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Compliance and effectiveness in HF and CHD closed-loop management

Deliverable 7.B

Public Report Nr.2

HeartCycle Concept descriptions

and

Overview on technical specifications and used technologies

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Table 1 Coordinator contact details

Public Project Website

The Public Project Website can be found on:
http://www.HeartCycle.eu

Publishable Deliverable 7

Summary

Dear Reader,

Thanks for your interest in HeartCycle

This public document comprises the publishable progress and findings of the research within the Integrated Project FP7-216695 HeartCycle Compliance and effectiveness in HF and CAD closed-loop management. It is the second public report from the HeartCycle consortium where we give an overview of selected parts of our current work.

Workpackage 1 (WP1) is progressing on the concept development and has been able to finalize the description of the application scenarios (use cases) we are going to address in HeartCycle. Our approach to further develop and enrich the HeartCycle disease management solution for Heart failure (HF) and Coronary Artery Disease (CAD) patients has been based on internal consulting with our medical experts, interviews, and workshops with patients and medical professionals to test and validate the HeartCycle concepts.

Workpackage 2 (WP2) presents the ECG software module with algorithms to be used by the different sensor devices that is provided to the consortium partners.

Workpackage 3 (WP3) “Multi-parametric Analysis and Decision Support” deals with the decision support system (DSS) and presents in this report on overview of models for treatment response.

Workpackage 4 (WP4), dealing with the patient loop, is the workpackage to model, design, and develop the patient platform, which will provide the users with a system to self-manage their health status and to educate them to adopt a healthy lifestyle. Motivation will play a crucial role for addressing the compliance. In this report several interventions and models are discussed that should help the patient to increase patient empowerment and motivation towards his disease management.

Workpackage 5 (WP5), dealing with the professional loop, provides an overview of the regulatory framework that applies in the countries that are subject to host trials for the HeartCycle project. The compilation of regulations has been organized in different sections: general, health record, telemedicine systems, electronic prescriptions and personal health data processing. Additionally, an outlook of the national strategy towards eHealth practices is given. Additionally, some technologies for careplan management are depicted.

WP6 and WP7 have worked out the details what needs to be considered in terms of clinical studies, validations, and CE certification for the software and hardware modules to be developed or used in the HeartCycle validation phase.

For more information, questions, or remarks please visit our website or contact me directly. I will than forward you to the respective experts in the HeartCycle consortium.

Harald Reiter
HeartCycle Project Manager

1 WP1 Concept creation and development process

1.1 Concept creation

HeartCycle starts from an application point of view, meaning that we first investigate, analyse, and validate the needs of patients and professionals for specific disease management solutions. The goal of the first year has been to identify and validate the requirements specifications of the HeartCycle concepts for coronary artery disease (CAD) and heart failure (HF). These requirements were generated iteratively through the consortium within the first 12 project months. A complete overview on the process used to define and focus the HeartCycle concepts is depicted in the figure below in more detail.

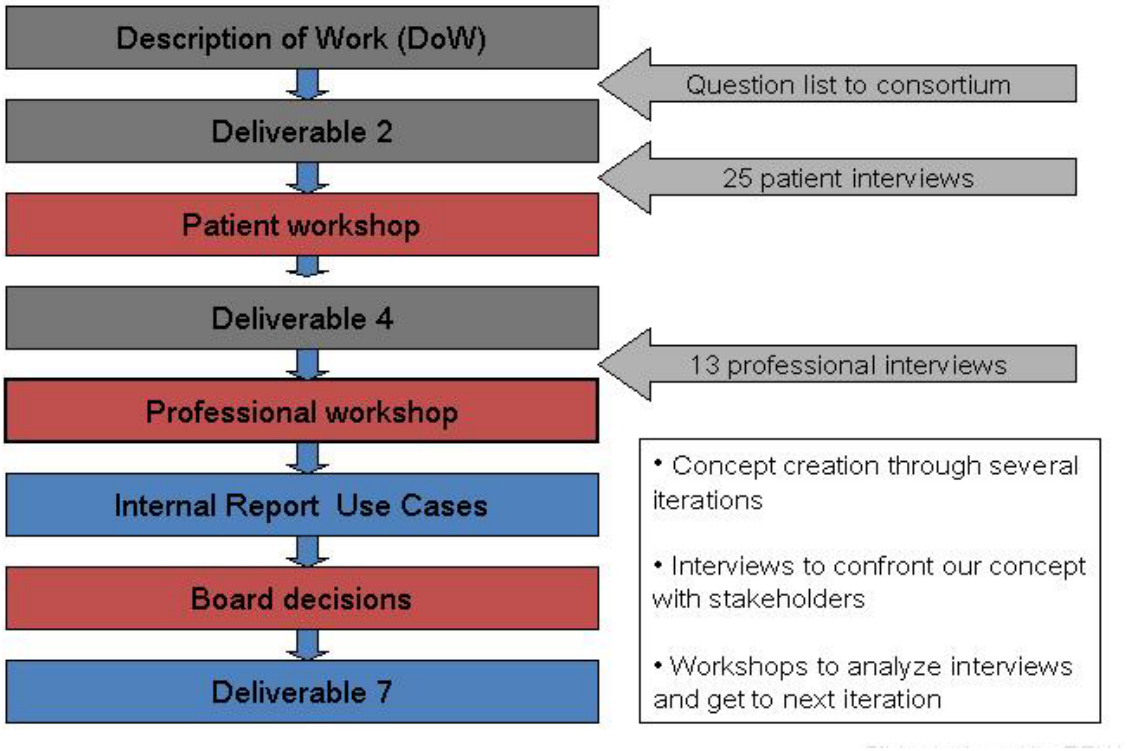

Figure 1: The concept creation process in HeartCycle

Starting from the HeartCycle description of work (DoW), the concept champions generated a first list of clarifying questions that were answered by all work packages. The refined scope for the HeartCycle concepts was then reported in deliverable D2.1.

The 25 patient interviews and the subsequent patient workshop lead to a further refinement of the concepts, especially taking the needs of patients into account. In deliverable D4.1, the results of the workshop and the connected requirements list for the concepts were reported.

The professional workshop, based on interviews with 13 nurses and physicians, lead to the identification of professional needs and complemented the picture of the patient workshop. The HF and CAD concepts were further refined. The results of interviews with nurses and physicians were analysed and the responses used to further concretize the concepts. The results of this workshop and the connected HeartCycle use cases are reported in detail in deliverable 7.1.

Focusing the concepts resulted in 10 key use cases identified in the professional workshop that were further worked out in terms of detailed descriptions, sequence diagrams and an outline of key innovations contained. All work packages contributed to this process, which lead to an internal report on the HeartCycle use cases. In the HeartCycle board meeting in Valencia on 20.1.2009, the concept

champions presented the chosen use cases to the board, where it was agreed that the proposed cases should be the scope for the project to work on in the remainder of the project lifetime.

Trough the iterative process chosen, it was ensured that all partners and work packages could contribute to the concept generation. The use of interviews with patients and professionals helped to identify the stakeholder needs and to ensure that HeartCycle delivers meaningful innovations that have the potential to improve the delivery of care to heart failure and coronary artery disease patients.

With the requirement specifications finalized, the technical work packages in HeartCycle can start deriving specifications for the choice of technologies and subsequently develop first modules and integrate them into a first generation system.

1.2 Development process

Considering the clinical evaluations that the HeartCycle developments will pass, a sound development process is required. After analysing in depth the legal and standardisation requirements that that implies, the board have finally agreed on the meeting held in Valencia on January 20-21 on the HeartCycle development process for the technology that will be developed and integrated in the HeartCycle systems. The HeartCycle development process is shown in the figure below.

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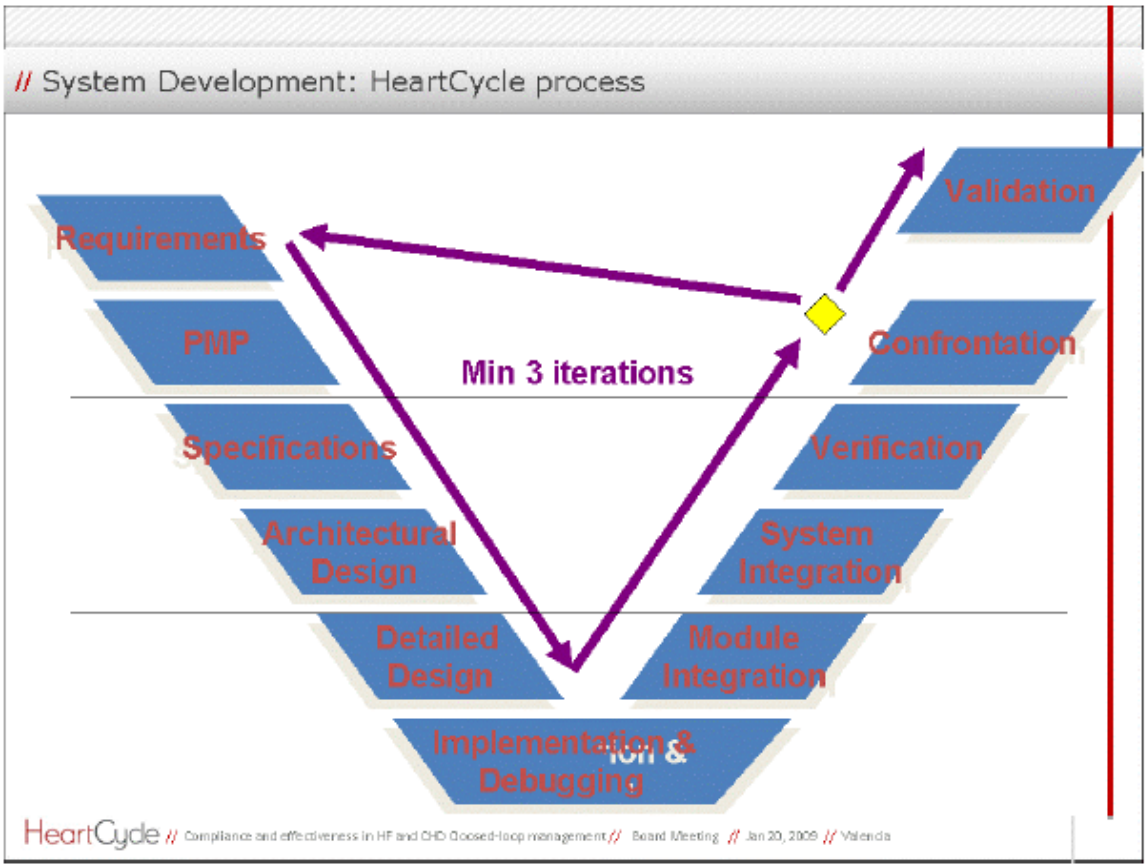


Figure 2: The HeartCycle system development process

The system development process is inspired by professional software development best practices and based on the harmonised standard IEC 62304:2006 for Medical device software –Software lifecycle processes.

Phases of the iterative HeartCycle development process

The figure above represents the development process with the following steps:

- Customer requirements specifications: The concept champions and the medical board define the customer requirements and the validation strategies for all the systems including the intended use environment and user needs. These requirements are detailed in this deliverable and will be the reference for the first iteration.

- Project Management Plan: A more detailed plan is being developed in order to get the HeartCycle systems ready on time for the different agreed milestones. This task is lead by the system owners (concept champions)

- System Requirements Specifications: Functional and non functional specifications of the HeartCycle systems, which are defined in parallel with the architectural design. The specifications are derived from a risk analysis based on EN ISO 14971:2007 (safety and security requirements) and describe in detail the “external appearance” of the systems, constructed as series of testable elements, which are parts of a traceability map. This task is lead by the technical manager.

- Architectural design: Definition of the architecture of the HeartCycle systems, which is described in parallel to the SPRS. This task is lead by the technical manager. After this phase there is a design review control point performed by the project management.

- Detailed Design Specifications: Design of the modules that integrate the products. This task is lead by the WP leaders. After this phase there is a design review control point performed by the project management.

- Implementation and Debugging will be done at the WP development level following the software processes and using the agreed tools. This phase will be tested via code Inspection, walkthrough and unit Testing

- Module integration will be done at the WP level following the tools and processes agreed by the HeartCycle software team. Integration tests ensure the quality of this stage.

- System integration is done under the umbrella of WP5 with the leadership of the technical manager and following the integration tests.

- Verification demonstrates conformance to specifications following a verification plan. This task is lead by the technical manager.

- Confrontation demonstrates that user's needs have been met by direct discussions and tests with the users, as defined by the concept champions and the medical board.

- Validation demonstrates that user's needs have been met in a clinical evaluation.

2 WP2: ECG Module

provided by University of Coimbra

This section describes the ECG algorithms that have been developed and implemented during the first phase of the HeartCycle project as was foreseen in the deliverable D2.2. These algorithms have been integrated and are available through a MATLAB ECG analysis algorithm toolbox. Specific interfaces, corresponding to each specific algorithm, are provided. Namely:

- ***ECG segmentation and Intervals computation***: relates to the identification of the main fiducial points, such as start and end of P wave, R peak detection, as well as relevant intervals computation, such as PR interval duration;
- ***Premature ventricular contraction*****:** identification of normal and abnormal beats;
- **Atrial fibrillation** episodes detection;
- **Ventricular arrhythmias** episodes detection, including ventricular tachycardia and ventricular fibrillation;
- **Heart rate variability** analysis, including time domain, nonlinear and frequency domain parameters.
- **ST deviation**: estimation of ST segment deviation at several different points.

2.1 Algorithms

2.1.1 ECG segmentation and intervals computation

The ECG segmentation algorithm was based on morphology transform concepts. In particular, the algorithm proposed by Sun[1] was implemented, which consists of a multi-scale morphological transform methodology. Using morphology analysis, the most important fiducial points have been determined, enabling to characterize the QRS complex, the P and T waves, as well as the relevant intervals based on those waves.

Segmentation: P wave P onset, P peak and P offset indexes; QRS complex: Q onset, Q peak, R peak, S peak and S offset indexes; T wave: T onset, T peak and T offset indexes.

Intervals: RR, heart rate (bpm), PR interval, corrected QT interval, Q wave width, Q peak height, R peak height, QRS complex duration and corrected JT interval.

2.1.2 Premature Ventricular Contractions

Most of the algorithms reported in literature share the same characteristic: they are based on features derived from the QRS complex, independently from the surrounding ECG morphological characteristics. However, patients can exhibit several physical, clinical, and cardiac conditions, which can affect the ECG morphology in numerous ways. For example, a wide QRS complex may be considered normal in one patient, while it may suggest the presence of a Premature Ventricular Contraction (PVC) in another patient. Since most of the algorithms proposed in literature are based on unrelated features and classifiers are trained with limited datasets, correct identification of PVC events in patients with unexpected conditions can become a difficult task. The proposed algorithm approaches this problem by assuming that measurements extracted from PVC characteristics can be compared to normal, patient specific ECG beat characteristics and that these exhibit inter-individual resilience, i.e., in order to capture patient specific ECG characteristics, for each beat the measurements are compared with those extracted from the neighbouring beats.

[1] Sun Y., Chan K. L. and Krishnan S. M., “Characteristic wave detection in ECG signal using morphological transform”, BMC Cardiovascular Disorders 2005; 5:28

The PVC detection algorithm is based on morphological transform and information theory techniques, as well as on temporal characteristics such as the QRS wave length[2]. The proposed PVC detection module considers, for each beat classification, a comparative analysis using the ECG signal in close proximity to the current beat.

