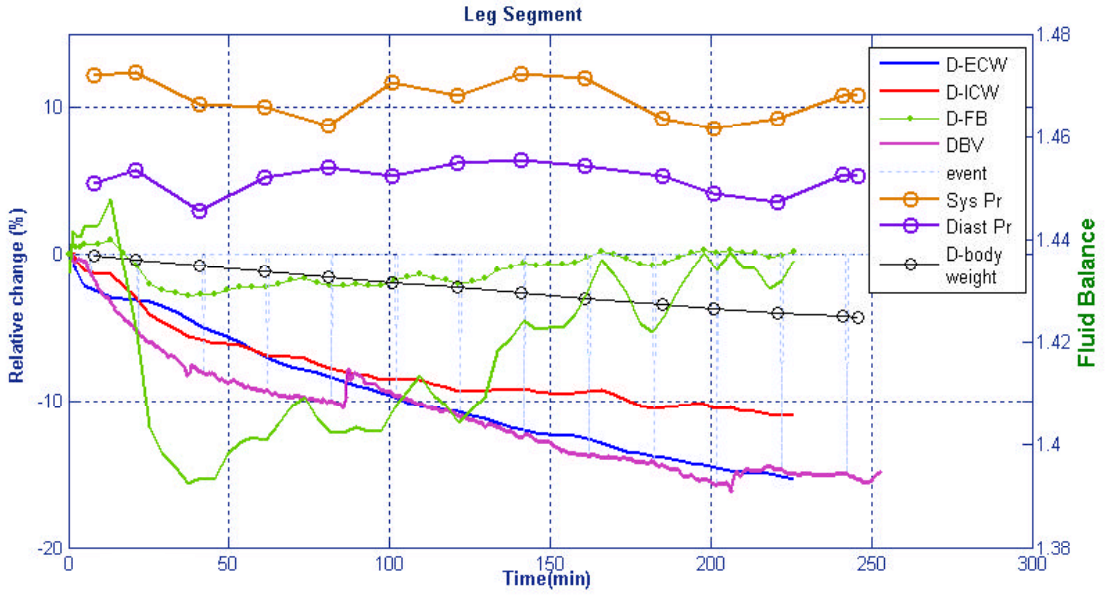

Figure 7: Summary of recorded variables

The Clinical Trial was originally planned as a unicentric essay to be conducted in the same Hospital than the Clinical Investigation, but with extended population, 50 patients, and different inclusion criteria. This number of patients, also to be monitored through 6 consecutive HD sessions, thus yielding in total 300 observations, was considered statistically representative in view of the budgetary and schedule constraints that somewhat limited the conduction of the trial.

However, in response to the UE's recommendation made to the consortium at the end of the first reporting period about considering the "presence of more than one clinical site" the Clinical Trial planning was modified accordingly so that it became a multicentric trial over three Hospitals, all located in the Barcelona region, namely:

- *Corporació Sanitària Parc Taulí*, in Sabadell (same as for the Clinical Investigation), with 26 patients
- *Hospital de Terrassa* , with 12 patients
- *Hospital de Mollet* , with 12 patients

The organization of the Clinical Trial in three different hospitals required a larger than originally planned effort:

- Production of additional HAEMOSCAN units in order to allow parallelisation of the trials in more than one Hospital with the aim at maintaining the schedule within reasonable limits (twelve new units produces, as explained in par. 1.3.4.2.
- Evaluation of Ethical issues and approval of the proposed Clinical Trial Protocol by three different Ethical committees of the three Hospitals, instead of only one as originally planned. In consequence, the approval process until became more cumbersome and time consuming.
- Increase in the logistics demands, as the test set-up had to be replicated in three different locations. In addition, three medical personnel groups (including practitioners and nursery staff) had to be trained for the conduction of the trials (devices and test set-up manipulation, and data collection).

