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

D6.1: Acceptance Criteria of the d-LIVER system

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RE	Restricted to a group specified by the consortium (including Commission Services)	
CO	Confidential, only for members of the consortium (including Commission Services)	

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Document Main Author(s): **Stephan Dasen (CSEM)**

Document signed off by: **David Wenn (iXscient)**
Calum McNeil (UNEW)

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1. Executive Summary

Deliverable D6.1 defines the acceptance criteria for the instrumentation platforms of the d-LIVER project. The acceptance criteria are the conditions that the instruments must satisfy to be accepted by the project. Accurately defining the acceptance criteria is one of the most important elements of successful development.

This document will review the three instruments that were defined in the Description of Work (DoW) of the d-LIVER project. It will also explain why one of these instruments is no longer required. It will also define the concept of the two other instruments and finally a table of acceptance criteria will be presented.

2. Introduction

The aim of WP6 is to provide the d-LIVER instrumentation platforms that will service its requirements. The design of the instruments will be based on the framework developed in WP2.

According to the DoW, three instruments were initially planned to be developed:

1. A Blood Biochemistry Instrument (BBI) for use with the microfluidic cartridges developed in WP4
2. A wearable device for continuous collection of physiological patient parameters
3. Instrumentation to interface with the sensor systems incorporated within the bio-artificial liver developed in WP5

After a few months working on the clinical requirements and device specifications, it appears that the third instrument (instrumentation to interface the bio-artificial liver) does not require development work by WP6. Although there is still a requirement for a user interface, this does not need any hardware development, and so the user interface will be developed by WP7.

The role of the present deliverable is to define a few criteria permitting the acceptance, or not, of the successive versions of the instrument. Criteria have been formulated following the functionality description and hardware requirements extracted from the DoW and deliverables D1.1, D2.1 and D2.2, and after discussion with various partners.

3. General Concepts of d–LIVER instruments

In the DoW, it has been defined that the wearable device (called logging device in the DoW) had to communicate with the BBI in order to gather the collected physiological patient parameters. From there, data would have been transmitted to the Liver Patient Management System (LPMS). It has, however, been decided that the central unit collecting data from both the wearable device and the BBI will be developed by WP7. This unit is called the Personal Health Manager (PHM). Figure 1 shows the whole Liver Patient Management Architecture in which the wearable device, the BBI as well as Commercial off-the-shelf (COTS) devices described in section 4.1, can be seen to transmit data to the PHM.

Both instruments are used by the patient in the Home setting. The instruments should thus be very user friendly, intuitive to use and not require too much handling. The wearable device will measure continuous physiological parameters; COTS devices may be used for some sporadic physiological parameters; and the BBI used for measurement of the blood parameters. All these information will help the liver expert to diagnose deficiencies in liver function and will allow early intervention and early discharge of patients at/from hospitals.