2.1.2.1 Features

The first four features are directly related to the characteristics of PVCs: *R* wave length, area and centre of mass of *QRS* complex, *T* wave deflection and amplitude, *P* wave absence and *RR* interval variability (see Figure 1).

$$f_1(i) = QRS_{area}(i) \times \log\left(\frac{QRS_{area}(i)}{\overline{QRS_{area}}}\right), \quad i = 1,\ldots,nbeats \qquad (1)$$

$$f_3(i) = CoM(i), \quad i = 1,\ldots,nbeats \qquad (2)$$

$$f_2(i) = QRS_{length}(i) \times \log\left(\frac{QRS_{length}(i)}{\overline{QRS_{length}}}\right), \quad i = 1,\ldots,nbeats \qquad (3)$$

$$f_4(i) = CoM(i) \times \log\left(\frac{CoM(i)}{\overline{CoM}}\right), \quad i = 1,\ldots,nbeats \qquad (4)$$

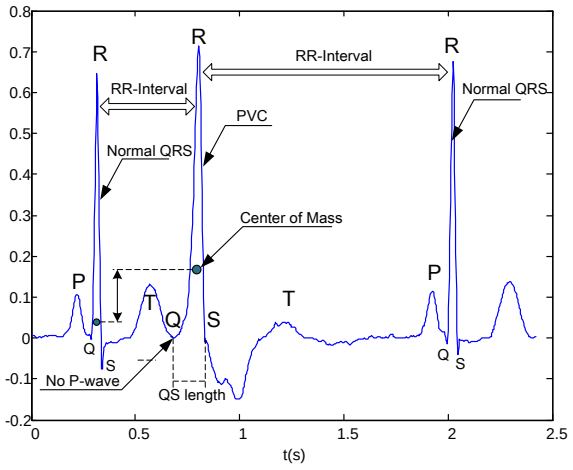


Figure 1 Features extracted directly connected to ECG characteristics.

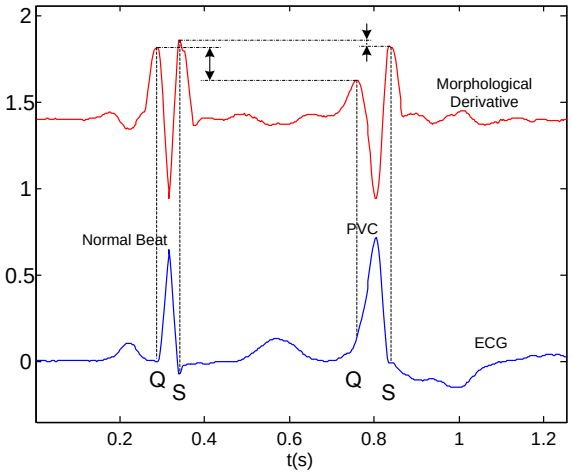


Figure 2 Comparison of amplitude differences between normal beats and PVCs morphologic derivatives.

The next two features are related to the characteristics of the waves that precede/succeed the QRS complex under analysis. When a PVC occurs it is observed that the T wave after the respective QRS exhibits a more elevated peak with opposite curvature to the main deflection of QRS complex (see see Figure 1). On the other hand, no P wave precedes the PVCs' QRS complex. The amplitude of each T wave is compared with the average amplitude (T_{peak}) of all T waves inside the analysis window, resulting in the feature described in (6).

$$f_5(i) = T_{peak}(i), \quad i = 1,\ldots,nbeats \qquad (5)$$

$$f_6(i) = T_{peak}(i) \times \log\left(\frac{|T_{peak}(i)|}{\overline{|T_{peak}|}}\right), \quad i = 1,\ldots,nbeats \qquad (6)$$

Since *P* waves are difficult to identify and to discriminate in an ECG, a template-based approach is followed to assess its presence. First a model is extracted by averaging all annotated *P* waves found in the *QT* Database from Physionet. Let $\overline{P_{wave}}$ be the aforementioned model and let P_{wave} be the *P*

[2] Couceiro, R., P. Carvalho, J. Henriques, M. Antunes, On the Detection of Premature Ventricular Contractions, EMBC -2008, 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Vancouver, Canada, August 20-24, 2008.

wave under analysis. The existence of a *P* wave is assessed by eq. (7) using the correlation coefficient between P_{wave} and $\overline{P_{wave}}$.

$$cc(i) = \left| corrCoef\left(P_{wave}(i), \overline{P_{wave}}\right) \right| \quad (7) \qquad f_7(i) = \max(cc) - cc(i), \quad i = 1,...,nbeats \quad (8)$$

One of the main characteristic of a PVCs is its premature occurrence. Therefore a feature relating the RR interval lengths of heart cycles adjacent to the PVC was used.

$$f_8(i) = \frac{RR(i)}{RR(i+1)}, \quad i = 1,...,nbeats \quad (9)$$

The remaining features have been defined using feature extraction methods based on the morphological derivative, spectral and information content. Two features are based on the ECG signal's morphological derivative. It is observed that PVC complexes exhibit lower slop before or/and after each *R* peak. The slop from the *Q* peak to the *R* peak can be measured by calculating the morphological derivative's peak amplitudes in this segment (QR_{amp}, see Figure 2). Analogously, the slop after the *R* peak can be represented by the amplitude of the *RS* peak segment (RS_{amp}). An approximation to the normal beat *R* wave left and right slops can be estimated by calculating the averages of *QR* and *RS* amplitudes. Let these be $\overline{QR_{amp}}$ and $\overline{RS_{amp}}$, respectively. The relations between QR_{amp} and $\overline{QR_{amp}}$, and the relation between RS_{amp} and $\overline{RS_{amp}}$ provide two original features:

$$f_9(i) = QR_{amp}(i) \times \log \frac{QR_{amp}(i)}{\overline{QR_{amp}}}, \quad i = 1,...,nbeats \quad (10) \qquad f_{10}(i) = RS_{amp}(i) \times \log \frac{RS_{amp}(i)}{\overline{RS_{amp}}}, \quad i = 1,...,nbeats \quad (11)$$

Chick *et al.*[3] proposed that the *QRS* complexes' morphology differences between PVCs and normal beats might be evaluated using frequency spectrum signatures. Namely, PVC spectrums tend to be more concentrated in lower frequencies, while spectrums from normal beats tend to be more dispersed. The following features are based on this observation. The entropy of each normalized QRS spectrum assesses the concentration of each spectrum. The logarithmic comparison between the entropy (*H*) and the average of all entropies ($\overline{H}$) leads to the feature given by eq. 12. Another feature is calculated using the *Kullback–Leibler* divergence ($\overline{H}$) between every normalized spectrum (Sp) and the average of all spectrums ($\overline{H}$). This feature expresses the similarity between each spectrum and a spectrum that is an approximation of a normal *QRS* complex spectrum.

$$f_{11}(i) = H(i) \times \log \frac{H(i)}{\overline{H}}, \quad i = 1,...,nbeats \quad (12) \qquad f_{12}(i) = D_{kl}(i)(Sp(i), \overline{Sp}), \quad i = 1,...,nbeats \quad (13)$$

$$D_{kl}(i)(P(X), Q(X)) = \sum_{x \in X} P(x) \log\left(\frac{P(x)}{Q(x)}\right) \quad (14) \qquad f_{13}(i) = \frac{\sum_{k=k_1+1}^{nsp} Sp(i,k)}{\sum_{k=1}^{k1} Sp(i,k)} \quad (15)$$

[3] Chick, M, N. Gbelgacem and F. Reguig; "The use of artificial Neural networks to detect PVC beats", Lab. de Génie Biomédical. Dép. d'électronique, Univ. Abou Bekr Belkaïd, 2003.

2.1.2.2 Classifier

The proposed classifier consists on a three layer (thirteen-twelve-six-one) feed-forward neural network, trained with the Levenberg-Marquardt algorithm. Normalization of the input feature vector has been performed in order to fit into the dynamic range of the used log-sigmoid transfer function.

2.1.3 Atrial Fibrillation

The AF detection algorithm is inspired on the analysis of the three main physiological characteristics of AF: i) P wave absence ii) heart rate irregularity and atrial activity (AA).

2.1.3.1 Features

The absence of P waves during the fibrillation event before the QRS complexes is an important characteristic of AF episodes. Although ECG segmentation methods can be very accurate in the detection of ECG fiducial points, it is observed that these algorithms tend to breakdown for the detection of P waves during AF episodes. To avoid these misclassification errors, a template-based approach is proposed. First a model is extracted by averaging all annotated *P* waves found in the *QT* Database from Physionet. The existence of a P wave is assessed by the correlation coefficient between the P wave candidate and the P wave template (eq. 7), as used in the PVC detection. The rate of P waves in each window is accessed by relating the number N_S of selected P waves (P waves whose index S is greater than 0.2) and the number N_{CB} of cardiac beats.

$$R = \frac{N_S}{N_{CB}} \tag{16}$$

The second class of features relates to the variability of the RR interval. Basically, the R-R interval sequence is modelled as a three-state Markov process being each interval classified as one of the three states (S-short, R-regular or L-long). Intervals are called short if they do not exceed 85% of the mean interval duration, long if they exceed 115% of the mean interval duration, and regular otherwise. Thus, the RR interval sequence can be assumed as a stationary first-order Markov process, characterized by its state transition probability matrix. The regularity of heart rate is characterised by the probability of transition from state R to itself (described by eq. 17), since this transition is more likely to occur when the RR intervals present approximately the same length[4]. It should be noted that, in order to perform this analysis, first PVCs are identified and eliminated.

$$P(R \mid R) = \frac{P(R \cap R)}{P(R)} \tag{17}$$

Using this approach it is possible to determine the similarity between a probabilistic distribution under analysis and a model that represents AF episodes. Based on MIT-BIH Atrial Fibrillation database, a model for the AF episode probability distribution (defined by $\overline{P_{AF}(x,y)}$) was extracted. Using *Kullback–Leibler* divergence (D_{KL}) the similarity between the distribution $\overline{P_{AF}(x,y)}$ and the distribution under analysis ($P(x,y)$) is evaluated, as given by eq. 18.

$$D_{KL}\left(P(x,y), \overline{P_{AF}(x,y)}\right) = \sum_{i=1}^{3}\sum_{j=1}^{3} P(x,y)\log\left(\frac{P(x,y)}{\overline{P_{AF}(x,y)}}\right) \tag{18}$$

The last class of features is based on the atrial activity analysis. AF episodes are characterized by a fibrillatory wave with specific frequency between 4 and 10 Hz. To obtain a valid frequency domain characterization of AF episodes it is needed the extraction or cancellation of the signal components

[4] Moody B. G. and Mark R. G., "A new method for detecting atrial fibrillation using R-R intervals", IEEE Computers in Cardiology 1983.

associated to ventricular activity (VA), that is, the QRS complex and the T wave (QRST). For this propose, the methods reported by Senhadj *et al.* [5] and Sanchez *et al.*[6] have been followed. The QRS-T cancellation is conducted in the frequency domain by excluding the values corresponding to the QRS-T segments and the values above a predefined threshold. This approach guaranties the minimization of the influence of miss-segmented QRS-T complexes in the cancelled signal. Spectral analysis is performed on the residual ECG signal using a Fast Fourier Transform. Once the frequency spectrum has been calculated, it should be parameterized in order to find specific characteristics for AF episodes. The two main characteristics of AF episodes, observed in the frequency spectrums, are the concentration around the main peak, which is positioned in the interval [4, 10] Hz. The concentration of each spectrum is assessed by calculating the entropy of each normalized cancelled ECG window spectrum. Based on the spectrums extracted from the MIT-BIH Atrial Fibrillation database, an AF specific spectrum model has been extracted. Let $P(x)$ be the spectrum under analysis and $Q(x)$ be the aforementioned model. The similarity between $P(x)$ and $Q(x)$ is related to the likelihood of the time window under analysis to be an AF episode. This similarity is evaluated by the *Kullback–Leibler* divergence (D_{KL}) between the two distributions. This feature is described by eq. (19).

$$D_{KL}\left(P(x),Q(x)\right)=\sum_{x\in X}P(x)\log\left(\frac{P(x)}{Q(x)}\right) \tag{19}$$

2.1.3.2 Classifier

In order to detect AF events, the extracted features have been considered as inputs to a neural network classifier, that categorizes each window of ECG data into two classes: with/without AF.

2.1.4 Ventricular Arrhythmias

For the identification of ventricular arrhythmias (VT-ventricular tachycardia and VF-ventricular fibrillation) two algorithms have been developed and implemented. The first one consists of three independent neural networks, designed for specific detection tasks: signal quality (Noise), ventricular tachycardia (VT) and ventricular fibrillation (VF)[7]. Time and frequency domain features, obtained from the electrocardiogram (ECG) form the inputs of these neural modules. The outputs of these neural models feed the a second layer, which consists of a global classifier providing the global result of VA module. The second algorithm proposes a non-linear dynamic signal processing approach to address the problem[8]. Based on the phase space reconstruction of the ECG, some features are extracted for each ECG time window. Features from the current and the previous time windows are provided to a dynamic neural network classifier, enabling arrhythmias detection.

2.1.4.1 Algorithm 1: Features

The selection of the most relevant features for VT and VF discrimination was performed through a correlation analysis procedure. This approach took into consideration a set of available features found in literature and developed within this work and their dependency with respect to the desired task. Concerning temporal domain markers, five morphological features were chosen. These represent information about the shape of the ECG signal:

[5] Senhaji L., Wang F., Hernandez A. I. and Carrault G., "Wavelets Extrema Representation for QRS-T Cancellation and P Wave Detection", IEEE Computers in Cardiology 2002; 29:37-40.

[6] Sanchez C., Millet J., Rieta J. J., Castells F., Ródenas J., Ruiz-Granell R. and Ruiz V., "Packet Wavelet Decomposition: An Approach for Atrial Activity Extraction", IEEE Computers in Cardiology 2002; 29:33-36.

[7] Henriques, J., P. Carvalho, P. Gil, A. Marques, T. Rocha, B. Ribeiro, M. Antunes, R. schmidt, J. Habetha, Ventricular Arrhythmias Assessment, EMBC-2007, 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Lyon, France, August 23-26, 2007.

[8] Rocha, T., S. Paredes, P. Carvalho, J. Henriques, M. Antunes, Phase Space Reconstruction Approach for Ventricular Arrhythmias Characterization, EMBC-2008, 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society Vancouver, Canada, August 20-24, 2008.

i) Percentage of time above or below thresholds is defined as the relative amount of time of beat peaks, which are above a high threshold or below a low threshold[9]. This parameter is a characteristic of the temporal ECG morphology: a normal ECG presents a very small PTABT and a ventricular tachycardia/fibrillation exhibits a larger value of PTABT.

ii) Another feature was based on an algorithm presented by Jekova and Krasteva[10]. Following this approach, a particular band pass digital filter is applied to the original signal. Then, from the filtered signal a set of time domain parameters are extracted, enabling the rhythm classification.

iii) A feature comparable to the heart rate was extracted. This feature employs a nonlinear transform, derived from multiplication of backward differences (MOBD), providing an estimation of extreme variations in the ECG[11].

iv) Another feature was obtained from a two dimensional phase space reconstruction diagram, a tool able to identify chaotic behaviour of signals. Fundamentally, if the signal is non-chaotic (normal sinus rate), the curve in the phase space diagram showing a regular form is concentrated in a restricted region of the plot. However, a chaotic signal (VT/VF) produces a curve that is uniformly distributed over the entire diagram.

v) For detection of abnormal signal amplitudes and slopes, appropriate markers were implemented. These markers were evaluated inside a specific window (10 seconds) by assessing the portions of small and high derivatives in the ECG signal: i) the number of points close to the baseline where the derivative is small (signal is almost horizontal) and ii) the number of points where the derivative is high (signal is almost vertical). The baseline (*bLine*) as well as the respective derivative (*dLine*) was found. The number of points close to the baseline (*horizontalP*) and the number of points, where the derivative is high (*verticalP*) were computed. Variables *lowT*, *highT* and *baseT* define three thresholds, which are established based on the amplitude of the ECG signal. The number of points (*horizontalP* and *verticalP*) is evaluated for every window and allows the estimation of the time interval where the signal is almost horizontal or vertical.

Regarding frequency features, those were based on spectral power distribution. Basically, frequency domain energy contain in different frequencies were used as an approach for characterizing and classifying ECG signals. The PSD was evaluated by windowing segments of the time signal domain and computed using the Welch's method.

