Grant Agreement no. 287596

d-LIVER

ICT-enabled, cellular artificial liver system incorporating personalized patient management and support

INSTRUMENT: Collaborative Project (Integrating Project)

OBJECTIVE: ICT-2011.5.1

D1.1: Specification of the clinical requirements for d-LIVER support

Due Date of Deliverable: 31st March 2012
Completion Date of Deliverable: 30th March 2012

Start date of project: 1st October 2011 Duration: 48 months

Lead partner for deliverable: Charité

Revision: v1.0

Project co-funded by the European Commission within the 7th Framework Programme (2007-2013)		
Dissemination Level		
PU	Public	✓
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including Commission Services)	
CO	Confidential, only for members of the consortium (including Commission Services)	

Document History

Issue Date	Version	Changes Made / Reason for this Issue
12th February 2012	v0.1	First draft
24th February 2012	v0.2	First revision
2nd March 2012	v0.3	Revision based on feedback from partners
24th March 2012	v0.4	Revision after internal review
27th March 2012	v0.5	Revision by Management Team
30th March 2012	v1.0	Final version

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1. Executive Summary

Chronic liver disease continues to be a frequent problem in the population worldwide. Progressive liver tissue destruction results in inability to perform normal organ function and in turn in development of frequent complications.

The d-LIVER system will aim to provide a complete solution to improve the management of chronic liver failure patients. Currently outpatient clinic follow-up offers only intermittent review of health status and blood parameters by liver experts on a weekly or monthly basis. Taking into account this situation, d-LIVER aims to meliorate the monitoring by means of development of reliable sensor-based patient home systems. It is likely that comparatively simple steps such as standardized vital sign measurements might result in substantial information on patient health status and hence increase the quality of medical care provided. Furthermore, more frequent measurement of selected biochemical parameters can improve the predictive value of changes in patient health status. In the light of current check-up procedures, many chronic liver failure patients may benefit from home monitoring, and an outcome of d-LIVER will be a decrease in the frequency of consultation and waiting times in the outpatient clinic.

This deliverable therefore sets out the background to the various clinical scenarios to be investigated in the d-LIVER project, provides the partners involved with an overview of the clinical inclusion/exclusion criteria for d-LIVER system evaluation by patients and describes the technical specifications and performance requirements required for the different d-LIVER system components.

2. Introduction

The essential aim of the d-LIVER project is to develop an ICT-based monitoring and ICT-enabled bio-artificial liver system, for remote and safe management of patients with chronic liver disease outside the hospital. Before development of mechanical and IT devices is initiated, clinical needs for patient monitoring have to be defined and a mutual understanding of d-LIVER systems between technology developers and clinicians created early within the project lifetime.

The aim of this deliverable is therefore to provide the partners involved with an overview of the clinical requirements and to outline the technical specifications required for the different system components. Deliverable D2.1, developed in parallel with this document, will provide details of the functional specifications of the system components to be developed.

Section 3 provides an overview, from the clinical perspective, of how liver failure may arise from different origins and how the clinical requirements of the d-LIVER system are linked.

Section 4 describes the inclusion and exclusion criteria for enrolling patients in the system evaluation studies to be carried out in advance of full clinical validation which will take place after the end of the 4-year d-LIVER project.

Section 5 describes the main d-LIVER components from the clinical perspective and will serve as a starting point to identify a concept that is broadly accepted by both the technical and clinical partners. One challenge will be to merge technical feasibility and clinical requirements to provide a solution that is acceptable to d-LIVER users i.e. patients and healthcare professionals.

Finally, Section 6 highlights additional applications relating to quality-of-life which will have to be built-in to the d-LIVER monitoring systems in order to account for possible encephalopathic episodes and general well-being.

3. Liver disease scenarios in d-LIVER

3.1. Chronic liver failure

The liver plays a central role in the human organism. It is a frequent disease all over Europe (1-4). Single or multifactorial underlying processes such as alcohol dependency, hepatitis C infection as well as obesity (which may lead to non-alcoholic fatty liver disease) can all lead to cirrhosis. Major complications include hepatic encephalopathy (5), ascites (6), hepato-renal syndrome (7) and variceal bleeding.