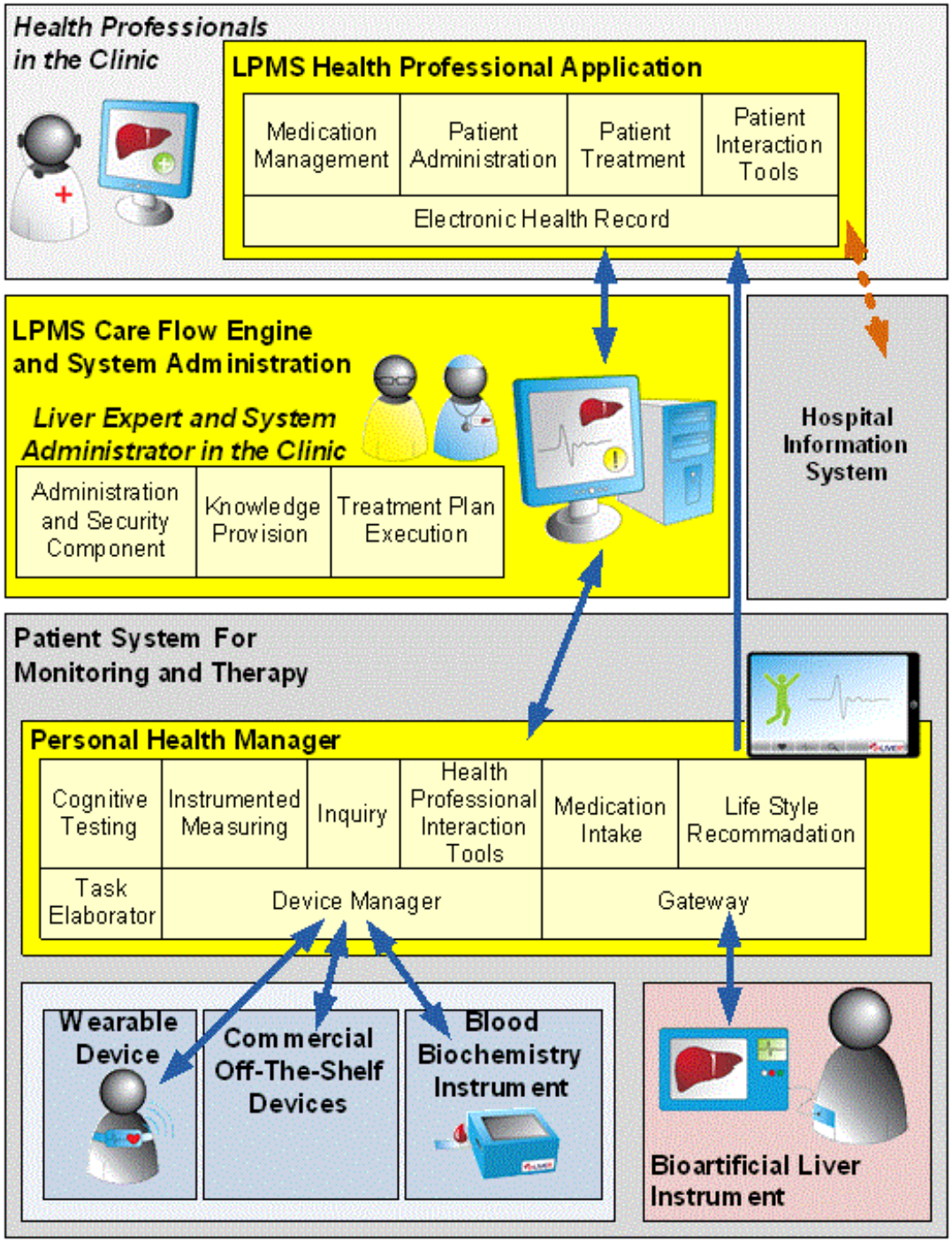

Figure 1: Liver Patient Management Architecture.

4. Wearable Device

4.1. Background and design constraints

The d–LIVER wearable device is outlined in the project DoW as a device to be used by the patient as a means for capturing vital signs during daily activity. Specifically, the DoW outlined the following parameters to be of interest on a sustained basis:

- heart rate
- blood pressure changes
- skin temperature

In the work leading to deliverable *D1.1 Specification of the clinical requirements for d–LIVER support,* it was clearly expressed that the d–LIVER patients should only have to use one main user interface at home, now termed the Personal Health Manager (PHM). Hence, the inclusion of a mobile phone type portable terminal was discouraged beyond the use of it for dialling and possibly sending text messages. In discussions with WP1 clinicians, the focus has also turned from an emphasis on continuous measurements towards daily point measurements as part of the patient monitoring procedure. In particular, blood pressure, heart rate, body core temperature and weight are now requested on a daily basis. Nevertheless, the ability of the wearable device to perform continuous measurements over a short period of time will be retained because this may prove useful during therapy sessions.