2.1.4.2 Algorithm 1: Classifier

A global classifier implemented using an ANFIS (*Adaptive-Network-Based Fuzzy Inference System*) scheme forms the final stage of the proposed algorithm platform. This classifier performs the decision-making, based on the outputs of the simple two-class NN classifiers applied for each ventricular arrhythmia, deciding on whether the current signal is a normal or abnormal signal, i.e. if it is NSR, PVC, VT or VF. For this classifier, a hybrid learning algorithm was implemented, combining the subtractive clustering technique with the least-squares method. Subtractive clustering has been utilized to partition the training sets and to generate the structure, i.e., to determine the number of rules and membership function parameters (the membership functions of the input fuzzy sets were selected in the form of Gaussian functions). The parameters (weights) associated with the membership functions were tuned using the least square method.

2.1.4.3 Algorithm 2 – Phase Space Reconstruction

The algorithm is evaluated by windowing segments of the ECG under analysis considering, for each window, a phase space reconstruction procedure. Then, from the obtained two-dimensional trajectory, some relevant features are extracted. Features from current and previous windows are provided to a time delay neural network classifier (TDNN), enabling the characterization of VA. For the decision system four features have been considered. The first, spatial filling index, has been successfully employed to distinguish NSR from VT and VF[12,13]. The other three features, exclusively developed

[9] Tian, L. and J. Tompkins; "Time domain based algorithm for detection of ventricular fibrillation", Proceedings of the 19 Int. Conference IEEE/EMBS Oct 30-Nov 2, Chicago, USA, 1997.

[10] Jekova I., and V. Krasteva; "Real time detection of ventricular fibrillation and tachycardia", Physiol. Meas. 25, 1167–1178, 2004.

[11] Kunzmann U, G. Schochlin and A. Bolz; "Parameter extraction of ECG signals in real-time". Biomed Tech (Berl). 4, 2:875-8, 2002.

[12] Tratnig, R., "Reliability of new Fibrillation Detection algorithms for Automated External Defibrillators", PhD Dissertation, Technische Universit¨at Graz, 2005.

within this work, exploit the distribution characteristics of the reconstructed phase space trajectory. Phase space reconstruction is a technique used to represent the non-linear characteristics of a dynamic system, consisting of a simple plot of signal time-lagged vectors[14]. Considering the signal as a time series *x*(1), *x*(2), …, *x*(n), where *n* is the number of points, the time lagged vectors of the multidimensional phase space are determined according to eq. 20.

$$Xi = \left[x_i \quad x_{i+\tau} \quad \dots \quad x_{i+(d-1)\tau} \right] \; i = 1 \; \dots \; n-(d-1)\tau \tag{20}$$

where τ is the time delay between the points of the time series, and *d* is the embedding dimension which corresponds to the number of phase space coordinates. The PSR is carried out by plotting the original signal against the delayed versions of itself. The present work uses a two-dimensional PSR (*d*=2) and a time delay τ equal to 7, which was established as a suitable choice in the case of ECG signal[14]. As it can be seen in Fig 3, the PSR (τ=7) has the capacity to distinguish between the three types of signals: NSR, VT and VF. In fact, the shape of the trajectories is clearly distinct for each case.

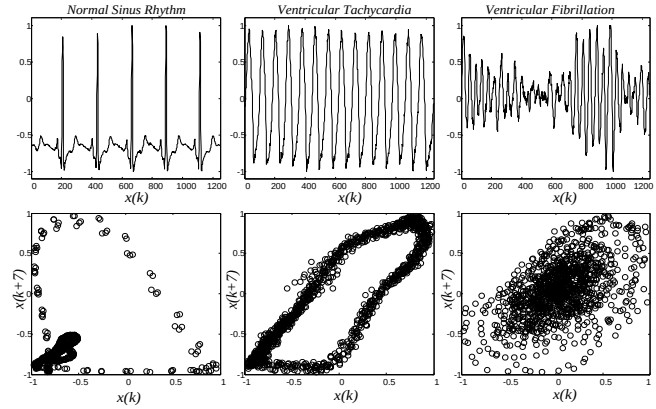


Figure 3 PSR for NSR, VT and VF signals.

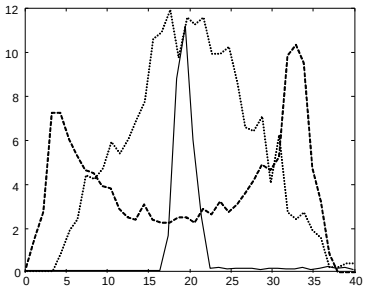


Figure 4 C matrix column averages: NSR (—), VF(…), VT(---).

2.1.4.4 Algorithm 2 – Features

***Spatial filling index*:** The first step to determine the spatial filling index is to reconstruct a two-dimensional phase space of the ECG signal. Given the ECG signal *x*(1), *x*(2), …, *x*(n), the *A* matrix is obtained as eq. 21.

$$A = \begin{bmatrix} x(1) & x(1+\tau) \\ x(2) & x(2+\tau) \\ \dots & \dots \\ x(n-\tau) & x(n) \end{bmatrix} \tag{21}$$

Dividing each element (*i*,*j*) of matrix *A* by $q=max|x(k)|$ ($1 \le k \le n$), a normalized matrix *B* is obtained. In two dimensions, the phase space plot corresponding to *B* matrix ranges from -1 to +1 on either axis. This phase space area is divided into small square areas of size $R \times R$, originating $N=2/R$ grids (being $2/R$ an integer number). The phase space matrix *C* (dimension $R \times R$), is determined with each element $C(i,j)$ equal to the number of phase space points falling into the grid $g(i,j)$. A new matrix *P* is obtained, dividing each element of *C* by *M*, given by eq. 22.

[13] Faust, P., R. Acharya, S. Krishnan, L. Min, "Analysis of cardiac signals using spatial filling index and time-frequency domain", BioMedical Engineering OnLine, 3:30, 2004.

[14] Krishnan, S., D. Dutt, Y. Chan, V. Anantharaman, "Phase Space Analysis for Cardiovascular Signals", Advances in Cardiac Signal Processing , Chap 15, 339-354, Springer, 2007.

$$P = \frac{1}{M} C, \quad M = \sum_{i,j=1}^{N} C(i,j) \tag{22}$$

Each element $P(i,j)$ represents the probability that a phase space point falls into the grid $g(i,j)$. Squaring each element of P, the R matrix is determined. Being S the sum of all points of R, the spatial filling index (η) is finally obtained as eq. 23.

$$\eta = \frac{S}{N^2} \tag{23}$$

***Standard deviation of the curve of C column averages*:** Taking the average of each column of C matrix, a curve characterizing the distribution of points in the phase space is obtained, inspired by the idea of Radon transform[15]. Figure 4 depicts examples of these curves, for the NSR, VT and VF signal types, revealing their discrimination capacities. The second feature is the standard deviation of the curve.

***Area of the curve of C column averages*:** The third feature is the percentage of area in the extremities of the curve of C column averages. From Figure 4, it is clear that the area under this curve can be used to distinguish between ECG signal types. As seen, for VT signals, the area under the curve near the extremities is higher than in the other cases.

***Ellipse based feature*:** The fourth feature is based on the phase space points distribution. As it is depicted by Figure 3, in the NSR case, the distribution of the points is concentrated on a centre; in the VT case, the points are grouped in an elliptic shape; in the VF case, the points are randomly distributed (by the interior, the border and the exterior of the ellipse). The number of points in each one of these regions (centre, border and remaining) is used to discriminate the signals. Given a representation of a signal in the phase space the method proposed by[16] is used for fitting ellipses to scattered data.

2.1.4.5 Algorithm 2: Classifier

The classifier consists of a dynamic neural network (time delay neural network), where the number of hidden neurons has been determined experimentally (10): small enough for fast training and generality, but sufficiently large to give adequate accuracy. The parameters (weights and bias) that characterize the NN, have been trained using the Levenberg-Marquardt algorithm.

2.1.5 Heart Rate Variability

Various measures of heart rate variability have been proposed in literature, which can generally be subdivided into time domain, frequency domain and non-linear measures. The algorithms implemented here to determine these measurements follow common approaches found in literature[17,18] and no special effort was made to derive new measurements. It is expected that HRV analysis will be profoundly improved by integrating the work that is being carried out by the partners from POLIMI. Currently the following parameters are available:

Time Domain: mean: mean of RR intervals; SDNN standard deviation of RR intervals; SDSD standard deviation of the differences between heart beats (DHB); RMSSD root mean square of the DHB; NN50 number of RR intervals that fall within 50 milliseconds; pNN50 percentage of total NN50.

[15] Deans, S., "The Radon Transform and Some of Its Applications", New York: Wiley, 1983.

[16] Fitzgibbon, A., M. Pilu, R. Fisher, "Direct Least Square Fitting of Ellipses", Pattern analysis and machine intelligence, 21, 5, 1999.

[17] Niskanen, T., M. Tarvainen, P. Ranta-aho, A. Karjalainen, Software for advanced HRV analysis, University of Kuopio Department of Applied Physics Report Series ISSN 0788-4672, 2002.

[18] Tarvainen , M, Niskanen, J: Kubios HRV Analysis, version 2.0 beta, University of Kuopio, Kuopio, Finland, 2006. (http://bsamig.uku.fi/).

Frequency domain: PSD frequency content (Burg and Welch method are available); pVL percentage of very low frequency content [0 - 0.04]; pLF percentage of low frequency content [0.04 - 0.15]; pHF percentage of high frequency content [0.15 - 0.40]; rLF ratio pLF/pHF.

Nonlinear: FApen approximate Entropy (ApEn) of a signal; Poincaré plot: Poincaré plot fits heart rate data points to an ellipse that is fitted to two intersecting lines, SD1 and SD2.

2.1.6 ST deviation

The algorithms implemented to evaluate ST segment deviation follow basically two stages. First, the ECG signal is broken into cardiac cycles and a baseline removal process is applied to each individual interval. The main goal of this step is to guarantee that the isoelectric line is coincident with the zero line to facilitate ST segment shift evaluation. The second stage involves several measures of the aimed deviation. In effect, the literature shows a great variety of approaches to assess this ECG feature. Four measurements of ST deviation are available. This way, the person analyzing the ST segment deviation, has three different values to support decision making. The first three were chosen from literature, whose details are presented below, and make use of the ECG segmentation method presented in section 2.1.1. A new algorithm was developed and implemented based on the Wigner Ville transform.

2.1.6.1 Baseline removal

Based on R peaks localization, the entire ECG signal is broken into cardiac cycles using the average of the distances between consecutive R peaks. Each cardiac cycle is then submitted to a process of baseline removal using Wolf's[19] method. This method starts to determine the initial and final heights (H1 and H2) of the interval, using the average of the first five samples and the average of the last five samples, respectively. Then, the line segment connecting H1 to H2 is subtracted from the ECG, originating a corrected signal in terms of baseline.

2.1.6.2 ST segment deviation measurement

The first algorithm, proposed by Akselrod et al[20], measures ST amplitude in the point localized 104 ms after the R peak. The second algorithm, introduced by Taddei et al.[21], considers ST deviation 80 ms after the J point or, in case of sinus tachycardia (heart rate > 120 bpm), 60 ms after the referred point. This approach has the disadvantage of depending on the accuracy of J point detection. The third method, introduced by Pang et al.[22], measures ST segment deviation in a point that depends on heart rate, according to the following table.

Heart Rate	ST Segment Deviation Measuring Point
HR ≤ 100	R + 120 ms
100 < HR ≤ 110	R + 112 ms
110 < HR ≤ 120	R + 104 ms
HR > 120	R + 100 ms

It is recognized that time-frequency methods are especially adequate for the detection of small transient characteristic hidden in the ECG, such as the ST segment. Based on this observation we developed another approach for the estimation of ST deviation using the Wigner-Ville transform. The Wigner-Ville distribution is a time-frequency representation that considers a time analytical signal. Regarding the ECG, the equivalent analytic signal of the initial real signal $x(n)$ was obtained by adding to the real signal its Hilbert transform H[.] as the imaginary part, eq. (24)

[19] Wolf, A, Automatic Analysis of Electrocardiogram Signals using Neural networks, (in Portuguese), PUC-Rio, Ms. Thesis, nº 0210429/CA2004.

[20] Akselrod, S., Norymberg, M., Peled, I., Karabelnik E., Green, M. S. (1987). "Computerised Analysis of ST Segment Changes in Ambulatory Electrocardiograms", Medical and Biological Engineering and Computing, v. 25, p. 513-519.

[21] Taddei A, Distante G, Emdin M, Pisani P, Moody G B, Zeelenberg C and Marchesi C, The European ST Database: standard for evaluating systems for the analysis of ST-T changes in ambulatory electrocardiography Eur. Heart J. 13 1164–72, 1992.

[22] Pang L, Tchoudovski I, Bolz A, Braecklein M, Egorouchkina K and Kellermann W 2005 Real time heart ischemia detection in the smart home care system 27th Annu. Int. Conf. Eng. Med. Biol. Soc., 2005. IEEE-EMBS 2005

$$y(n) = x(n) + jH\left[x(n)\right] \tag{24}$$

The basic idea followed here consists in the division of the time frequency map into characteristic areas and, within each specific area, to perform the evaluation of particular characteristics. With respect to the ST estimation, two time bands and one frequency band was considered. Regarding the time band, the areas considered were those on the left (isoelectric line) and on the right (ST segment) of the R peak (assumed to be previously determined). For each time band it is expect to determine regions were there is no signal activity (isoelectric line, interval between the end of P wave and the begin of QRS complex, and ST segment, interval between the end of QRS complex and the begin of T wave). Thus, for those time bands, high frequency band were considered and, in particular, the region where high frequency components presents minimum values. Figure 5depicts this idea, were an electrocardiogram and its corresponding high time-frequency components are shown (between 0.5 and 1.0, half of the normalized range). By evaluating the minimum of the sum of the high frequency components in each time band, isoelectric and J points can be obtained. Having determined these points, the ST deviation is straightforward estimated as the difference between J and isoelectric values.

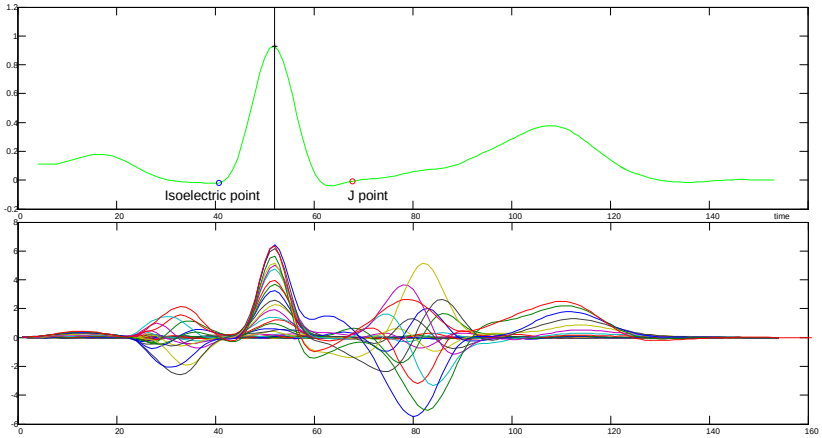


Figure 5 Example of and electrocardiogram and the corresponding high frequency components (Wigner-Ville transform).

2.2 Validation

2.2.1 ECG segmentation and intervals computation

The ECG segmentation algorithm validation has been performed using all 105 records from MIT-QT Database. Record lead configurations most similar to MLII have been chosen for testing the algorithm. Table 2 shows the SE-sensibility and PP-positive predictivity results regarding ECG segmentation and intervals computation.