Chronic liver failure is frequently asymptomatic until decompensation occurs. Accordingly, chronic liver failure patients would be enrolled either to monitor organ function and potential deterioration of health status or after an episode of acute on chronic liver failure after early discharge from hospital. Using systems to be developed in d-LIVER, changes in liver function and patient health status may be detected early and may enable the liver expert to make appropriate changes to therapy in order to avoid further deterioration.

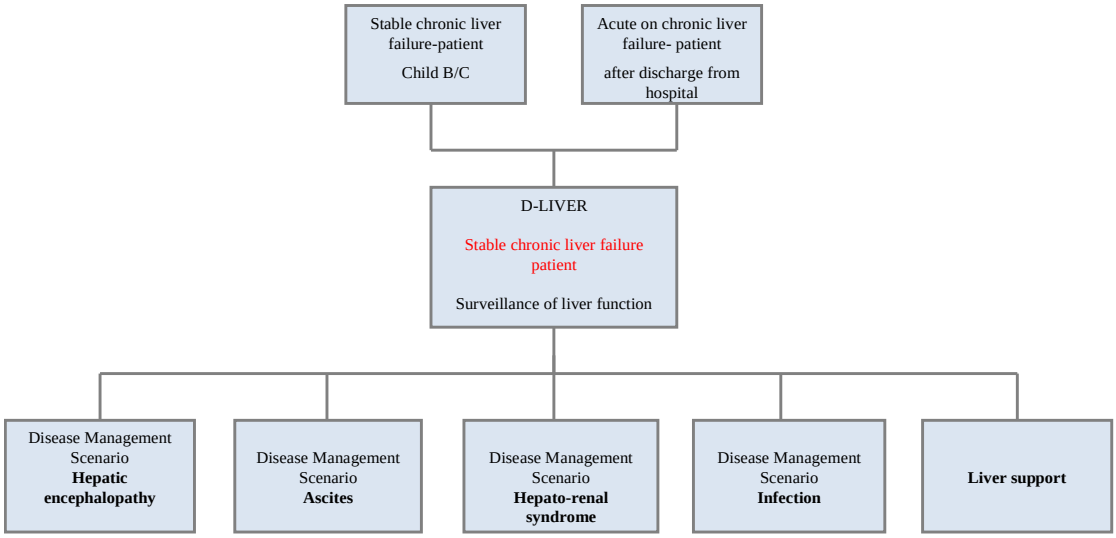


Figure 1: Chronic liver surveillance structure

3.2. Chronic cholestatic itch

Pruritus/itch presents an unpleasant sensation, which causes scratching. This sensation is caused by various underlying diseases ranging from skin diseases and neural diseases to systemic diseases (8).

Patients suffering from primarily cholestatic hepatobiliary diseases, as well as other liver disease with a cholestatic element frequently report of pruritus (9, 10) The mechanism of pruritus in this setting is unclear, although it is suggested that retention of entities normally excreted in the bile (including hydrophobic bile acids) may be directly or indirectly involved (11). Itching can exceed tolerable levels, cause significant sleep deprivation and limit daily activity causing significant impact on quality of life. Chronic cholestatic itch shows a circadian rhythm with maximum values in the evening. A number of therapies are beneficial in treating cholestatic-itch, however, some patients are un-responsive to all medical therapies (12, 13). Case reports have suggested beneficial effects of extracorporeal procedures such as MARS (molecular absorbent recirculation system) (14) or plasma separation and anion absorption (15), although there is no clear guidance on the approach to use and no consensus in clinical practice. Liver transplantation is a recognised and typically highly effective treatment option for patients who have failed all other forms of treatment(16, 17). In the d-LIVER setting regular detoxification and elimination of culprit factors may play a key role in avoiding early or unnecessary transplantation (patients probably have sufficient residual liver function meaning that transplantation is not indicated for prognostic reasons) and improving patient quality of life (QoL). Liver support may therefore be used to treat pharmacological resistant itch and may become a valid treatment option for pruritus in cholestatis. Future validation studies will allow the verification of this vision.