- Need to initiate a new authorisation request process to the Spanish Health authorities (AEMPS) for the Clinical Trial, as it became a multicentric one (this additional request would not have been needed in case of unicentric trial, as a simple extension of the previous authorisation given for Clinical Investigation would have sufficed).

With all these issues in hand, the request for authorisation was presented to the AEMPS on 18/12/06 and the authorisation was granted on 06/02/07. The Clinical Trial started shortly after first at the Sabadell's hospital and later in the other two. At the time of writing, tests in the first hospital have been completed and in the other two hospitals are about to conclude.

Patients included in the Clinical Trials were unstable, i.e. suffering from symptomatic hypotension crises while going through the HD treatment. The test set-up used in the trials is shown in Figure 6.

At the time of writing this report tests have not been completed and only partial results have been evaluated. The preliminary conclusions of this analysis indicate a clear difference in the body shift behaviour (determined from the bioimpedance measurements with the HAEMOSCAN device) measured in the stable group of patients and in the unstable one. This analysis is to be completed with correlations between hypotension crises detected in the HD line pressure measurements taken over the unstable population (recorded through the SinedBox™ data interface shown in Figure 6) and the direct bioimpedance measurements obtained with the sensor over the same population (right branch in Figure 6). Such correlation must confirm the ability of device in the early detection of the rise of hypotension crisis during HD.

1.3.5 Data analysis and production of the estimators

During the Clinical Investigation and Clinical Trials a large quantity of data has been generated. In each HD session, with an average duration of four hours, the following data were recorded:

- Bioimpedance data: recorded by every HAEMOSCAN device used in the test, consisting of a set of modulus and phase pairs measured at 6 different frequencies sampled every 4 minutes for the entire HD session duration.
- Hematocrit and blood volume data: recorded by the CritLine® device at 1 measurement every 20 s fro the entire HD dialysis session duration
- Intradialysis events, recorded manually using an Acess ™ data base over the entire HD session duration
- For the Clinical Trials, due to the inclusion of the SinedBox™ in the test set-up, it was possible to record additional parameters, notably the HD machine blood line pressure at a 1 sample per minute rate (which, for this key parameter, is virtually continuous recording)