	P waves	***R peaks***	***T waves***
SE	*88,09*	*99,30*	*96,83*
PP	*91,27*	*99,80*	*96,33*

Table 2

2.2.2 PVC

The PVCs' detection algorithm validation has been performed using 46 of 48 MIT-BIH database records. Non MLII lead configurations records have been removed from the training and testing

datasets, preserving coherence in the morphological characteristics of ECG records. 1965 PVCs and 11250 normal *QRS* complexes from the aforementioned dataset, compose the training dataset. Validation was performed using all dataset records. The SE-sensibility and SP-Specificity values achieved results are presented and compared in Table 3 with state of the art algorithms.

	SE	***SP***
PVC detection	*96,35*	*99,15*

Table 3

2.2.3 AF

To validate the proposed AF detection algorithm, 23 records from MIT-BIH Atrial Fibrillation were used (lead MLII). Respectively 19161 and 29893 windows of 12 seconds, corresponding to AF and non AF episodes, compose the training dataset. Validation has been performed using all 23 dataset records (238321 and 59785 AF and non AF episodes, respectively). The results obtained by the proposed algorithm are presented in Table 4.

	SE	**SP**
AF detection	93.8	96.09

Table 4

2.2.4 Ventricular Arrhythmias

The performance of the two algorithms for PVC detection (MIT) as well as for noise, VT and VF (MIT/MVA/CVT) detection are presented in Table 5. A data base of 51 signals was created, involving the three ECG signal classes (normal sinus rhythm, VT and VF). For MVA and CVT data sets, the number of windows was 420 (35 minutes) and 102 (8.5 minutes), respectively.

		VT/VF			
		MIT	MVA	CVT	ALL
SE	Algorithm 1	99.7	90.7	91.8	89.3
	Algorithm 2		95.1	92.8	92.3
SP	Algorithm 1	98.8	95.0	96.9	94.1
	Algorithm 2		98.7	96.4	98.2

Table 5

As seen from the results in Table 5, the detection results are higher when considering independently each database. Applied to all databases the method has a sensitivity of 89.3% and specificity of 94.1%. Moreover, the highest result was obtained with the MIT records. This fact can be justified, since MIT records are mainly composed of regular signals with some PVCs and VTs. The performance of the phase space algorithm, presents superior results. Applied to all databases the method has a sensitivity of 92.3% and specificity of 98.2%, revealing its capacity to perform detection tasks.

2.2.5 ST deviation

A truly validation process could not be done. In fact, the available databases in this area, namely, the European ST-T Database and the Long-Term ST Database, were created to be used for evaluation of algorithms that detect or differentiate between ischemic ST episodes, axis-related non-ischemic ST episodes, etc. This is not the case of the present algorithm, which only considers discrete values of the ST segment deviation without further processing. For this reason, a correlation analysis was carried out. The average results obtained are presented in the Table 6.

Method	Correlation coefficient	Records
Taddei's method	0.512	'e0105','e0213','e0403','e0107','e0305','e0405','e0111', 'e0409','e0113','e0411','e0115','e0119','e0413','e0121',
Pang's method	0.575	'e0415','e0127','e0501','e0123','e0129','e0515','e0125', 'e0417','e0139','e0601','e0147','e0603','e0151','e0607',
Akselrod's method	0.576	'e0605','e0159','e0609','e0163','e0161','e0203','e0817', 'e0613','e0205','e0615','e0207','e0801','e0303','e0211',
Wigner Ville	0.546	'e0103','e0305',

Table 6

3 WP3: Models of Treatment Response

provided by University of Thessaloniki

3.1 Overview

Mathematical modeling of a drug can be used to observe how the concentration of a drug in the body changes with time or how for example blood pressure changes over time following the administration of a drug that is designed to reduce blood pressure. There are two possible approaches for drug modeling (Cobelli & Carson, 2008).

The first approach also termed data-driven modeling relies on the available drug-related data collected on the system. Essentially, mathematical descriptions of data derive from experimental data and correspond to the underlying physiology. This type of mathematical modeling is particularly suitable when the knowledge of the underlying physiology is deficient and learning these mechanisms is not prioritized.

The second type of modeling, termed theoretical model, aims at explicitly describing the underlying physical and chemical processes. The advantage of this approach compared with the data-driven models is that the variables incorporated into the drug modeling directly fit to a greater or lesser extend to the physiological parameters.

3.2 Theoretical Models

3.2.1 Pk/PD Models

Pharmacokinetics is dedicated to the study of the concentration of drugs administrated to the body, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion [23]. The mechanisms of Absorption (Drug entering the body) , Distribution (Drug is spreading to different areas of the body), Metabolism (Drug is being changed to new chemical compounds) and Elimination (Drug is removed from the body) are taken into account and properly modelled.

PK models:

- *One compartment*: The administrated drug is evenly distributed into a single compartment in the body, and is eliminated from the body in a first-order fashion. Appropriate for drugs which rapidly and readily distribute between the plasma and other body tissues. It has only one volume term, the Volume of distribution (Vd).
- *Two compartments*: Includes a peripheral compartment into which the drug may distribute. Common designations are:

  Comp 1 (central) - blood and well perfused organs, e.g. liver, kidney, etc.; "plasma"

  Comp 2 (peripheral) - poorly perfused tissues, e.g. muscle, lean tissue, fat; "tissue"

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect[24].

PD models:

- The immediate response models (alone or linked to a pharmacokinetic model)
- The turnover models (only linked to a pharmacokinetic model)

[23] http://www.rxkinetics.com/pktutorial/1_1.html

[24] http://www.cop.ufl.edu/safezone/pat/pha5127/multicpt/2-cptmt.htm

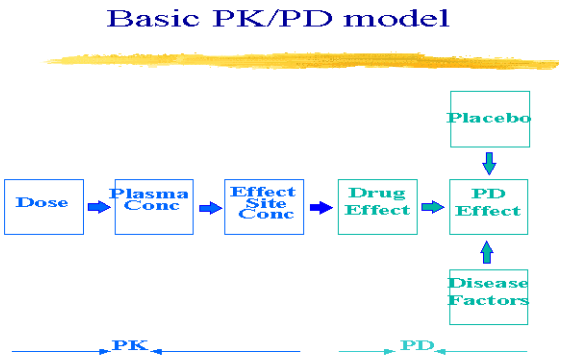


Figure 1. General view of a Ph/PD approach

Such Pk/PD models are used

- To provide a simplified description of the observations.
- To describe the time course of drug action.
- To suggest appropriate doses and dosing intervals
- To make predictions of future situations

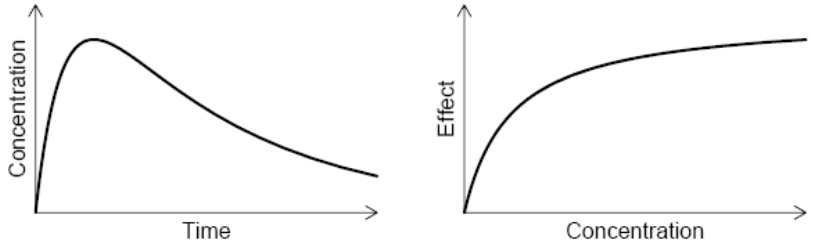
The effect drug E(t) is expressed as

E(t)=S(t)+A(t)

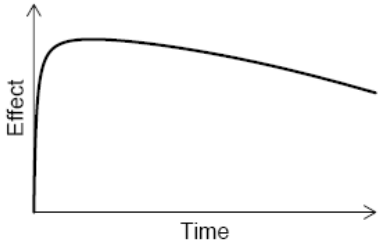
Where A(t) models drug action and S(t) corresponds to the disease model. A(t) is a function of the drug concentration C(t), for example in the linear assumption, A(t)=Aconstant*C(t) or Michaelis-Menten relationship[25]. S(t) can be a constant, a linear or exponential function, etc, modeling the disease progress in a relevant manner. The drug concentration corresponding to multiple-day drug administration can follow the form $C(t) = \sum_{i=1}^{n} a \cdot e^{-k(t-t_{Di})}$, and additionally a second exponential factor can describe the clearance of the substance from the blood.

Individual and population based models are considered, and optimization methods are used to estimate the model parameters.

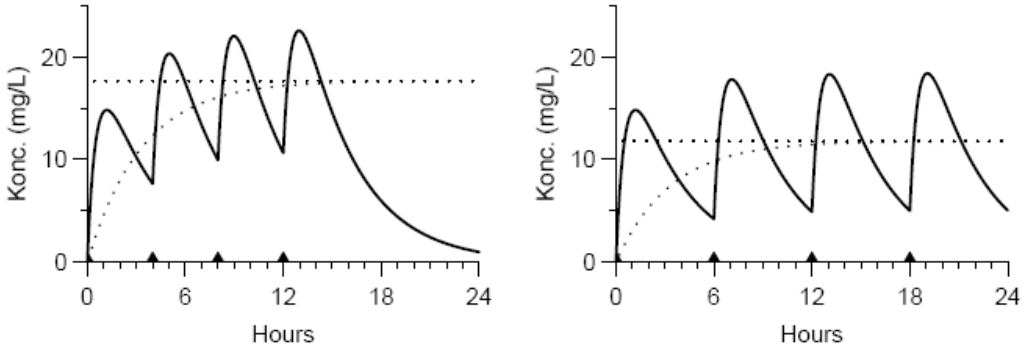
[25] http://en.wikipedia.org/wiki/Michaelis-Menten



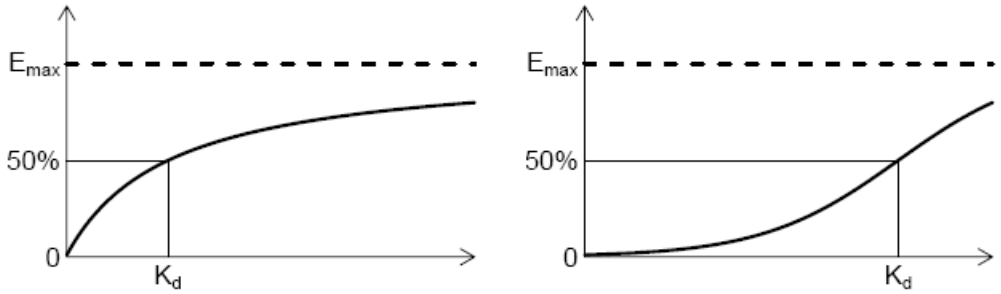
(a) PK model (b) PD model



(c) Combined PK/PD model



(a) 4 hours between oral dosing (b) 6 hours between oral dosing



(a) Response vs. Conc. (b) Response vs. log(Conc).

Figure 2 from[26] (Up) Pk/Pd concepts, (middle) Concentration , Multiple dosing of 4g paracetamol with 4 oral doses of 1g shown as a thick line. The dotted line is a constant rate infusion at a corresponding rate. (Down) Michaelis-Menten relationship with response. (PD)

[26] http://orbit.dtu.dk/getResource?recordId=228815&objectId=1&versionId=1

A well known academic open source application for the analysis of non linear mixed effects models is MONOLIX[27] . Pk/Pd analysis packages are also available in R-package[28]

NONMEM is a software package developed at University of California, San Francisco (UCSF) for use in population PK/PD modelling (Beal and Sheiner;2004), based on ordinary differential equations and state-space approaches.

The Pk/Pd approaches can produce very accurate results. However, among the disadvantages of such approaches is the need for dense concentration samples, making this approach unrealistic in a telemonitoring scenario.

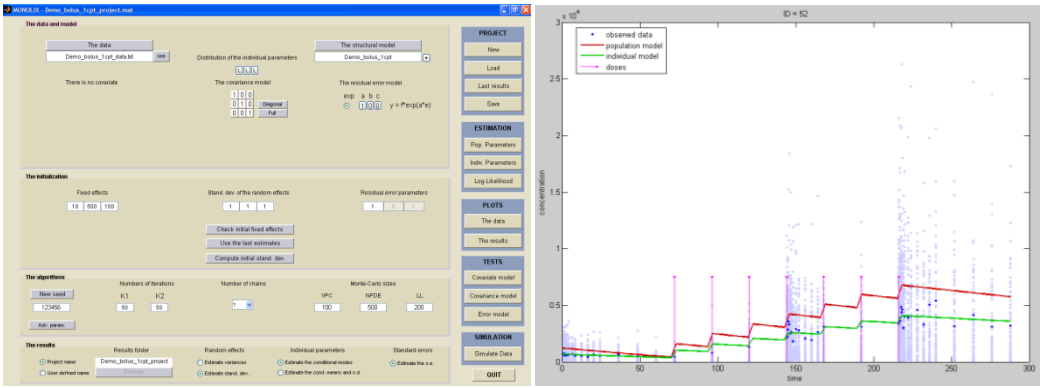


Figure 3. a) Monolix interface, b) estimated concentrations

[27] http://software.monolix.org/

[28] http://cran.r-project.org/web/packages/drc/index.html

3.3 Data-driven models

The advances in the area of soft computing, especially the resurgence of artificial neural networks and the increasing popularity of fuzzy set theory, have influenced the area of pharmacokinetic and pharmacodynamic modeling (Bellazzi, 1992; Veng-Pedersen and Modi, 1992; Bellazzi et al., 1994; Brier et al., 1995; Sproule et al., 2002; Gaweda et al., 2003; Guerrero et al., 2003).

3.3.1 Neural Networks

The advances in the area of computational intelligence, especially the resurgence of Artificial Neural Networks (ANN), have influenced the area of PK/PD modeling. A number of ANN models for PK/PD analysis have been used to address different dose modeling problems (Brier et al., 1995; Veng-Pedersen & Modi, 1992). The data-driven learning capabilities of ANNs has been proved particularly important for the drug-effect modeling (Veng-Pedersen & Modi, 1992). An effective and cost-efficient strategy that allows the prediction of patient response to the drug has been implemented for patients with renal failure (Gaveda et al., 2003). The proposed approach is based two different types of ANN a multi-layer perceptron network and a radial basis function network that perform drug dose-effect modeling. In addition, a neural network model is proposed for dose-response of foodborne pathogens. The output of the neural network has one neuron representing the probability of infection, while the ingested doses are the inputs along with other factors affecting the probability of infection such as age and gender (Xie et al., 2000).

3.3.2 Fuzzy Models

The prediction of the pharmacotherapy results is difficult mostly due to the wide range of pharmacokinetic and pharmacodynamic variations e.g. gender, age, weight, genetic profile etc. (Rowland & Tozer, 1980). In pharmacology, fuzziness and fuzzy logic systems have been applied to: a) control mechanical drug delivery devices, b) pharmacokinetic modeling and, c) pharmacodynamic modeling. A typical dose-response example using fuzziness would be to cluster output (response) into overlapping fuzzy sets that are defined so that the internal distances are minimized and the distance between clusters are minimized (Figure 4).

For example, a fuzzy logic-controller has been used to administer atracurium during surgery, where the amount of drug administered is adjusted according to patient's individual response (Ross et al., 1997). In addition Dazzi et al. developed a control system using fuzzy logic and neural networks to adjust intravenous insulin doses in critically ill diabetic patients (Dazzi et al., 2001). The number of the 'if-then' rules is then determined by the number of fuzzy sets [Sproule et al., 2002].

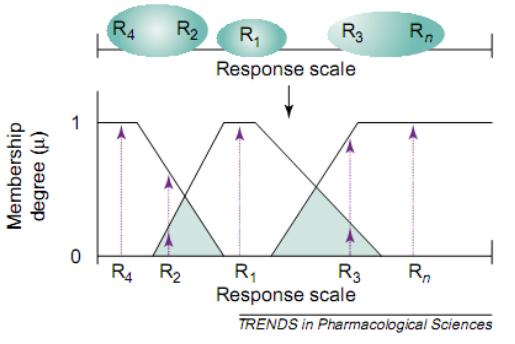


Figure 4: Responses are clustered into three overlapping clusters such that responses 2 and 3 (R2 and R3) are each members of two clusters using fuzzy set theory.