3.3. Bridging therapy

Transplant candidates undergoing assessment for liver transplantation, or patients already listed, can be monitored in this scenario. Potential indications for liver transplantation are any kind of life-threatening liver disease that shows a progressive irreversible course.

According to the individual patient liver function, the current waiting period can be up to 2 years, therefore enhanced screening of parameters, with potential to alter treatment- strategies if indicated, will be the main aim within this application scenario. There is still an unmet need for proper clinical management of chronic liver failure patients awaiting transplantation.

New solutions of monitoring patient health status to assess the individual health risk and prevent deterioration need to be investigated.

d-LIVER could provide a complete solution for remote ICT-enabled home monitoring of the chronic liver failure patient awaiting transplantation. In case of further deterioration, liver support sessions and admission to hospital may be considered. This scenario differs only slightly from the long-term surveillance. However, these patients have to be monitored with a higher degree of attention and maintenance of nutritional status and physical activity in order to improve overall health status is of vital importance.

3.4. Acute liver failure

Both acute liver failure and acute on chronic liver failure lead to acute deterioration of liver function and, in turn, to life-threatening complications. The causes of acute liver failure are numerous (18). A recently proposed system classifies according to the onset of encephalopathy and deterioration in coagulation hyper-acute (< 7 days) acute (7 - 28 days) and sub-acute (28 days to 6 months) liver failure (19). The aim of home monitoring will be to prevent deterioration of the patient condition by providing regular monitoring, support and guidance. However, patients with acute or sub-acute liver failure may be monitored and supported in the future by liver sessions in the home setting, but at a certain point manifest acute liver failure requires treatment in special departments (i.e. intensive care units (ICU)).

This application scenario therefore will be mainly situated within the clinic. Biochemical parameters will be measured by in-hospital laboratories and vital signs by local devices. Therefore, data migration to the LPMS to acquire useful information and to permit enhanced monitoring of early-discharge patients will be necessary.

4. d-LIVER inclusion criteria for system evaluation and expected capability

Clinical decision criteria for enrolling patients in the d-LIVER evaluation studies will be continuously reviewed throughout the project and finally decided after the development stage. The age of patients suffering chronic liver failure varies significantly. Depending on their underlying disease, mature patients are more likely to suffer from organ dysfunction, although this can also affect younger patients. Thus, an easy user-friendly monitoring system is a major requirement to ensure effective use by patients outside the hospital in the home environment. While a future commercial system will have to address the needs of all patients, within the lifetime of d-LIVER, in order to generate meaningful data regarding acceptability, feasibility and technical realisation, only a defined subset of patients will be enrolled to carry out user tests. For example, these might represent patients who are already experienced in ICT systems, who have no impairment in fine motor skills and vision, and who do not suffer from recurrent encephalopathic episodes.. The data generated should allow conclusions to be drawn regarding any required future system refinements which can be incorporated into the full post-project clinical validation studies.

Notwithstanding the above, it is possible to define the preliminary clinical criteria for patient inclusion or exclusion in the evaluation studies, as shown in

Table 1.

Table 1: Preliminary patient criteria for inclusion/exclusion in system evaluation studies.

d-LIVER home monitoring evaluation studies		
Inclusion criteria		**Exclusion criteria**
(1) Patients with chronic liver failure in stable conditions (Child-Pugh class B/C) (2) Patients awaiting liver transplantation (3) Chronic cholestatic itch patients (4) Suitable IT skills		(1) Patients with mild chronic liver disease in stable condition (Child-Pugh class A) (2) Cognitive and mental disorders/cognitive impairment (dementia, psychiatric disease) (3) Current drug or alcohol abuse (4) Impairment of vision or fine motor skills
Precise clinical inclusion criteria will be further elaborated using patient clinical data.		Precise clinical exclusion criteria will be further elaborated using patient clinical data.