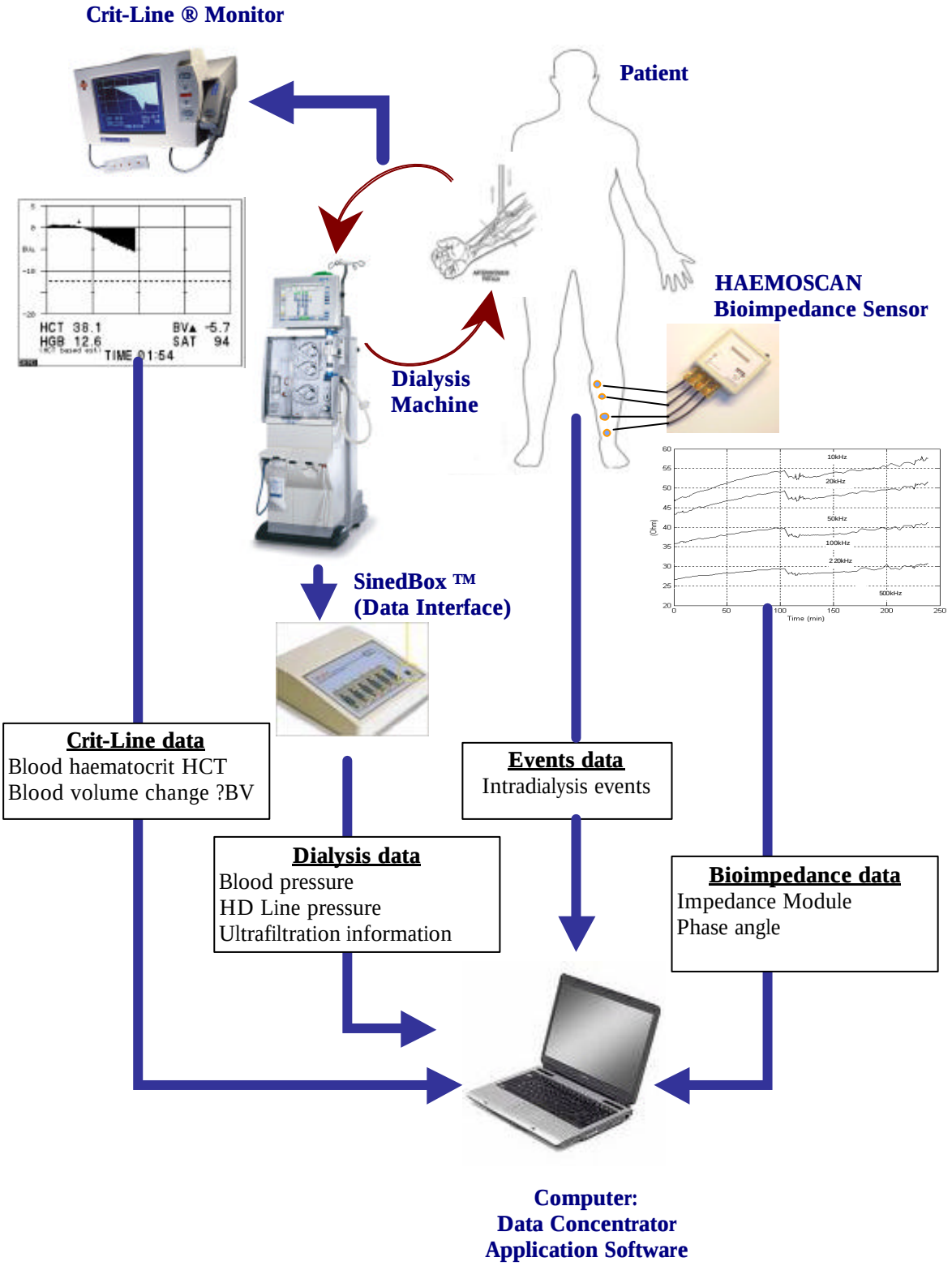

Figure 8: Clinical Trial set-up

Raw bioimpedance data had to be post processed according to certain algorithms in order to obtain useful bioimpedance data that can be used to build up volume and/or volume shifts estimators. Two these, data coming from sources other than bioimpedance were added in order to obtain compact graphical information as that shown in Figure 5, per each patient / session / sensor location (arm, leg or abdomen).

Estimators have been derived from the Bioimpedance Analysis theory. The basic estimators are:

- Water compartments estimators
  - Extracellular Water
  - Intracellular water
- Fluid changes estimators
  - Extracellular Water
  - Intracellular water

These estimators have been used to compute body fluid shift variations obtained from the processed bioimpedance data and have been used to establish correlations with benchmark body fluid measurement devices like CritLine®, with good results.

1.3.6 Product definition

In parallel to the clinical investigation actions leading to the definition of a potential commercial device have been taken, with the design and prototyping of a casing (Figure 9) and fixed electrodes and adaptation of the design to implement a CANbus interface, usually used in haemodialysis equipment.