Rather than a single, wearable device, d–LIVER will therefore turn towards implementing a set of sensing devices, including the DoW-envisioned wearable device, as well as the possibility to interface with additional COTS devices for capturing information such as weight and body core temperature. The wearable device, as well as the COTS devices, will be interfaced to the Personal Health Manager by means of wireless communication employing Bluetooth. The device interaction with the Personal Health Manager will be dealt with by the Device Manager, which is an application running on the PHM and which controls all Bluetooth interaction. In the present instrument development context, we will deal explicitly with the Wearable device to be developed within d–LIVER in the following sections.

4.2. Concept

Home monitoring will be used in d–LIVER to detect changes in liver function and patient health status at an early stage, and may thereby enable the liver expert to make appropriate changes to therapy in order to avoid further deterioration. The combination of blood biochemistry measurements and "vital signs" measurements offer a "virtual bridge" for the doctor into the patient's home on a daily basis.

Truly continuous vital signs monitoring on a sustained basis (all day, every day) is only needed for a very few patients, typically belonging to intensive care patient groups, who would thus not be suitable for home monitoring. Many more patient groups can benefit from using continuous measurements during shorter time sequences (days-weeks-months); typically for monitoring the effects of medical interventions. These interventions can for example be grouped as follows:

1. Start a new treatment programme (such as d–LIVER enrolment).
2. Life style change, outcome assessment and patient motivational tool (life style changes such as exercise, substance abuse, diet...).
3. Assessment of effect of medication adjustments.
4. Monitoring requested by medical personnel for patient status assessment.

Regarding the use of the wearable device in d–LIVER, a likely scenario is to use it extensively during the first month or so after d–LIVER enrolment in order to establish a patient base line. This time span will also help the patient learn more about their own physiology (thereby contributing to patient empowerment), and it may also be possible to see the effect of, for example, changes in activity/exercise. Following this introductory use of the wearable device, we further expect that the device will be valuable for less frequent measurements, e.g. once a week, on a prolonged basis to ensure that values stay or move into an acceptable range. It may also be valuable to use the device more frequently during periods of therapy changes. Finally, the liver expert could request the patient to use the device for a certain time span if the expert considers that this can improve the foundation for concluding the need for making interventions.

The outline of the d–LIVER device proposed by SINTEF has been described in deliverable *D2.1 System Concept Definition Including Functional Units*. The basic architecture is given in Figure 2: Architecture of the d–LIVER wearable device.

The targeted device will have sensors for collecting the following primary information:

- heart rate – extracted from differential ECG measurements
- arterial pulse wave pattern – most likely extracted from optical plethysmograpic measurements
- acceleration in three axis – using an integrated MEMS accelerometer
- skin temperature – most likely using an infra-red (IR) temperature sensor

The combination of these sensor readings will allow one to simultaneously and continuously measure the following parameters:

- heart rate
- pulse wave velocity time – which varies with blood pressure, and then can indicate changes in blood pressure
- skin temperature (which can be correlated to core body temperature)
- activity
- posture