Fuzzy logic has also been evaluated on pharmacodynamic modeling through dose-response studies. For example, the relationship between clinical variables and dose-response has been evaluated by analyzing the association between hemodynamic variables, auditory evoked potentials and the inspired fraction of isoflurance (Jensen et al., 1999). In another example, a combined fuzzy linear-regression method has been used to evaluate the dose-response association between nitrate exposure and cancer risk (Lee et al., 2001).

On the whole, fuzzy logic can be used to compliment current drug modeling approaches while it might be not necessary to model linear systems unless any of the variables are inherently fuzzy.

3.3.3 Decision Tree Models

Decision trees have been employed in drug modeling to allow clinicians to predict which patients will likely respond to treatment and thereby guide clinical decision making. In (Andreescu et al., 2008) two models, one minimizing false predictions of future response and one minimizing false predictions of future non-response have been proposed for the treatment of late-life depression. These two models, corresponding to an aggressive treatment and a conservative treatment approach respectively, were used to identify the hierarchy of predictors in treatment response using signal detection theory in two binary decision trees (Figure 5).

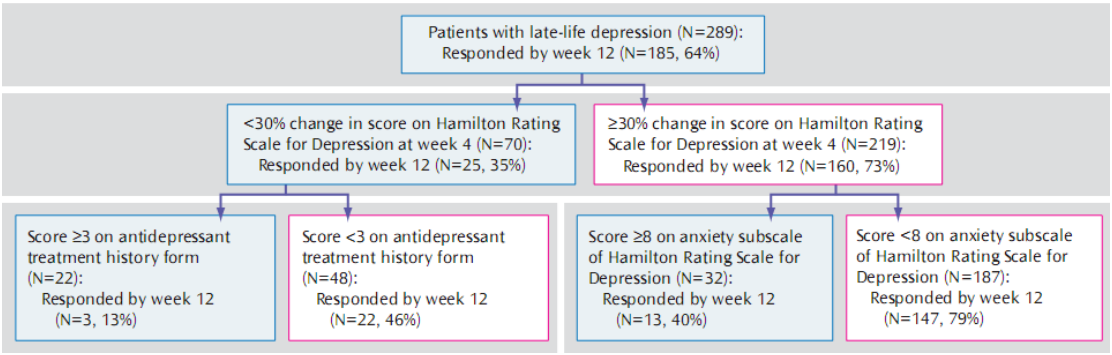


Figure 5: Hierarchy of predictors in treatment response

3.3.4 State-Space Models

State-space models are models that use state variables to describe a system by a set of first-order differential or difference equations, rather than by one or more *n*th-order differential or difference equations. State variables *x(t)* can be reconstructed from the measured input-output data, but are not themselves measured during an experiment.

The *model order* for state-space models is an integer equal to the dimension of *x(t)* and relates to the number of delayed inputs and outputs used in the corresponding linear difference equation.

Types of Supported Data:

- Real data or complex data in any domain
- Single-output and multiple-output
- Time- or frequency-domain data

Considering continuous stochastic processes, linear with additive noise, the basic formulation of state-space equations is as follows:

$$x(t+Ts) = Ax(t) + Bu(t) + Ke(t)$$

$$y(t) = Cx(t) + Du(t) + e(t)$$

An example of the estimation can be seen in Figure 6.

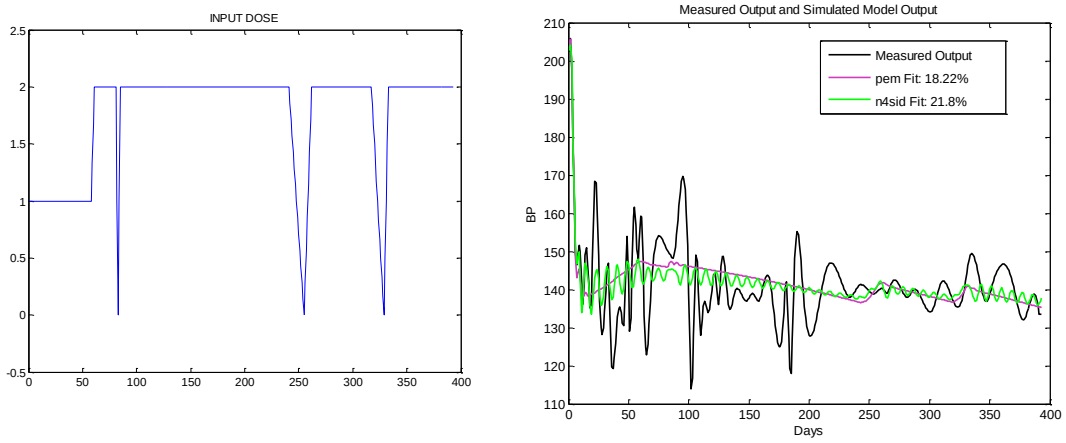


Figure 6. A simple Matlab state-space example.with rather sparse and interpolated blood pressure data and dose level data. Input u(t): dose, State variable y(t): health parameter, Assumption: state variable progresses according to input and to its internal properties (disease)

In the work of [Yoshinori Kawasaki et al;2007] a structural time series model with an intervention has been proposed to model dose-response, from dense vital signs data. Among their findings is that a trend term and the stationary AR term play an important role to extract dose effects accurately.

A more sophisticated approach, Stochastic Differential Equations (SDE) describe the time evolution of quantitative state vectors in continuous time. More generally, a measurement equation can be joined to the dynamical system (continuous discrete state space model) in order to model measurement error, factor loadings and latent variables (e.g. time derivatives, person specific and random time effects).

CTSM is a program for performing estimation of state space models based on Stochastic Differential Equations (Kristensen and Madsen 2003, Kristensen et al. 2004). The program been developed at DTU Informatics and has been used for PK/PD modelling using SDEs in e.g. Tornoe et al. (2004a, 2004b) and Kristensen et al. (2005).

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4 WP4: Motivation and coaching strategies
provided by VTT

4.1 Methodology

Several interventions and models have been developed to increase patient empowerment and motivation towards his disease management. In this section, we give brief descriptions of existing interventions and models. In the end of each section, we suggest, how each model could be used in the HeartCycle project. The proposed motivation and coaching strategies for HeartCycle are summarized in sections 4.2 and 4.3.

4.1.1 Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) is a form of psychotherapy that focuses on influencing negative emotions and behaviours. The negative emotions often contribute to inaccurate appraisal of events and may lead to harmful behaviour. For example, if a patient makes a mistake and therefore believes: "I'm useless and can't do anything right". This worsens his mood and leads to feelings of depression. The problem may be worsened, if the person reacts by avoiding the activity in which he made the mistake, because he/she then behaviourally confirms his or her negative belief. As a result, a successful experience becomes more unlikely.

The key elements in CBT therapy are:

1) cooperative and equal relationship between the therapist and the patient
2) identifying, questioning and testing the patient's own beliefs (e.g., "I'm not able to quit smoking")
3) keeping a diary of events and related feelings, thoughts and behaviour relevant to the problem
4) recognition of activities and thoughts that are being avoided (e.g. smoking cessation) and exposure to those activities and thoughts
5) finding new, better and flexible behaviours and thoughts

The goal of CBT is to recognize the thoughts and beliefs that cause, influence and maintain the patient's problematic behaviour. When the patient has identified his or her problematic thoughts the therapist questions and tests the beliefs trough Socratic questioning in order to the patient to be able to change his or her beliefs. The identifying of problematic beliefs and thoughts can be accomplished through different diaries. After questioning the beliefs the patient tests his or her old beliefs in real life and establishes new more flexible beliefs. Through exposure the patient is exposed to situations and activities she or he has avoided. Usually the exposure is executed gradually from the easiest to the most avoided situation. Through exposure the patient has the experience of coping with the emotions.

CBT is usually started with education of the disease and different factors that influence it. In addition to education, CBT uses both cognitive and behavioural techniques. Behavioural techniques are for example creating different timetables (for the day or to the whole week), tasks that progress with baby-steps, practising social skills through role play, exposure tasks and practising relaxation techniques. Cognitive techniques include the techniques used in identifying and questioning the patient's beliefs and also techniques concerning the examination of different alternatives (pros and cons) and working with the patient's images. An essential part of CBT is different homework that is carried out at home between the sessions. CBT and used techniques should be planned individually to every patient in agreement with the patient but usually cognitive techniques are emphasized first but without commitment they can be ineffective.

The ultimate goal is to educate the patient so that he or she can act as his or her own therapist. With CBT it is possible to practice the patient's cognitive skills, emotion regulation, social skills and also skills concerning the life control. In order to the patient to change it is necessary to restructure his or

her behaviour and the problematic beliefs. CBT is recognized as one of the most widely used, evidence-based psychotherapy. It has been identified to be cost-effective and have long-term effects, often longer-term effect than medication [Butler 2006]. Recently, CBT has been adapted for wide range of disorders and problems [Butler 2006]. Also treatments utilizing the Internet [Cuijpers 2008] and electronic diaries [Lamminmäki 2005, Lappalainen 2005] have been inspired by CBT. With cardiac patients, CBT has been used to treat depression [O'Hea 2008, Shapiro 2007].

In HeartCycle, patients with CHD and HF often have behavioural problems, such as inactive lifestyle, unhealthy diet, smoking or medication non-compliance. The focus of CBT in this context is to treat the problems by first recognizing the behaviours that are harmful to the individual patient and then gradually change the behaviours. A key element is again self-monitoring. The patients are taught to 1) observe their behaviour, 2) identify the harmful behaviours, 3) make changes to their daily habits and 4) monitor the effects of the changes. With help of long-term self-monitoring, the patients gradually learn which behaviours have positive effect on their health and which have negative effect. By learning this, they can work on the problems that are relevant to themselves. Useful methods in HeartCycle would be different relaxation techniques and diaries. Also different timetables and lists with pros and cons could help the patient to realize that they have to change their behaviour and give suggestions on where to start.

4.1.2 Computerized Cognitive Behavioural Therapy (CCBT)

Computerized Cognitive Behavioural Therapy (CCBT) is a computerised CBT, which integrates psychological therapies and multimedia software. There are different implementations of CCBT for different disorders. For example, "Beating the Blues" (Ultrasis UK LTD, London, the UK) is a CCBT programme for mild and moderate depression and anxiety. It has been clinically validated and found to be a cost-effective and time-efficient way of helping people to get better and stay better [Proudfoot 2004, McCrone 2004]. The program is recommended by NICE in the UK (National Institute of Health and Clinical Excellence).

Beating the Blues is designed for people with no previous computer experience. It is an 8-session self-help treatment, during which the users identify specific problems and realistic treatment goals. The program consists of 1) cognitive modules, 2) problem-directed behavioural components and 3) action planning and relapse prevention. The cognitive modules focus on identification of automatic thoughts, thinking errors, distractions and core beliefs. With problem-directed behavioural components the patients can focus, e.g., on activity scheduling, problem solving and sleep management, depending on their own specific problems.

The computer program utilizes interactive modules, animations and voice-over to motivate the user. An important feature is a series of filmed case studies of fictional patients, who model the symptoms of anxiety and depression and help demonstrate the treatment by CBT. In UK, Beating the Blues is used as the first-line treatment for mild depression, before drugs are described. It is especially useful for people in waiting lists for encounter with a medical professional.

The programme includes: 1) one year online access to Beating the Blues, 2) 8 online sessions (Table 1) lasting approximately 1 hour each, 3) projects to do between sessions to consolidate progress and learning, 4) 3 scheduled phone calls from a specialist team to support during the program, 5) 24 hour access to telephone and email support by dedicated support team for a 16 week period. It is possible to return and review any of the sessions as many times as the patient likes during the 1 year period. The eight sessions deal with 1) getting started, 2) goal setting and "automatic" thoughts, 3) thinking errors, 4) challenging the thoughts, 5) inner beliefs, 6) attributional style, 7) more on attributional style and 8) planning ahead. The program shows how the thoughts (and especially thinking errors and inner beliefs) can affect feelings and therefore cause depression. The attributional style refers to how people give reasons for things that happen to them in life and tries to teach new, more positive way of thinking. Education, goal setting and checking progress are important factors of the program.

For HeartCycle, the CCBT approach is an interesting example of how to build a motivating computer program for a patient. CCBT addresses especially depression, which is also a common symptom with cardiac patients. Thus, a same type of approach could be useful for cardiac patients as well.

4.1.3 Acceptance and Commitment Therapy (ACT)

The key element in acceptance and commitment therapy is the attempt to change the meaning of the experience, not like in other therapy methods in changing the personal experience [Lappalainen 2004]. The patients are supported in accepting the things they cannot change and secondly changing the things that are possible to change. The acceptance and commitment therapy focuses on presence not on the past. The therapy is based on the relational frame theory. The acceptance and commitment therapy tries to avoid too rigid behaviour which is behaviour controlled by different rules and increasing the influence of own experiences. One of the basic tasks of acceptance and behavioural therapy is to realize and change the behaviour controlled with ineffective rules by clarifying the actual consequences of these rules. The essential processes in acceptance and commitment therapy are listed below:

- focus on the presence
- acceptance
- decreasing the verbal control
- the self is seen as a context
- values
- dedication to life accordant with values

The acceptance and commitment therapy starts with different assumptions where the most important is that patient's attempts to solve the problem have been part of the problem and one of the first goals is to have a clearer understanding of what has not worked. In acceptance and commitment therapy it is also possible to use for example different relaxation techniques and exposure techniques.

An important part in the acceptance and commitment therapy is the working with patient's values [Hayes 2006]. It is easier for the patient to engage in the alteration work when the direction of his or her life has been specified. So the goal is to dedicate to actions accordant with values.

In HeartCycle the focus is also in the presence not in changing the past. The patient's acceptance of his or her illness is also an important feature in HeartCycle. The patient's engagement to rehabilitation could be increased through the use of patient's values.

4.1.4 Trans-theoretical model ("Stages of Change")

Behavioural change (e.g., increase of exercise, changes in diet, smoking cessation, etc.) is often the first solution that is offered to a person having symptoms of a cardiovascular disease. Success in achieving a behavioural change is very individual, because of different learned habits, environments, etc. Different models have been developed to better understand the behaviour change. Trans-theoretical model of change (TTM) focuses on health psychology and explains or predicts the person's success in achieving the behavioural change. TTM highlights that the support for patient should be matched to the stage of change the patient is in for optimal progress.

There are several advantages if patients are di1vided to stages based on their readiness to engage in self-management approach and take this information into account when making treatment decisions [Hofkamp 2008]. With the assessment of stages it is possible to allocate the information given to the patient. The patient gets the information she or he is ready to receive. With right kind of information it is possible to support the patient to shift to the next stage when the patient receives better outcomes and comes more motivated to continue the rehabilitation. So with the assessment of stages it is possible to plan the rehabilitation from the patient's point of view. With the assessment of stages the

patient carries out only those tasks that are on her or his stage so the patient won't be overwhelmed with too difficult tasks that might interrupt the progress or lead to drop-out. That is why also the progress and moving to the next stage should be monitored and measured. It is also possible to drop to earlier stages and then the demands should also be accommodated to the previous stage.

It is important that the patients accept the notion that substantial effort is required from them. This can be improved if the stage of the patient is known. [Hofkamp 2008] and with the assessment of stages it is possible for the patients to make early-treatment successes which improve the motivation. With assessment of readiness to change, treatment efforts can be directed at providing information about the positive effects gained through altering exercise and diet habits to those patients who have not taken responsibility of their cardiac health [Hofkamp 2008]. Without the assessment of stages it would be difficult to support those patients who are not taking responsibility of their cardiac health and it is possible that these patients would not benefit from the expensive rehabilitation.

Patients who changed their attitude toward readiness to adopt a self-management approach in early stages of treatment appeared to benefit more from treatment than did patients who did not change [Hofkamp 2008]. By knowing the stage where the person is it is possible to predict the outcomes gained with rehabilitation.