5. d-LIVER devices

5.1. User interfaces

User interfaces include any interface that provides potential d-LIVER users access to the d-LIVER patient management system. The following points will specify, from a clinical point of view, interfaces suitable for efficient patient management.

5.1.1. Patient User Interface

The Patient User Interface (PUI) represents the main interface and provides the patient enrolled in d-LIVER access to the Liver Patient Management System (LPMS). The PUI will offer the patient guidance to complete daily procedures correctly, serve for testing applications (e.g. testing for hepatic encephalopathy and answering clinically important questions) and will communicate issues to other d-LIVER users (contacting the liver treatment expert or other health professionals).

Table 2: Requirements of Patient User Interface.

Module	**Patient User Interface** 
Definition/Functionality description	One big screen located in the home environment presents the main user interface for the patient. The system will incorporate a touch screen in order to accomplish encephalopathy tests and for communication issues. Moreover it will provide system and health status information from data forwarded by wireless devices and the blood biochemistry instrument (BBI).
Minimum clinical requirements	It seems to be reasonable to integrate a large touch sensitive screen with a 17- 21 inch display to ensure a reasonable symbol and font size.

	Large symbols or pictures should be displayed full screen to advise the patient to complete certain tasks. Taking into account different scenarios, examples could be: • visual warnings indicating problems. • a picture of a scale might be displayed to indicate the patient should perform body weight measurements. • a picture of the heart rate blood parameter device might be displayed to indicate patient to complete heart and blood pressure measurements. • in case of wrong positioning or incorrect measurements, the patient might be alerted to readjust instruments. In the case that the user is not in front of the screen, any urgent messages can be delivered using a mobile phone.

5.1.2. Clinic User Interface

Liver experts and healthcare professionals will access the LPMS via the Clinic User Interface. Different servicing levels enabling access according to individual expertise might be necessary.

Table 3: Requirements of Clinic User interface.

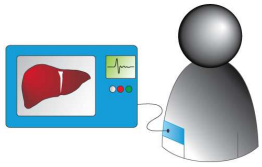
Module	**Clinic User Interface** 
Definition/Functionality description	A computer will be situated in the clinic to provide access to the LPMS. Healthcare professionals will have different access levels depending on their role.
Passive Decision Support	Passive Decision Support is proactive assistance where the software system, e.g. LPMS, will propose alternative intervention plans to the liver expert (or health professional) who in turn will decide which alternative is used to proceed.
Patient Prioritising Module	The LPMS will automatically list the patients in order of priority of medical intervention. The liver expert will address any necessary actions after reviewing available information.
Record Function	From regulatory perspective it will be necessary to record each intervention or each review of medical data. Therefore, interaction with an Electronic Patient Record is deemed necessary. Also from a regulatory and legal perspective, clinicians have a duty to document all treatment and management decisions and are required to store this documentation for several years. Thus a function for personal memos will be important from a clinical perspective.

5.1.3. BAL User Interface

A User Interface will be required to operate the Bio-artificial Liver support unit (BAL). Initiation and termination of the therapy session will be activated from here and

measurements relating to the health and efficacy of the BAL (e.g. pH, CO_2,NH_3, cell viability and cell density) will be displayed.

Table 4: Requirements of BAL Interface.

Module	**BAL User Interface** 
Definition/Functionality description	A specially trained healthcare professional will operate the BAL in the clinic. From a clinical perspective, it will not be an absolute requirement to incorporate communication tools in the BAL. However, communication tools to transmit data from the BAL to the LPMS will be considered.

5.2. Wireless monitoring of physiological parameters

The wireless sensor solutions should be designed to be simply and comfortably positioned by the patient and should provide reliable results while the patient is ambulatory. Moreover, integration of several sensors in a single wearable unit would be preferable, but this is not an absolute requirement. It may be useful to display certain parameters to the patient, e.g. heart rate, via the PUI. The final decision whether data is continuously transmitted or temporarily stored on the device will be decided in consultation with the technical partners as an outcome of the analysis of the added value of real time continuous data monitoring.

If there is a future requirement for additional parameters to be measured, the use and integration of commercial devices could be considered (e.g. weighing scale, activity meter).