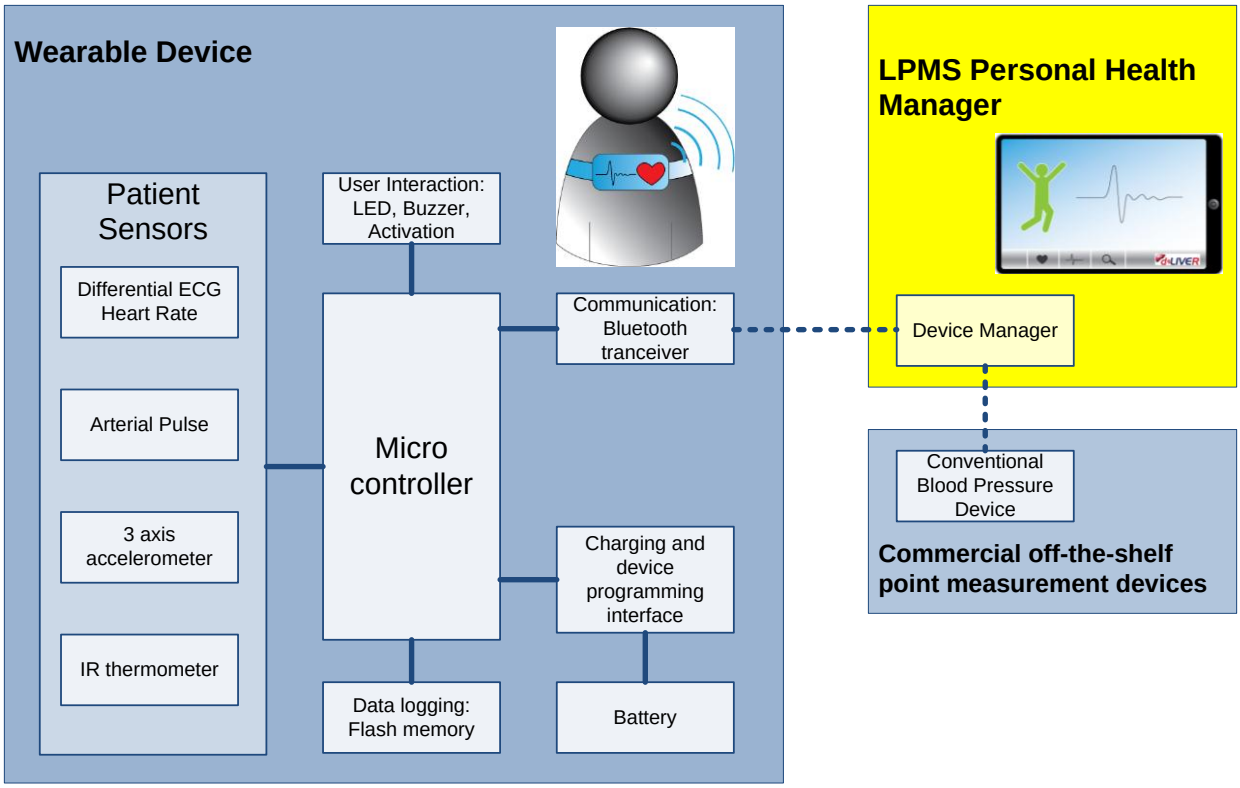

Figure 2: Architecture of the d–LIVER wearable device.

In addition to the accelerometer value as an indicator for movement giving rise to noise artefacts in e.g. heart rate measurements, the accelerometer can also provide invaluable information about the patient activity and posture. SINTEF has experienced in previous projects that activity and posture information is very valuable in assessing patient activity and well-being in continuous home monitoring systems. Several representations of activity are possible. The two most probable candidates to report in d–LIVER are:

- step counter – analyse the raw data to extract the number of steps the patient takes
- mean acceleration – to report mean acceleration (in m/s^2) experienced during the past reporting time frame.

As the wearable device will only provide indirect information on blood pressure and blood pressure changes, the wearable device pulse wave velocity measurements will have to be regularly calibrated by conventional cuff-based blood pressure instruments. This will be done in cooperation with the PHM. This is illustrated by the additional interface to the Device Manager in Figure 2.

5. Blood Biochemistry Instrument

5.1. Background and design constraints

The BBI is an instrument that the patient will use in the home setting to monitor the variation of blood biochemistry parameters. It must be user friendly and easy to use by the patient. This includes the requirement that the blood will be collected by a finger pricking system, similar to that used by diabetics. The parameters the BBI will measure are the following:

- Bilirubin (total)
- Bile acids
- Creatinine
- Sodium (Na^+)
- Potassium (K^+)
- Ammonia (NH_4^+)
- Albumin
- Clotting (Prothrombin time)