TTM explains that individuals go through six stages when adopting new healthy behaviours or cessation of unhealthy behaviours [Prochaska 1997]. These six stages are [Prochaska 2001]:

1) **Pre-Contemplation** is the stage in which there is no intention to change behaviour in the foreseeable future (usually in the next 6 months). The individuals are unaware or under-aware of their problems. Their families and friends are often well aware that the pre-contemplator has problems. The pre-contemplators can be described as resistant or unmotivated, because they tend to avoid information and discussion regarding the behaviour change.
2) **Contemplation** is the stage in which the individual is aware that a problem exists and is seriously thinking about overcoming it (in the next 6 months) but has not yet made a commitment to take action. It is common that people remain stuck in the contemplation stage for long periods.
3) **Preparation** is a stage in which the patient has both intention and some behaviour towards the change. Typically, the patients in this stage are intending to take action in the next month and have unsuccessfully taken action in the past year. They often report some small behavioural changes, but have not yet reached effective action (e.g., abstinence of smoking).
4) **Action** is the stage in which the patients modify their behaviour, experiences and environment in order to overcome their problems. Action involves obvious behavioural changes and requires considerable commitment of time and energy. The patients are classified into action stage if they have successfully altered their problem behaviour for a period from 1 day to 6 months.
5) **Maintenance** is the stage in which the patients work to prevent relapse and consolidate the gains attained during action. People are classified into maintenance stage, if they have remained free of the problem behaviour and engaged in a new behaviour for more than 6 months.
6) **Termination** is the stage in which people have completed the change process and no longer have to work to prevent relapse. Termination is defined as total confidence or self-efficacy across all high-risk situations and zero temptation to relapse (e.g., skipping exercise results frustration rather than pleasure).

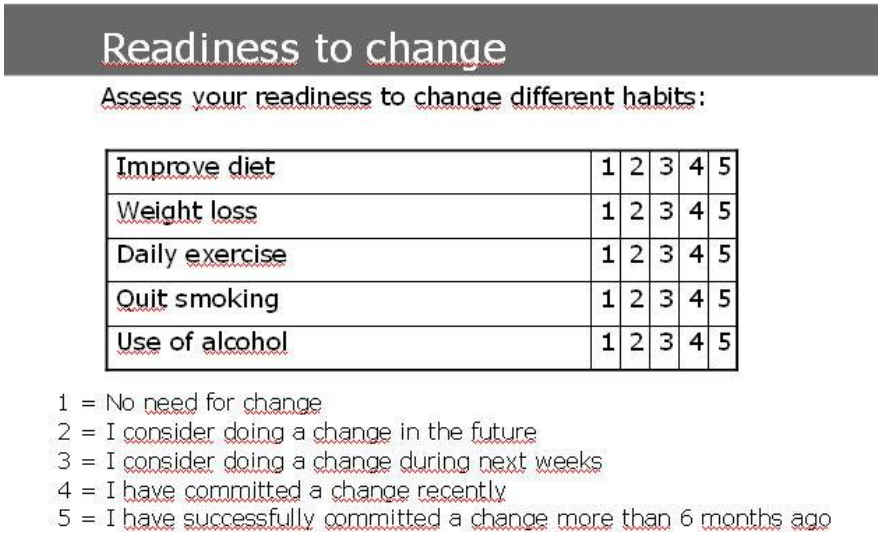
There are many ways to measure the stage of change for an individual patient. The most common way is to ask questions. The stage of change is then determined based on the answers. Suggestions of questions for finding out the stage of change:

1) **Pre-contemplation**, if the patient answers "No" to question: "Are you seriously intending to change the problem behaviour in the near future, within 6 months?"
2) **Contemplation**, if the patient answers: "Yes" to question: "Are you seriously intending to change the problem behaviour in the near future, within 6 months?"

3) **Preparation**, if the patient answers “Yes” to question: “Are you intending to change the behaviour in the very near future?”
4) **Action,** if the patient answers “Yes” to question: “Have you successfully altered the problem behaviour for a period of 1 day – 6 months?”.
5) **Maintenance**, if the patient answers “Yes” to question: “Have you been able to remain free of the problem behaviour and are you constantly engaging in the new behaviour since more than 6 months?”
6) **Termination,** if the patient answers “Yes” to question: “Do you have total confidence through all risk situations and zero temptation to relapse?”

In HeartCycle, the TTM can be used to determine the stage of change the individual patient is in. This can be done, e.g., by using questionnaires and frequency of measurements done. Questionnaires have been developed to measure the cardiac patient’s readiness to engage in self-management approach: Multidimensional Cardiac Health Readiness to Change Questionnaire (MCHRCQ; Hofkamp & Burns, 2008). The questionnaire has 29-items. MCHRCQ evaluates the variety of skills a cardiac patient should have. Patients respond on a 1-to-6 scale how ready they are to engage in certain behavior. The categories used are exercise, diet, stress management, cognitive control, task persistent and risk-factor management. It is possible that cardiac patients suffer from different kind of additional health problems that might affect the rehabilitation. So it would be beneficial to have questionnaires concerning depression, physical health, exercise and nutrition as well.

When the stage of change is known for an individual patient, it can be better estimated, which type of support is useful and which is frustrating. Thus, it is possible to select, what type of information is shown to the patient. In pre-contemplation and contemplation stages the information given to the patient is emphasized on increasing the knowledge of the consequences and hazards if keeping up the same way. It is also possible that the system can offer CV risk questionnaires to make the patient understand that he or she has a problem that requires action. The main feature in pre-contemplation and contemplation stages is in increasing the awareness of the disease and its risks. In preparation stage the patient is aware of the different consequences and now has the possibility of choosing what to do according to the knowledge he or she has. In this stage also an outburst of feelings is important because if the emotions are kept inside symptoms may be somatic. In preparation stage it is also important to engage the patient to take responsibility of his or her actions. In action and maintenance stages the patient needs concrete instructions on what to do and it would be beneficial if the patient could monitor his or her progress in order to have positive feedback. For patients in the maintenance stage, it is also important to show information that guides how to avoid relapse. In every stage positive feedback of the progress and effort is extremely important for the motivation.



Readiness to change

Assess your readiness to change different habits:

Improve diet	1	2	3	4	5
Weight loss	1	2	3	4	5
Daily exercise	1	2	3	4	5
Quit smoking	1	2	3	4	5
Use of alcohol	1	2	3	4	5

1 = No need for change
2 = I consider doing a change in the future
3 = I consider doing a change during next weeks
4 = I have committed a change recently
5 = I have successfully committed a change more than 6 months ago

Figure 6: A simple example of a tool for finding out patient's readiness to change different habits [modified from Turku 2007].

4.1.5 Chronic Disease Self-Management Program (CDSMP) / Expert Patients Programme (EPP)

Chronic Disease Self-Management Program (CDSMP) is a self-management program for people with one or multiple chronic illnesses [Lorig 2001]. The same program is used across many different chronic illnesses, such as arthritis, diabetes, heart and lung diseases. The program is a 6-week (originally 7-week), small-group intervention program that is taught by peer instructors from a highly structured manual. The program emphasizes patients' psychosocial skills: problem solving, decision making and confidence building.

The CDSMP program has been largely evaluated, e.g., with American [Lorig 2001], Dutch [Elzen 2007 and Smeulders 2006] and Chinese patients [Siu 2007]. In the UK, the program based on CDSMP was developed under name Expert Patients Programme (EPP) [Richardson 2008].

The CDSMP program consists of six sessions, lasting 2.5 h each. Each session has two leaders and number of patients in each group intervention is about 10. The program topics cover 1) techniques to deal with problems such as frustration, fatigue, pain and isolation, 2) appropriate exercise for maintaining and improving strength, flexibility, and endurance, 3) appropriate use of medications, 4) communicating effectively with family, friends, and health professionals, 5) nutrition, and, 6) how to evaluate new treatments. The topics covered in the sessions are [Lorig 2001]:

- Overview of self-management and chronic health conditions
- Making an action plan
- Relaxation/cognitive symptom management
- Feedback/problem solving
- Anger/fear/frustration (managing negative emotions)
- Fitness/exercise
- Fatigue management
- Healthy eating
- Advance directives
- Communication
- Medications

- Making treatment decisions
- Depression
- Informing the health care team
- Working with health care professionals (prepares patients to collaborate with health care professionals and the health care system)

The patients taking part in the program, experienced small, but statistically significant improvements in health status, health behaviours, and self-efficacy. In addition the patients taking part in the programme made fewer visits to emergency department. The program has been found cost-effective: cost-to-savings ratio of 1:4, the cost being about $200 per patient [Lorig 2001]. The study in China found the program applicable for Chinese population [Siu 2007]. In Chinese population the program primarily increased self-efficacy, exercise behaviour and application of cognitive coping strategies of the participants.

Several of the topics covered in the CDSMP program are relevant for HeartCycle project and there are several lessons to learn when designing the computer-assisted patient education system in HeartCycle. Especially interesting is the focus on teaching the patients communication skills to better communicate with health care professionals and the health care system.

4.1.6 Health coaching

There are many different definitions of coaching. For example coaching can be seen as “the practice of health education and health promotion within a coaching content, to enhance the wellbeing of individuals and to facilitate the achievement of their health-related goals” [Palmer 2003]. They key aspects in coaching include enhancing wellbeing, learning, facilitation, tutoring, instruction, development of skills and improving performance [Palmer 2003]. Although there are many different definitions of coaching, only a limited number of studies are available.

The COACH program (Coaching patient On Achieving Cardiovascular Health) was developed for patients with cardiovascular health problems [Vale 2002]. It is a training program for patients with coronary heart disease in which a training health professional coach trains patients to pursuit the target levels for their particular risk factors while working in partnership with their doctor. The patients are regularly coached by telephone calls and emails. The coaching includes knowledge of patient’s risk factor levels, the target level for their risk factors and knowledge on how to achieve those target levels. Patients are initiated to see their doctor in order to get appropriate medication. Coaching is a method of training patient to take responsibility for their achievement and maintenance of target levels of their risk factors. The COACH program also trains the patient to follow appropriate lifestyle measures. The COACH program uses a continuous five stage coaching cycle so every coaching session follows five stages which are introduced below:

- **Stage 1.** Asking questions to establish patient’s knowledge, attitude and beliefs about their risk factors (like knowledge of cholesterol, medication and nutrition)
- **Stage 2.** Explanation and rationale (patient is educated on reasserted things in stage 1.)
- **Stage 3.** Assertiveness training (the patient is trained to be assertive in the relationship with the treating doctor in order to be able to negotiate treatment need with the doctor)
- **Stage 4.** Goal setting (formation of a plan of actions and goals to be achieved before next coaching session)
- **Stage 5.** Reassessment at next coaching session (evaluation of the achievement in following the plan of action)

The coaching cycle is continued until the target level of risk factors is achieved. Effective coaching teaches the patient to get the most value from a consultation with their doctor in achieving their goals the goals of secondary prevention. The COACH program enables patient to take responsibility of their cardiac health. Through COACH program patients have achieved substantial improvements in

different coronary risk factors (improvements in blood pressure, body weight, BMI, dietary intake of total fat, saturated fat, cholesterol, and fiber, and well-being, mood, symptoms of chest pain, and breathlessness) when compared to usual care [Vale 2003]. Perhaps the good results of the COACH program are associated to the monitoring of the impact of the program and in providing feedback to the patients not just on education and empowerment alone.

The monitoring of progress and providing continuous feedback to the patient are also important factors in HeartCycle. It is also important to know the attitudes and beliefs the patient has of the disease and different risk factors because without influencing to the harmful attitudes and beliefs it is difficult to evoke behavioural changes.

4.1.7 Goal setting theory

Goal setting theory was formulated largely based on empirical research [Locke 2002].The focus of goal setting theory is on the core properties of an effective goal. The properties of an effective goal are specificity and difficulty but commitment to the goal, importance of the goal, feedback, task complexity and self-efficacy moderates the performance [Locke 2002]. Specific goals are measurable, unambiguous, and behavioural. The patient is well aware of what is to be done and in what means. Specific and difficult goals led to higher performance than just urging people to do their best. In order to be able to achieve demanding goals the patient's must be committed to the goal. The more difficult the task is the more commitment the patient must have in order to succeed. Patient's self-efficacy enhances goal commitment. The patient must also understand why it is important for him or her to achieve that goal. For different goals to be effective patients need feedback that reveals progress in relation to their goals. The goal theory states that the highest level of effort occurs when the task is moderately difficult, and the lowest level of effort occurs when the task is either very easy or very hard.

A practical rule of thumb for goals is that they should be SMART [Hargreaves 2008]. "S" stands for specific and significant, "M" stands for measurable and motivational, "A" stands for achievable and acceptable, "R" stands for realistic, relevant and rewarding and "T" stands for time-based. The SMART goal setting is used for activities, healthy eating, relaxation, etc.

In HeartCycle, the goal setting theory can be used when defining and specifying the goals for the patient. The goals should be well defined and they should specify to only one thing at a time. It is also important to take into consideration the patient's self-efficacy and commitment to the goals because without them it is difficult to gain results. Patient should also be tutored to use different strategies with what he or she will be able to achieve the goals. Goal setting has been studied concerning high performance so as a whole it is not suitable for motivation of change in patients suffering from chronic diseases.

4.1.8 5A's Model for Patient Education and Coaching

The 5A's model is designed as a tool for clinicians and educators to implement patient education. The approach consists of 5 phases: 1) Assess, 2) Advise, 3) Agree, 4) Assist and 5) Arrange [Glasgow 2003, Siminerio 2009]. The 5A's model creates for each patient a personal action plan, which contains a list of goals, list of barriers and strategies to cope with the barriers, follow-up plan. The plan can be shared with patient's friends and relatives to ensure social support in the lifestyle changes. More specifically, the model consists of: 1) Assessment of the patient's status. This includes knowledge, psychosocial needs, beliefs and behaviours. 2) Advise stands for educating the patient by giving information about health risks and benefits of change. This is based on the results of patient assessment and on patient's preferences. 3) Agree stands for collaboratively setting realistic goals. 4) Assist stands for actively assisting the patient in identifying barriers, in problem solving and in getting social support. 5) Arrange stands for agreeing follow-up and re-evaluating progress and results.

In HeartCycle patient UI assessment (1) can be implemented with help of questionnaires that the patient fills in using his UI device at home. The answers can be analyzed automatically and content for advise (2) can be tailored according to the results. Agree (3) can be implemented in software by first giving information on proper goal setting, then letting the patient set the goal he feels is right for him and finally by checking that the goal is in acceptable limits. Assist (4) can be implemented by giving information on the most common barriers and on the strategies on problem solving. (5) Arrange can be implemented by closing the loop to health care professionals and agreeing the next visits. Before the visit, questionnaires can be used to assess the progress and results.

Finally, the HeartCycle system user would have a list of realistic goals, list of personal barriers to lifestyle change and suggestions on how to solve the problems and a follow-up plan.

4.1.9 Eli Lilly “New Steps” program

Eli Lilly (Eli Lilly and Company, Indianapolis, Indiana, the USA) is conducting a patient-focused program in Australia to assist patients with schitzophrenia or bipolar I disorder to adhere to prescribed medication and lifestyle changes. The program is run under name “New Steps”. In the program, each patient receives 1) a welcome kit giving an overview of the program, 2) regular mailings giving practical information on how to maintain a healthy diet and take regular exercise, 3) regular, personalised phone calls to monitor the patient’s progress and motivate them after discharge from hospital, 4) regular SMS messages to promote medication adherence. One idea is to use as many different channels as possible, because the results show that use of many channels gives better results than use of one channel alone (e.g., mailer only).

The structure of this program is similar to many other programs and also to the planned HeartCycle program. In “New Steps”, the patient education is accompanied with regular phone calls and prompting SMS messages. In HeartCycle, education and prompting are planned as part of the program, but heavy involvement of healthcare professionals is currently not in focus.