Table 5: Requirements of wearable physiological sensors.

Module	**Wireless devices**
Definition/Functionality description	Liver patients will use these instruments in the home environment. Wearable devices will measure at least the following. • Heart rate • Blood pressure • Skin temperature
Blood pressure	Blood pressure presents an important vital sign which reflects individual health status. A wearable non-invasive device will be developed, based on pulse-wave velocity, to measure blood pressure repeatedly over a short period of time in order to calculate effective average blood pressure. Standard operational criteria will be developed to measure blood pressure and to ensure that results are valid.
Heart rate	Heart rate is a useful parameter which may be helpful in decision making. A wearable device will be developed to measure the patient heart rate on the basis of ECG.

Skin temperature	Detection of fever or elevated temperature is an important parameter to indicate possible infections which may complicate the treatment. An instrument will be developed to measure skin temperature based on optical or thermistor technology. An assessment will be made during the project of how this correlates to core temperature.

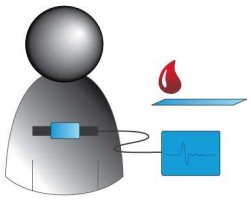
5.3. Blood Biochemistry Instrument

The BBI is planned to be a robust device for discrete measurement of a defined set of biochemical parameters. A drop of blood, obtained by finger prick, will be placed on a disposable lab-on-chip cartridge and the relevant parameters measured. From the clinical perspective, control of contamination issues will be addressed by the technical development partners. Obviously, effective blood sampling is extremely important, particularly as the system will measure up to 8 different parameters on the same cartridge. Therefore, a large blood volume could indicate a complex measurement scenario. However, already in the project development plan, the partners have defined that a sample volume of 20µl will be sufficient to carry out all blood biochemistry measurements in parallel.

The BBI and Patient User Interface should be closely situated to ensure that the patient can follow the displayed instructions.

Should additional biochemical measurements be indicated for particular d-LIVER scenarios (e.g. glucose), consideration will be given to instrumenting a commercial device to allow it to communicate with the LPMS and the PUI.

Table 6: Requirements for BBI and PUI

Module	**Blood Biochemistry Instrument (BBI)/Patient User Interface** 
Definition	Liver patients will use the instrument in the home environment. The BBI processes lab-on-chip cartridges with blood samples from the patient to measure the relevant blood parameters. Clinicians currently do not see the need for a display integrated in the BBI. Any problems (e.g. wrongly placed cartridge, insufficient blood etc.) should be displayed on the Patient User Interface along with corrective instructions.
Blood sample volume	At this stage of the project the technical partners anticipate a maximum of 20µl of blood will be required to carry out all measurements. Considering this relatively small volume of blood, the finger pricking approach is broadly comparable to established diabetic procedures. Charité investigated the actual blood volume resulting from a finger prick. Ten patients with chronic liver disease and accompanying diabetes mellitus used a BD Microtainer® contact-activated lancet for blood glucose measurements**.** The median blood volume obtained was 227 µl (minimum 40 µl; maximum 380 µl). Thus, blood sample volume is not expected to be an issue.

Module	**Blood Biochemistry Cartridge**
Definition	The patient has to insert a specially developed cartridge into the BBI before application of the blood sample. Due to contamination risks cartridges should be single use, disposable items. It is planned to have all parameter measurements on a single cartridge. If some parameters are not required to be measured for a particular patient, these will be excluded from the measurement protocol. Clinical partners will elaborate a parameter priority order within the cartridges to guarantee measurements of the most important parameters for the d-LIVER scenarios.
Coagulation measurement	Since in clinical practice prothrombin time (PT) [sec] and international normalized ratio (INR) [normal value 1] are commonly used, clinicians want to have monitored these two values by the LPMS. The Prothrombin Time (PT) test measures how quickly blood clots and is a very useful indicator of liver synthetic function. In d-LIVER its use would be a trend measurement in the same individual (i.e. looking for any changes from baseline). Since the preferred unit (either PT or INR) varies from country to country, results should be displayed in INR. INR represents the ratio of the measured PT to an international reference PT raised to the power of the International Sensitivity Index (ISI) which varies for any added test substances (e.g. tissue factors). Moreover, INR is a parameter that is used for calculation of the Child-Pugh Classification,