To achieve these measurements, different types of sensors have to be integrated into the instrument. Most of them are electrochemical sensors, but for one parameter (clotting), an optical technology may be a backup solution. These sensors are the following:

- Amperometric (for bilirubin, bile acids and creatinine)
- Potentiometric (for the ions)
- Impedimetric (for albumin and clotting)
- Optical (as back-up solution for clotting)

The bio-sensor technologies are being developed by WP3. Due to high complexity, the optical sensor will be integrated only if the impedimetric sensor for clotting does not give satisfactory results. Sensors will be integrated into the blood biochemistry cartridge (BBC) developed by WP4. This BBI will host the cartridge. The BBI will include all the required actuators to drive the fluids (blood and/or plasma as well as any other reagents and buffers) to the required place in the cartridge. These actuators include:

- Pumping capabilities
- Electrovalves
- Sensing capability to detect the passing of fluids at certain points within the cartridge (optical barriers)

The instrument will also ensure optimal conditioning for the measurements to take place such as temperature regulation and darkness for the optical sensor.

The readout devices (the acquisition electronics for the sensors) are developed by WP3 and integrated by WP6. These electronic boards will be integrated into the BBI. Special care has to be taken with the connection between the sensors on the cartridge and the readout devices in the BBI, as there will be many connection points and demands for accurate voltage/current measurements.

According to the user scenarios, the BBI will be driven by PHM from WP7 via Bluetooth. However, for development purposes, the BBI will include a touchscreen. In fact, this way of interaction will be valuable to demonstrate the BBI on its own. Moreover, this screen allows the instrument to display its status (idle/busy/error).

The BBI will be designed to avoid blood contamination or infection issues. For this purpose, the cartridge should be sealed before insertion into the instrument. The finger pricking system as well as cartridges will be disposable.

5.2. Concept

Figure 3 shows a block diagram of the BBI. It will mainly be an embedded computer with various boards connected to it through an internal communication bus. The technology of this communication bus will be chosen to make a modular instrument allowing easy addition of new boards.

A key element will be an electromechanical interface, the Biochemistry Cartridge Interface (BCI). This module will have to host the disposable Blood Biochemistry Cartridge (BBC) and will contain all the necessary actuators to drive the liquids (blood, reagents, and buffers) to the required places.

The actuators will be mounted on a Printed Circuit Board (PCB) inside the BCI. The actuators include pumping capabilities and electrovalves to allow the instrument to push or pull the liquids through the various inlets. To drive the turning valves on the cartridge, motors will be required. Optical barriers will allow detection of liquids at key points in the cartridge. Finally, a heating system will heat the detection zone of the cartridge to allow measurements under optimal conditions for temperature critical measurement parameters.

The power supply will provide the voltages and the currents required by the different electronic blocks. The power supply will be connected to external mains power of 230V / 50Hz. No compatibility with other standards is foreseen. A battery-powered instrument is not required.

The motherboard will contain the Central Processing Unit (CPU), the memory and all the required components for the various interfaces. It will probably be an embedded computer hosting a Linux- or Windows-based operating system (OS).

For development and debugging purpose only, the instrument will require connection of an external screen, mouse and keyboard as Inputs/Outputs (I/Os). Other I/Os may be required. A touchscreen will be used as user interface during the development and test phases, as well as to display the BBI status (idle/busy/error) while on.

The motherboard will have to communicate with the other boards through a communication bus. This communication bus is not defined at this stage of the project. It may be a multipoint serial communication bus like RS-485 (also known as EIA-485). The driver board will host all the required electronics to drive the actuators that allow the driving of the liquids within the blood biochemistry cartridge.