4.2 Assessment of the Patient

The patients are assessed by the physician in order to find out information like comorbidities, disease management skills and readiness to make different lifestyle changes. The patient comorbidities are diagnosed in the hospital and this information is available to the caring physician. However, patient’s disease management skills and readiness to change are currently not routinely assessed in most hospitals. Such questionnaires could be included into the HeartCycle system. Examples of such questionnaires are, e.g., the Heart Failure Self-care Behaviour Scale [Jaarsma 2003] and the Heart Failure Knowledge Scale [van der Wal 2005] questionnaires. The physician can further utilize, e.g., the stage-of-change questionnaires or different Health Beliefs questionnaires to further find out the patient readiness to change to different lifestyle change.

Yes/no
1 I weigh every day once per week
2 I keep my appointments with the doctor
3 In case of dyspnea/shortness of breath, I take it easy
4 When I am unable to do something because of dyspnea or fatigue, I ask for help
5 In case of dyspnea/shortness of breath, I alert my doctor or somebody else
6 When my feet/legs swell, I alert my doctor
7 I call a doctor in case of 2-kg weight gain in 1 week
8 I restrict my fluid intake
9 I take notice how much I urinate per day
10 If I feel anxious or insecure, I try to share this with some one else

11 If I experience increasing nausea, I alert my doctor
12 I restrict my activities
13 I plan my activities throughout the day
14 I rest during the day
15 If I experience increasing fatigue, I alert my doctor
16 I comply with a low salt (low sodium) diet
17 I take my medication as prescribed
18 I avoid persons that have a cold/the flu
19 I try to get some exercise on a regular basis
20 I elevate my legs when I sit down

Figure 7: Heart Failure Self-care Behaviour Scale [Jaarsma 2003]

After patient assessment, the physician selects from the educational content the material that is most relevant for the patient at each encounter. The physician can do this by selecting certain topics from the "table of contents" list. The same list with physician recommendations can be viewed by the patient at home. The purpose of this is to remind the patient, which are the currently important sections in the educational content. However, all educational content is available for the patient to read, in case he/she feels like reading more.

Topic	Relevance
Smoking	☑
Hypertension	☐
Elevated cholesterol levels	☑
Diabetes	☐
Arrythmias	☐
…	

Figure 8: An excerpt of patient overview to educational content recommended by the physician

4.3 Motivation and coaching strategies proposal

The HeartCycle motivation and coaching strategies focus on education, goal setting, feedback, rewards, and system help. These are functions that the system will provide to support the patient in long-term disease management.

4.3.1 Educational content

Already existing educational content will be used in the HeartCycle system to educate the patient, e.g., about heart conditions, comorbidities, lifestyle changes, medications, etc. An excellent and easy-to-read content is available, e.g., in the UK Heart Manual. Discussions with different publishers are ongoing. Ideally the content will include text, images, audio and video.

After studying the educational content, a "passport test" is organized by the system. The test can be implemented as a questionnaire into the Patient Loop system. The goal of the test is to ensure the patient has understood the educational content and can do proper self-management.

In addition to the traditional educational content, the HeartCycle system will incorporate a prediction tool that predicts the patient vital sign values given his/her current and past vital sign data and, e.g., full compliance to medication. The idea of the tool is to show the patient the importance of active disease management. By showing the effect of, e.g., 100% compliance and 0% compliance, the system can simulate the future values based on previous, general patient data. Such predictions are

not exact, as they use an “average patient model” (thus patient data from a large population), but they can indicate the importance of active disease management by showing the average effect.

4.3.2 Goal setting, feedback and rewards

The goals for patient vital signs (e.g., HR, BP and weight) and lifestyle changes are defined by professional together with the patient. The goals are updated at each encounter and the physician enters the new, agreed targets into the system. Small incremental steps motivate and give the feeling of control. However, the targets should always be measurable and time-based.

For the patient, the system shows a goal overview: 1) the ideal value, 2) next agreed target (with target date), 3) last measured value and 4) comments the user has added to the measured value for each factor (e.g., weight, blood pressure, exercise, smoking, etc.). The purpose of goal overview is to give the patient the possibility to check the agreed goals and ideal values with current status. In addition to the overview, the goals can be visualized also graphically, showing the past trend, the latest values and the agreed target. Educational content related to each factor can be offered in the overview screen.

The system checks progress after each measurement by analyzing the trend of each variable. The system has different actions for different progress states (Table 1)

Event	**System action**
Agreed target reached	Rewarding message: “Congratulations! You have reached your agreed target value! This brings you health benefits. Keep up the good work.”
Agreed target reached too fast	Reminder: “To change your lifestyle permanently, try not to work towards the targets too fast. Small incremental changes give you time to accommodate yourself to the new lifestyle”.
Ideal value reached	Rewarding message: “Congratulations! You have reached the ideal value. Continue using your current lifestyle to keep in the ideal range.”
Ideal value maintained for 6 months	Rewarding message: “Congratulations! You have maintained in the ideal range for 6 months. You have successfully adopted the healthy lifestyle.”
Trend to wrong direction	Supporting message: “You have been doing measurements actively. Would you like to have educational content on how to improve your results?” (If yes, educational content is triggered to show information on the problematic variable) If previous successes exist, these are shown graphically to encourage the patient: “You have done this before”.
Relapse	Reminder: “Remember that relapses are very common, most people experience relapses at some point. Try to identify what caused the relapse and think how to deal with similar situations in the future.”
Too large changes required by physician	Warning message to physician: “You have entered a goal requiring large changes from the patient. Are you sure you want to do this? The maximum recommended change to this person is 1 kg / month (for example).” (The physician can still make the final decision.)
Too many changes required simultaneously	Warning message to physician: “You have entered many goals, requiring many simultaneous changes from the patient. Are you sure you want to do this?”

The feedback is shown as messages and graphical visualizations with past measured values and the next agreed target. Immediate feedback is shown after each measurement. The patient can also move to the visualization screens anytime.

4.3.3 Help

The system help focuses on guiding the patient on use of the HeartCycle system. It gives instructions on how to use the patient loop software and how to do the measurements. The patient knowledge level can be tested with questionnaires and tests, e.g., as part of the passport test.

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5 WP5 Legal regulations for trials and care plan technologies provided by Itaca

5.1 Legal regulations

This section provides an overview of the regulatory framework that applies in the countries that are subject to host trials for the HeartCycle project. The compilation of regulations has been organized in different sections: general, health record, telemedicine systems, electronic prescriptions and personal health data processing. Additionally, an outlook of the national strategy towards eHealth practices is given.

5.1.1 Spanish profile

5.1.1.1 General regulatory framework

- Real Decreto 1030/2006, de 15 de septiembre, por el que se establece la cartera de servicios comunes del NHS y el procedimiento para su actualización[2]. BOE 16-09-2006 (RD 1030/2006 of 15 September, laying down the portfolio of NHS common services and the procedure for their update).
- Real Decreto 183/2004, de 30 de enero, por el que se regula la tarjeta sanitaria individual[3]. BOE 12-02-2004 (RD 183/2004, of 30 January, regulating the individual healthcare card).
- Ley 55/2003, de 16 de diciembre, del Estatuto Marco del personal estatutario de los servicios de salud[4]. BOE 17-12-2003 (Law 55/2003, of 16 December, of the Framework Statute of healthcare services' staff).
- Ley 44/2003, de 21 de noviembre, de ordenación de las profesiones sanitarias[5]. BOE 22-11-2003 (Law 44/2003, of 21 November, regulating the healthcare professions).
- Ley 16/2003, de 28 mayo, de cohesión y calidad del NHS[6]. BOE 29-05-2003 (Law 16/2003, of 28 May, of Cohesion and Quality of the Health National System).
- Ley 41/2002, de 14 noviembre, ley básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica[7]. BOE 15-11-2002 (Law 41/2002, of 14 November, regulating the patient's autonomy and rights and obligations concerning information and clinic documentation).
- Ley 14/1986, de 25 de abril, General de Sanidad. BOE 29-04-2006[8] (General Healthcare Law 14/1986, of 25 April).

5.1.1.2 National strategy towards eHealth

Currently, the Spanish strategy towards the eHealth policy is driven by two plans:

- Plan Avanza: first plan by the Spanish Government stimulating the development of the Information Society.
- Plan of the Quality of the National Health System: plan that fosters the creation of a trusted system to improve the pharmaceutical delivery for patients and encouraging mechanisms that will speed up the appointments of users

5.1.1.3 Regulatory framework medical records

- Law 41/2002 of 14 November regulating the patient's autonomy and rights and obligations concerning information and clinic documentation
- Law 16/2003, of 28 May, of Cohesion and Quality of the Health National System

5.1.1.4 Regulatory framework for telemedicine systems

Currently, there is no specific legal framework that covers telemedicine systems in Spain.

5.1.1.5 Regulatory framework for electronic prescriptions

- Law 29/2006 of Guaranteed and Rational Use of Medicines and Sanitary Products[9]*:* this law regulates electronic prescriptions and states. The information about medical prescription will flow through the NHS Communications Network

5.1.1.6 Regulatory framework for personal health data

- Organic Law 15/1999, of 13 December, on the Protection of Personal Data[10] and it's been expanded by the Royal Decree 1720/2007 of 21 December, approving the rule that develops the LOPD[11]*:* this law of data protection is very similar to the European one, here are the main coincidences:

5.1.2 German profile

5.1.2.1 General regulatory framework

- art. 291a SGB V[12]: basis for all telemedicine applications which require the electronic health card.
- Social Code Book: regulates all SHI-related issues
- Social Code Book V (SGB V): statutory health insurance amended and supplemented by numerous reform laws.

5.1.2.2 National strategy towards eHealth

The national eHealth strategy in Germany is focused on the implementation of the electronic health card (eGK). This strategy started in 2001 when the Federal German health minister and the colleagues on *Länder*-level recognized the importance of eHealth and telemedicine and supported to set up a German telematic platform to be realised by the GEMATIK-Group[13].

The electronic health card will hold all of the life-saving data that are needed in case of emergency. It will allow health professionals to store a medication history and keep a patient record. Thanks to this card, every physician - anywhere in Germany - will have easy access to the health details of their patients and be able to avoid treatment errors. The storage of these data will have to satisfy the most restrictive security precautions.

5.1.2.3 Regulatory framework medical records

- Art. 291a paragraph 3 sentence 1 n° 1 Social Code Book V (SCB V) and data within an electronic patient record according to article 291a par. 3 sentence 1 n° 4 SGB V: electronic patients' summaries must be exchanged through the electronic health card

5.1.2.4 Regulatory framework for telemedicine systems

- Art. 291a SGB V: regulates the electronic health card.

  There is not only one code for telemedicine. One important part is the regulated in
- Art. 67 SBV V states the paper based information and communication is to be transformed into computer based forms and electronic transmission.

5.1.2.5 Regulatory framework for electronic prescriptions

- Article 291a SGB V: determines that the electronic health card system must be able to support electronic prescriptions

5.1.2.6 Regulatory framework for personal health data

- *Bundesdatenschutzgesetz* (BDSG) of February 1, 1977: general legislation protecting the individual with regard to automatic processing of personal data. Ammended in 2001 to implement the European Directive 95/46/EC.

5.1.3 Dutch profile

5.1.3.1 General regulatory framework

For this study the following regulation and legislation is relevant:

- Health Insurance Act
- Medicines Act
- The Guideline for doctor-patient contact of the KNMG (September 2007).
- Act Use of the Citizen Service Number in the Health Care (10 April 2008)
- Change in the law for the use of the BSN with respect to the electronic exchange of information in the health care (May 2008)
- Professionals in Individual Health Care Act
- Medical Treat Agreement Act
- Personal Data Protection Act

5.1.3.2 National strategy towards eHealth

An overview of the Dutch eHealth strategy can be found in the October 2007 ERA Report “eHealth strategy and implementation activities in the Netherlands”[14] (Authors: Hans Haveman, Ministry Health, Welfare and Sport, Chris Flim, NICTIZ) and a Report of the Dutch Ministry of Health, Welfare and Sport “ICT in the Dutch Healthcare: An international Perspective”[15] of May 2006.

5.1.3.3 Regulatory framework medical records

- Wijziging van de Wet gebruik burgerservicenummer in de zorg in verband met de elektronische informatieuitwisseling in de zorg[16]: addresses issues such as security, data equality, authorization and access, standardization and the actual use of electronic health records.

5.1.3.4 Regulatory framework for telemedicine systems

No specific legislation in the Netherlands with regard to telemedicine systems.

5.1.3.5 Regulatory framework for electronic prescriptions

- Medicines Act, July 2007: introduces a ban on the prescription of medications over the internet to persons whom the doctor has never met in person

5.1.3.6 Regulatory framework for personal health data

- Personal Data Protection Act (Wbp): this act came into force on 1 September 2001 and implements the provisions of the European Directive 95/46/EC

5.2 Technologies for careplan management

5.2.1 Runtime adaptation of careplans using workflow technology

When a new careplan is created, it may contain incorrectness that make difficult the use of the system in first stages and must be debugged at runtime. The correction of such incorrectness needs to be applied as soon as possible to prevent rejection from professional users.

The process of modification of a careplan is a manual procedure that requires a lot of time and effort, as the amount of information to be revised in order to produce the correct changes can be considerable big. In addition, while the information is being revised, similar cases might occur. If no information about past decisions is available, bad decisions can be repeated and information on successful modifications may not be available.

The use of workflow technology eases the follow-up of the path followed by a patient inside a careplan. In addition, the modification of processes using graphical tools allows correcting in an easy way deviations from the original careplan by just adding new nodes or removing incorrect ones. Nevertheless, implementation of those features in workflow engines is a challenge by itself, as current engines introduce strong limitations in the modification of running workflow instances: some engines allow changing a small set of features while others directly forbid this feature.

Within this research line, HeartCycle will study the instance modification capabilities of current workflow engines, exploiting the possibilities of each one. When a potential workflow engine is selected for use, an authoring tool allowing the transparent creation and modification of workflow instances will be created.

5.2.2 Inference of new careplan templates from past history

The use of careplans can reduce the variability in daily clinical practice produced by disagreements between professionals. However, the variability due to population reasons cannot be avoided, as the treatment used for each person may differ from others. Ideally, a well designed careplan should reflect the treatment necessities for 60%-80% of the population [17], but current implementations in hospitals show that only 13’5% of the patients suffer serious variances from the original careplan [18]. In these cases, the patient is managed outside the careplan using traditional approaches. Processes followed by “out-of-careplan patients” can help in the correction of deficiencies detected in the careplan, but the storage of those deviations is needed in order to extract common patterns that can be added to a careplan.

This process can be improved by using computer aid systems based on pattern recognition techniques such as the “workflow mining” technology [19]. This technology is a research field that allows discovering new workflow models analyzing the data coming from past samples. In [20] an algorithm able to infer careplans represented as workflows is presented. This algorithm uses the information available from past executions of workflows to infer a new model. Another technology that can be used to infer model using past samples is the “distance measuring between workflows instances”. For example, this technique could help in finding a new model when a running workflow instance fails in achieving a goal, comparing it to the most similar one that did achieve it. In [21], an algorithm that measures the variance in workflow based careplans using “distance-edition” and “K-nearest neighbours” techniques is presented. That algorithm was defined within the scope of the European Project CAREPATHS[22].

Within this research line, HeartCycle will gather information of executing workflow instances, information that will be used to feed the above-mentioned algorithms. The outcomes from this analysis will be analyzed measure the potential prediction capabilities of each one.

5.2.3 Dynamic Service Invocation using ontologies

As the professional platform will rely on a Service Oriented Architecture (SOA), a viable research direction in the domain constitutes Semantic Web Services (SWS)[23] The XML-based standards for Web Services interoperation, such as Web Services Description Language (WSDL), address only syntactic interoperability, rather that the semantic meaning of messages. This limitation requires

programmers to reach specific agreements on Web Services interaction and makes automatic Web Services composition and invocation difficult. Thus, SWSs are built around universal standards for the interchange of semantic data, facilitating this way to programmers the combination of data from different sources and services without losing meaning. SWS technology involves the description of Web Services using ontology-based semantic attributes, enabling this way dynamic service invocation according to semantically defined criteria that consumers pose to the SOA. Towards this direction, the construction and offering of SWSs involves: a) service description, b) service publication, c) service advertisement and d) appropriate matchmaking mechanisms to enable searching for the appropriate services upon the criteria defined, all based on the semantic model employed.