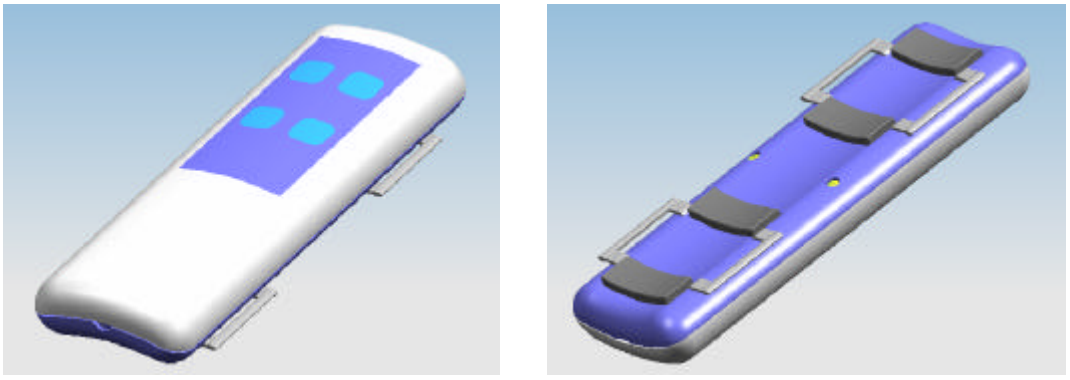

Figure 9: HAEMOSCAN market-oriented caging design

2. DISSEMINATION AND USE

2.1 PUBLISHABLE RESULTS

The consortium is not yet ready to provide publishable results. IPR issues are still open (method and/or apparatus patent request) pending of the finalisation of the Clinical Trials and the full statistical analysis and scientific interpretation of the results (expected around August 2007).

Nevertheless, the RTD consortium members UPC and TUG have produced some knowledge dissemination in the form of papers, oral presentations, etc. which are derived directly or indirectly after their involvement in the project. All these publications are related to the application of the bioimpedance analysis to study different clinical aspects and their contents have been scrutinised to prevent jeopardizing potential project's IPR issues. The list is as follows:

1. Francisco Bogonez, Francisco Vazquez, Omar Surakhy, Javier Sevilla, Pere Riu. **PORTABLE WIRELESS BIOIMPEDANCE MEASUREMENT SYSTEM FOR HD MONITORING** .World Congress on Medical Physics and Biomedical Engineering, Seoul (Korea) , August 28 - Se p. 1st 2006

2. **Invited speaker** : Omar Al-Surkhi, P.J. Riu, F.Bogonez, F. Vazquez. **MONITORING FLUID SHIFTS DURING HEMODIALYSIS (HD) USING ELECTRICAL BIO-IMPEDANCE TECHNIQUES.** Cairo International Biomedical Engineering Conference (CIBEC'06). Cairo, Egypt. December 21-24, 2006

3. Omar.I.Al-Surkhi, P.J. Riu, F, F. Vazquez, J. Ibeas. MD. **MONITORING COLE-COLE PARAMETERS DURING HAEMODIALYSIS (HD).** 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. August 23-26, 2007. Lyon, France

4. Omar I. Al-Surkhi, P.J. Riu1, F. Vazquez, J. Mas, A. Rodriguez-Jornet, M. García, J. Ibeas.MD. **LOCAL TISSUE BIOIMPEDANCE MEASUREMENT FOR FLUID SHIFTS DURING HAEMODIALYSIS**. 13th International Conference on Electrical Bioimpedance combined with the 8th Conference on Electrical Impedance Tomography. ICEBI `07.August 29th to September 2nd 2007 Graz (Austria).

5. P.J. Riu , Omar Al-Surkhi , and P. Bogonez. **IN VITRO ASSESSMENT OF HEAMATOCRIT CHANGES BY ELECTRICAL IMPEDANCE MEASUREMENTS.** The 3rd European Medical and Biological Engineering Conference EMBEC´05 Prague. November(2005).

6. Omar Al-Surkhi, P.J. Riu **.ELECTRICAL BIO-IMPEDANCE TECHNIQUES.PART I: REVIEW OF CLINICAL ACHIEVEMENTS.** International medical informatics and biomedical engineering symposium. (IMIBE-2006). Amman Jordan, March 2006.

7. Omar Al-Surkhi, P.J. Riu .**ELECTRICAL BIO-IMPEDANCE TECHNIQUES. PART II: IN-VIVO AND IN-SITU CHARACTERIZATION OF TISSUE ISCHEMIA**. International medical informatics and biomedical engineering symposium. (IMIBE-2006). Amman Jordan, March 2006.