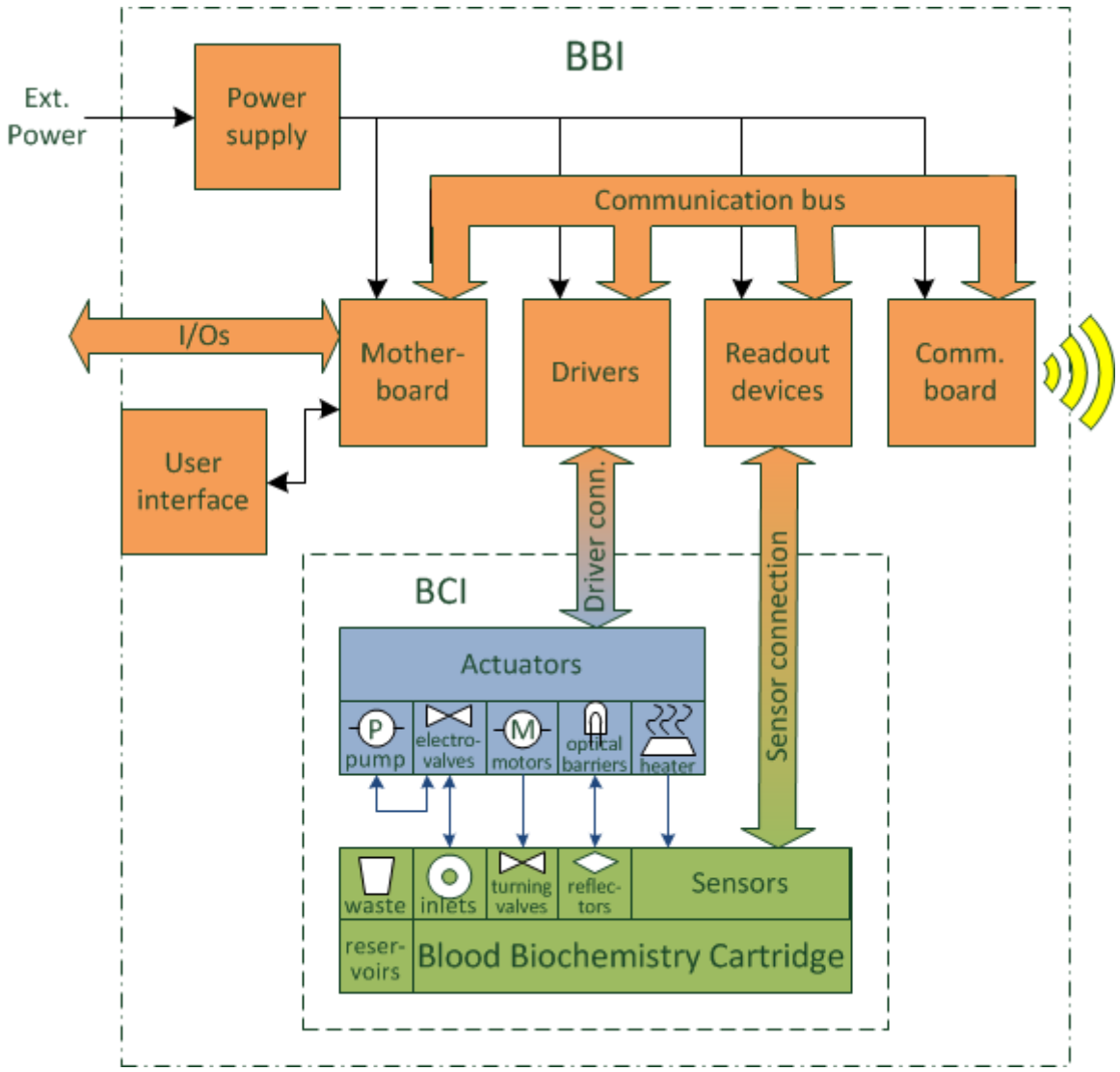

Figure 3: Blood Biochemistry Instrument block diagram.

The readout devices will contain all the electronics to gather the electrochemical measurements (potentiometric, amperometric and impedimetric) from the sensors on the microfluidic cartridge. It might be that all the devices can be hosted on a single board or several boards will be required. These devices will be developed by WP3 in close collaboration with WP6.