Standard cartridge parameters

Parameter	Measurement range	Measurement frequency	Trigger point
Liver function parameters			
Bilirubin (Total)	1.7-598 µmol/L	Daily	Significant rise above patient baseline
Ammonia	15-300 µmol/L	Daily	Elevation above baseline or 10% change in one day (>286 µmol/L)
Albumin	10-70 g/L	Daily	<20 g/L
Bile Acids	1-160 µmol/L	On demand	Elevation above baseline is clinically significant (>14 µmol/L)
PT / INR	10-120s 1	Daily	>14 s INR trend increasing >1 on successive days
Renal function and electrolytes			
Creatinine	2.7-2652 µmol/L	Daily	Levels above 150 µmol/L; Above daily baseline
Sodium	80-180 mmol/L	Daily	>150 mmol/L
Potassium	1.5-10.0 mmol/L	Daily	>5.2 mmol/L <2.8 mmol/L

6. d-LIVER special applications

6.1. Hepatic encephalopathy (HE)-test

Chronic liver failure patients frequently develop encephalopathic episodes due to restrictions in the detoxification function of the liver. This situation may occur within days, decrease patient quality of life and entail several risks, such as the development of sensory abnormalities and disorientation and in severe cases, coma. It is therefore clinically important to recognize and avoid development of hepatic encephalopathy.

A simple daily test paired with blood parameter analysis (and simple questions to the patient) may provide information to the physician to detect oncoming hepatic encephalopathy and to initiate early treatment.

The PUI will be developed to allow the HE test and the results will be compared with recent measurements and blood ammonia levels. This will be carried out for a defined time interval prior to the LPMS being utilised to consider alterations in therapeutic treatment.

Table 7: Requirements for BBI and PUI

Module	**Patient User Interface** 
HE-test	The HE test will be performed on the screen, by touching icons. The test will measure processing speed, attention and memory. The integration of classic hepatic encephalopathy testing methods such as number connection tests (connection of 21 numbered cycles starting with the cycled number 1) or digit symbol tests (finding a displayed symbol combination out of a pool) seems to be reasonable and will be evaluated by the clinical partners within the course of the project. Since encephalopathic episodes are frequent in patients with chronic liver disease and may rapidly occur, a screening tool is likely to be useful. This should be implemented as a switchable optional feature as the test will not be obligatory for individuals without encephalopathic episodes in their medical history.

6.2. Quality of Life questionnaire

Quality of life is an important parameter for any future systems which implement the d-LIVER approach, therefore, a study will be undertaken to develop a series of appropriate daily questionnaires which will target specific problems which may occur in patients suffering from chronic liver failure and which will be illustrated by means of work flow diagrams. The daily questionnaire, composed in a pre-defined format (YES-NO answers to ensure straight forward automated evaluation). The answers will be based on an ascending 1 - 10 scoring system (where 1 is the worst case) and will provide valuable information regarding current health status. A pre-defined set of basic questions will be devised and, if problems are indicated, optional questions will be displayed to further clarify the issues identified. Obviously it will be possible to ignore the questionnaire should no changes be apparent.

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8. Appendix A – *Abbreviations*

ALT	Alanine transaminase
AST	Aspartate transaminase
AoCLF	Acute on Chronic Liver Failure
BAL	Bio Artificial Liver
BBI	Blood Biochemistry Instrument
DoW	Description of Work
HE	Hepatic Encephalopathy
HIS	Hospital Information System
ICT	Information and Communication Technology
LPMS	Liver Patient Management System
MARS	Molecular Absorbent Recirculation System
MELD	Model of End-stage Liver Disease
NCT	Number Connection Test
QoL	Quality of Life
VAS	Visual Analogue Scales
VPN	Virtual Private Network

For additional information please see the **d-LIVER Glossary**