The communication board will enable wireless communication of the instrument. The instrument will be controlled by the PHM from WP7 through this gate. This board will be designed by the CSEM with the guidelines (technology and communication protocol) furnished by WP7 partners.

6. Acceptance Criteria

Acceptance Criteria are one of the most important elements of a successful development project and thus must be accurately defined. Acceptance Criteria can be translated as the conditions that a product/prototype must satisfy to be accepted by the user, customer or stakeholder. Google defines it as "Pre-established standards or requirements a product or project must meet."

A clear definition of Acceptance Criteria may avoid surprises at the end of the project and ensure a higher level of customer satisfaction.

Criteria are evaluated on three aspects:

- Relevance – has a connection with the story
- Measurability – is possible to observe and quantify
- Specificity – is explicitly defined and definite

6.1. Wearable Device

d-LIVER					
Acceptance Criteria Wearable Device					
No.	**Criteria Description**	**Criteria Category**	**Acceptance Criteria Evaluation**		
			Is this criterion relevant?	**Is this criterion measurable?**	**Is this criterion specific?**
1.	The wearable device must meet applicable requirements so that it can be cleared by relevant medical ethics approval bodies for use in human subject trials.	Regulatory	Yes	No	No
2.	The wearable device should be designed and made so that the risk of adverse events for users is minimized. This work will be documented in a risk management file.	Regulatory	Yes	No	No
3.	The wearable device will be ready for the first d-LIVER system integration activities by M24[1].	General	Yes	Yes	Yes
4.	The electronic device will be less than 100 g in weight.	General	Yes	Yes	Yes

[1] The logging device in its first version will be ready in M24. There may be significant iterations after this date to develop software algorithms, integration work towards the PHM and so forth

d-LIVER					
Acceptance Criteria Wearable Device					
No.	**Criteria Description**	**Criteria Category**	**Acceptance Criteria Evaluation**		
			Is this criterion relevant?	**Is this criterion measurable?**	**Is this criterion specific?**
5.	The device will include a rechargeable battery, and be able to operate continuously for at least 12 hours on a fully charged battery.	General	Yes	Yes	Yes
6.	Device will be able to store at least 24 hours of logged data.	General	Yes	Yes	Yes
7.	Working temperature between 4 and 40°C	General	Yes	Yes	Yes
8.	Working humidity between 20 and 95[2]%	General	Yes	Yes	Yes
9.	The device will be protected against water intrusion (splash protected) such that continuous on-body measurements can be carried out.	General	Yes	No	Yes
10.	The device will ensure confidentiality of sensitive data stored locally.	General	Yes	No	No
11.	Care must be taken in order to make the device user friendly.	User interface	Yes	No	No
12.	The device must be able to display device status and indicate malfunction.	User interface	Yes	Yes	Yes
13.	The most recent measurements from the wearable device can be displayed on the PHM if the user requests so.	User interface	Yes	Yes	Yes
14.	The device must measure blood pressure changes.	Measurement	Yes	Yes	Yes
15.	The device must measure heart rate.	Measurement	Yes	Yes	Yes
16.	The device must measure skin temperature.	Measurement	Yes	Yes	Yes

[2] The device will have to operate in close proximity to the skin where it can easily be condensing environments.

d-LIVER					
Acceptance Criteria Wearable Device					
No.	**Criteria Description**	**Criteria Category**	**Acceptance Criteria Evaluation**		
			Is this criterion relevant?	**Is this criterion measurable?**	**Is this criterion specific?**
17.	The device may measure activity[3].	Measurement	Yes	Yes	Yes
18.	The device may measure posture[4].	Measurement	Yes	Yes	Yes
19.	The device should provide Bluetooth communication with the PHM.	Communication	Yes	Yes	Yes
20.	Communication security should be implemented in the communication between the wearable device and the PHM.	Communication	Yes	No	No

6.2. Blood Biochemistry Instrument

d-LIVER					
Acceptance Criteria Blood Biochemistry Instrument					
No.	**Criteria Description**	**Criteria Category**	**Acceptance Criteria Evaluation**		
			Is this criterion relevant?	**Is this criterion measurable?**	**Is this criterion specific?**
1.	The BBI will be designed to avoid any contamination or infection issues.	Regulatory	Yes	No	No
2.	The BBI should be designed and made so that the risk of adverse events for users is minimized.	Regulatory	Yes	No	No
3.	The BBI should be small enough to be placed on a table in the patient home. A shoe-box size should be acceptable.	General	Yes	Yes	Yes

[3] Not required in the DoW but nice to have.

[4] Not required in the DoW but nice to have.

d-LIVER					
Acceptance Criteria Blood Biochemistry Instrument					
No.	**Criteria Description**	**Criteria Category**	**Acceptance Criteria Evaluation**		
			Is this criterion relevant?	**Is this criterion measurable?**	**Is this criterion specific?**
4.	The BBI should be transportable by the patient. Less than 5 kg is a target.	General	Yes	Yes	Yes
5.	Powered by single-phase 230V/50Hz. Less than 500W would be acceptable. Lower power consumption in standby mode.	General	Yes	Yes	No
6.	Permit the storage of about 100 patient results	General	Yes	Yes	Yes
7.	Working temperature between 4 and 40°C	General	Yes	Yes	Yes
8.	Working humidity between 20 and 80%	General	Yes	Yes	Yes
9.	The BBI will ensure confidentiality of sensitive data stored locally	General	Yes	No	No
10.	The BBI must be user-friendly and must automatically process all parameters without need for patient supervision.	General	Yes	No	No
11.	The patient can interact with the BBI while the instrument gives some basic instructions to handle the cartridge.	User Interface	Yes	Yes	No
12.	Malfunction as well as status of the instrument is displayed on the BBI screen as well as transmitted to the PHM.	User Interface	Yes	Yes	No
13.	Capable of driving various buffers to the required areas	Measurement	Yes	Yes	Yes
14.	The BBI must measure voltages that should be representative of ion levels (Na^+, K^+ and NH_4^+).	Measurement	Yes	Yes	No

d-LIVER					
Acceptance Criteria Blood Biochemistry Instrument					
No.	**Criteria Description**	**Criteria Category**	**Acceptance Criteria Evaluation**		
			Is this criterion relevant?	**Is this criterion measurable?**	**Is this criterion specific?**
15.	The BBI must measure currents that should be representative of creatinine, bile acid and bilirubin levels.	Measurement	Yes	Yes	No
16.	The BBI must measure impedance that should be representative of albumin level.	Measurement	Yes	Yes	No
17.	The BBI must provide an impedimeter or an optical sensor that should allow one to visualise blood clotting.	Measurement	Yes	Yes	No
18.	The BBI must accept one or several cartridge designs.	Chip interface	Yes	Yes	No
19.	The BBI provides means for auto-alignment of the cartridges.	Chip interface	Yes	Yes	Yes
20.	The BBI provides fluidic, electrical and mechanical interfaces to the cartridges.	Chip interface	Yes	Yes	No
21.	The BBI should provide Bluetooth communic-ation with the PHM.	Communication	Yes	Yes	Yes
22.	Communication security should be implemented in communication between the BBI and the PHM.	Communication	Yes	No	No

7. Conclusions

A preliminary description of both the wearable device and Blood Biochemistry Instrument has been provided. The background of each instrument has been elaborated and their design concept explained.

Furthermore, the acceptance criteria for both instruments have now been defined. These criteria should be respected unless unforeseen factors forces to project to change priorities, for example due to serious rise of complexity of the sensors or the cartridge, or a complete change of the d-LIVER architecture. In the case it turns out that any criteria cannot be respected, this will be justified in future WP6 reports (D6.2 and D6.3 for example).