To this end, several approaches have been proposed and established for such a development, e.g. OWL-S (Web Ontology Language Semantics)[24], WSMO (Web Service Modelling Ontology)[25], and WSDL-S (Web Service Semantics Language)[26], focusing particularly on ontology-based service description, while there are several attempts to extend the cornerstone of service registries, namely UDDI (Universal Description Discovery and Integration), such as the FUSION semantic service registry [27]. In particular, the service matchmaking process in FUSION requires the description of service characteristics, so as to enable service specification accordingly. Among functional characteristics of services that include descriptions of inputs, outputs, preconditions and effects (IOPE), FUSION semantic registry encompasses the first two characteristics (i.e. inputs and outputs). In this regard, data-level interoperability is inspected between the I/O of a service advertisement and a service request, so as to assure that a service produces all output data that a consumer expects, providing in turn all the required input data. Among various non-functional characteristics of services (e.g. policy compliance, QoS. etc) FUSION elaborates on service categorisation according to a classification scheme. This allows the semantic matchmaking of a service categorisation by detecting the subsumption degree of the requested service. Accordingly, FUSION uses OWL-DL as a formal model for description and classification of services incorporating properties such as service categorisation, as well as input and output data.

The added value in adopting a SWS enabling framework (such as a semantic registry) in the professional platform of HeartCycle includes: a) formal description of services, b) semantics-based service registration, c) advanced service discovery/matchmaking, d) dynamic service invocation and e) potentially the definition of service pipelines in terms of workflows, coupling the research direction presented in the previous section. The ultimate advantage of following a SWS-oriented approach in HeartCycle will be the construction of an open and extensible SOA platform, avoiding coupling and hard-coded service interfacing.

Up to now, we have committed research on the abovementioned technologies so as to investigate their maturity, while experimenting with available open-source software solutions, such as FUSION [28], Web Services Modelling Toolkit [29] and WSMO Studio [30]. Upon final definition of the HeartCycle use cases from the technical viewpoint of WP5, the potential and actual design and development of a SWS approach is going to be further assessed in terms of its suitability for the professional platform of the project.

6 WP6 / WP7 Clinical studies, validation, and CE certification **provided by University of Thessaloniki and Medtronic**

6.1 Clinical Study: Timelines

6.1.1 General Information on clinical studies

What is a clinical trial?

Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol.

- *Interventional studies* are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured.
- *Observational studies* are those in which individuals are observed and their outcomes are measured by the investigators.

What are the different types of clinical trials?

- *Treatmen*t trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- *Prevention* trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.
- *Diagnostic* trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- *Screening trials* test the best way to detect certain diseases or health conditions.
- *Quality of Life trials* (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

What are the phases of clinical trials?

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

- In **Phase I** trials, researchers test an experimental drug or treatment or device in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

- In **Phase II** trials, the experimental study drug or treatment or device is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

- In **Phase III** trials, the experimental study drug or treatment or device is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
  In the case of HeartCycle, the trials comprising the new usage indication devices should fall in this category.

- In **Phase IV** trials, post marketing studies delineate additional information including the drug's / devices' risks, benefits, and optimal use.
  In the case of HeartCycle, the trials comprising the regular usage indication devices should fall in this category

From Phase I-III it's the pre-marketing studies, were drug/device is not yet market release and doesn't have CE mark or a new indication is tested (process of approval is longer, needs Competent Authority approval , apart from MEC).

Phase IV are post-market release drugs/products use as intended in the label and in current approved indications. The studies can be control studies (need MEC approvals) or observational studies (may not need MEC - depending on country legislations) patient informed consent and/or data use consent (for data protection) are needed.

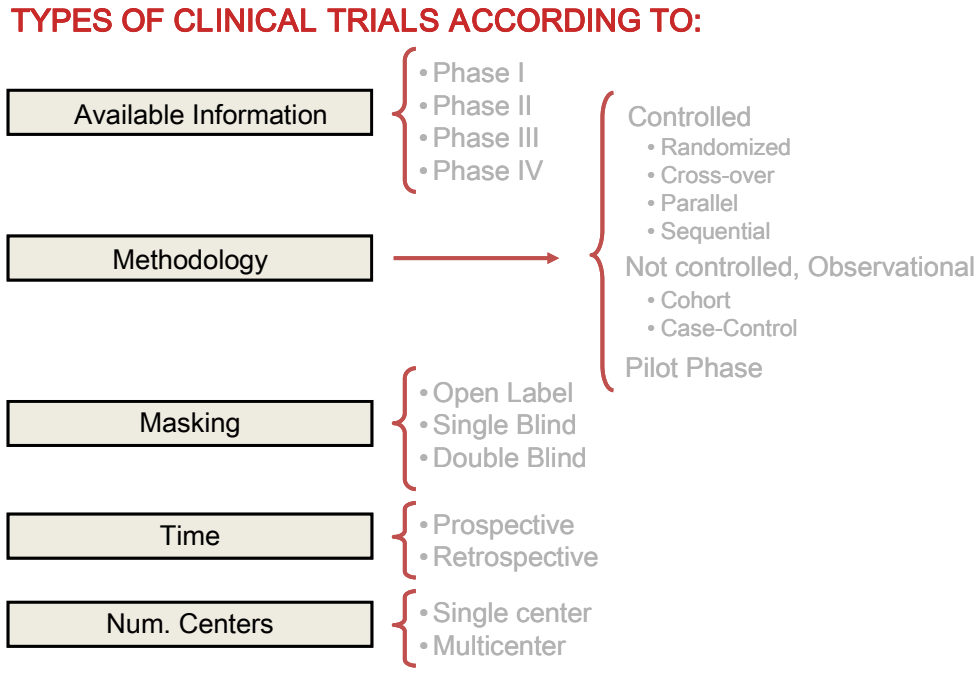


Figure 9. - Clinical Trials Classification

6.1.2 Timeline for clinical study design and certifications acquisition

This will depend on the type of the study and its objectives.

The time for acquiring the information needed to write the protocol is variable (1 week to 6months and may depend on the expert assessment/Steering committee meetings time and decision process) and the outcome is to have clear objective definition, endpoint definition, population targeted (inclusion/exclusion criteria) & variables to recollect.

The process of writing the protocol can take between 2-6 weeks (provided you have ALL the relevant information) depending of the trial, objectives, variables and CRFs complexity.

Once the protocol is written and signed, the process of approvals and time to start will depend on the type of the study (phase III or phase IV, country legal requirements…etc).

Taking the example of the more complex study situation; In a control clinical trial the timelines are approximately the following:

Presentation and MEC (Medical Ethics Committee) approval will take between 1-3months.

Contracts with the investigator centres can take 1week to 3 months.

If Competent Authority approval is needed then it will take about 60 days , depending on the EU country.

Concluding the start-up period could take between 1 and 6-8 months.

Documentation like study brochure, training of the investigators, field people, etc. can be acquired in parallel, so it should not add extra time.

In the following figure it is possible to see how the European normative for clinical trials is integrated into the Spanish legislation and, therefore, the different public health organisms that might intervene in the approval process.

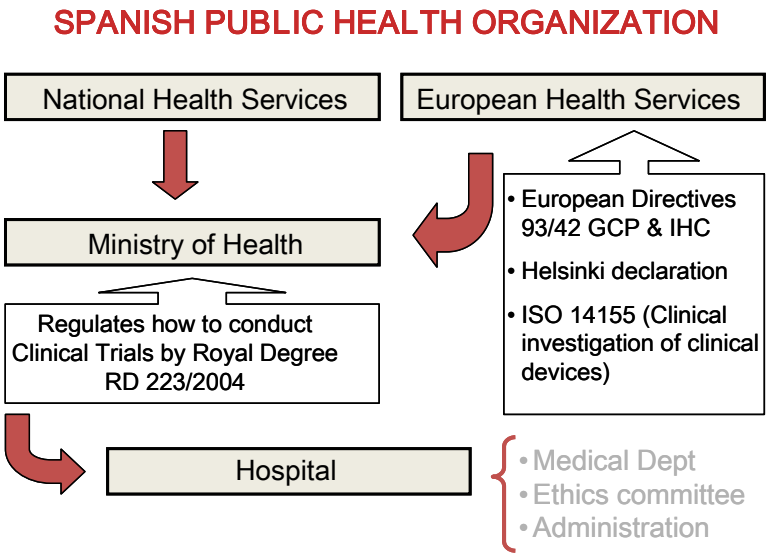


Figure 10.- Spanish public health organization

6.1.3 Flowchart of a Clinical Study

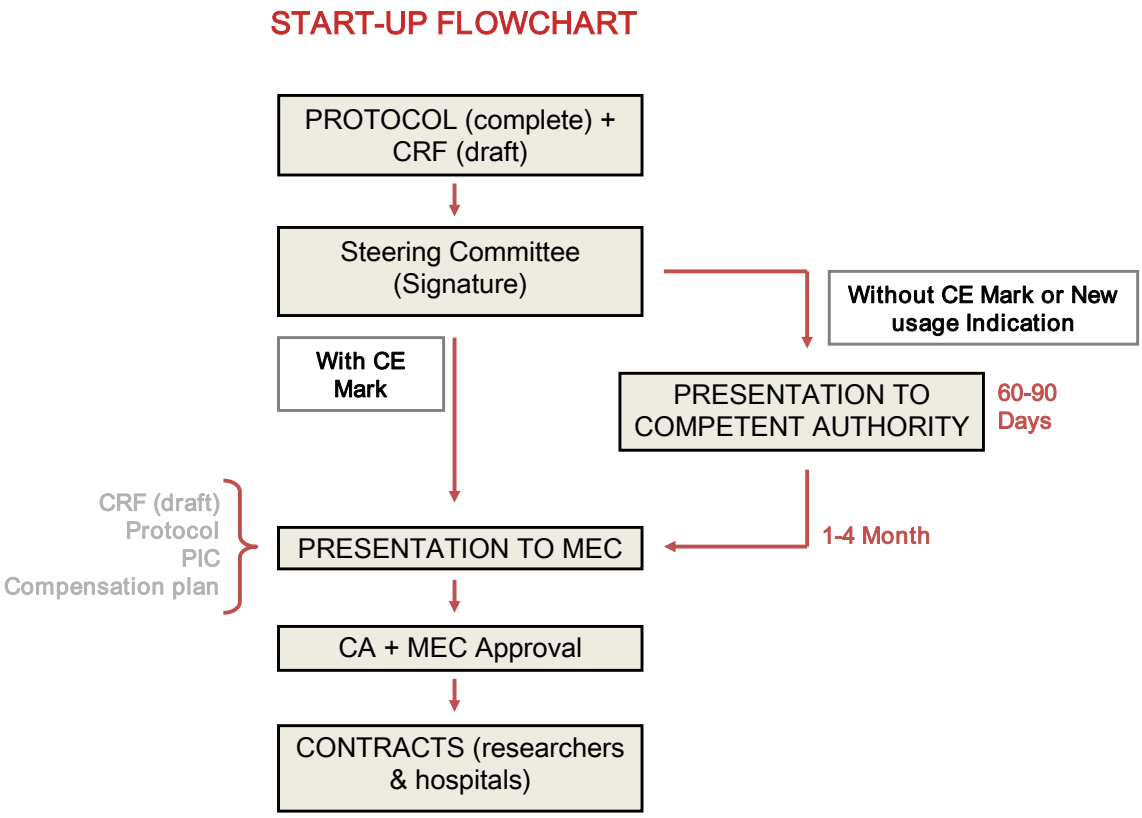


Figure 11.- Clinical Study Start-Up flowchart

6.2 Validation

The objectives of the Validation work package in the project are:

- To validate the proposed hypotheses and model with data from the HeartCycle clinical study
- To Provide users insights and test clinical hypotheses
- To support other WPs in collecting data from the users

Therefore, WP6 will complete its tasks according to the project structure performing smaller tests to validate the intermediate technical results and to prepare the final clinical study in phase 2. The role of WP6 in this phase is to define procedures for validation, supply templates to the technical WPs and support them in terms of legal procedures required for the tests including ethical and privacy aspects. In case of clinical tests the clinical partners will take their role in performing these tests.

In phase 2, WP6 will organize and conduct the final validation study.

As well as providing the correspondent templates and guidelines to the rest of the WPs, WP6 will compile all the documents related to the different validation processes that will take place in the frame of HeartCycle and that will provide the necessary tools to carry out a final clinical study to validate the HeartCycle system.

The aim persecuted is to ensure the coherence and consistency of the different tests and processes developed in order to be able to use the results obtained in each of them to facilitate the obtaining of the certifications needed to perform the final clinical studies.

In this project “validation” is a term that does not restrict to technological devices validation, but refers also to concept and strategy validation. In this case, WP6 will act as a storage deposit for the validation processes description that the responsible WPs will provide for its integration in the compilation document.

It is also responsibility of WP6 to make aware all the partners of the different tests going on in each moment, in case they are interesting for any other WP.

6.2.1 Validation processes and procedures

The definition of the different small test that will be carried out in HeartCycle will depend on the requirements of the WPs that need to evaluate the performance and features of certain devices with users.

According to the conclusions extracted during the last three months, the type of tests that will take place along the following 36 months have been identified and categorized in two main groups:

1. Small tests using certificated monitoring devices
   1.1. Following current indications for the use of the devices:
      In this case the monitoring devices used in the tests will be utilized according to regular clinical usage
      1.1.1. Measuring healthy subjects at home / lab / office
      1.1.2. Measuring patients in hospitals
      1.1.3. Measuring patients at home (or without direct medical supervision)
   1.2. Following new indications different from regular ones in the use of the devices:
      In this case the monitoring devices intervening in the tests may be used in a different way than the regular clinical usage, i.e. during a longer period of time, in a different timeframe, in a different location, etc.
2. HeartCycle devices (development devices without certification)
      2.1.1. Measuring healthy subjects at home / lab / office
      2.1.2. Measuring patients in hospitals
      2.1.3. Measuring patients at home (or without direct medical supervision)

To facilitate the classification of the tests into these categories, this document includes a form that the WP responsible for the test must fulfil in order to provide all the information related to the objectives and the study of the test. This way WP6 will be able to choose the proper guidelines and make the right recommendations according to European regulation and specific countries regulatory systems.

6.2.2 Steps to follow to prepare and organize small tests

In order to acquire all the information needed related to the procedures to carry out for the small tests, the responsible for them should stick to the following steps:

- Make aware WP6 leader about their intention to run a small test
- Fulfil the information form and provide it to WP6
- Receiving the appropriated guidelines for the proper function and validation in the small test
- Make the other WPs aware that there is a test going on (WP6 task) in case they are interested in participating and/or may need the results.

It is very important that all the small tests are carried out following the right procedures, not only to keep a record about them, but also to ensure the validity of the results obtained and to avoid the repetition of the test afterwards.

6.2.3 Information Form

Test Name	
Responsible for the test:	
- WP *- Contact person*	
Objectives	
Clinical Participation	
Location (country)	
Center (University, Hospital, Lab, home, etc…)	
Type of device	
- Description *- Classification*	
Type of data	
- Extracted *- To compare with*	
Reference Population	
- HF *- CHD* *- Others*	
Patients Profile (age, gender, etc…)	
Number of patients	
Variables to acquire	
Type of tests to be performed	
Material used in the tests	
Duration of the tests	
- Total days *- Hours / day*	

Table 7.- Information form

6.2.4 Guidelines

Depending on the type of study needed to test a specific device, It will be necessary to fulfil some regulatory requirements or specific tests requirements depending on if the devices used in the trials (CE certificate yes/no) and purpose/objective of the trial.

According to the European Commission, directive 2001/20/EC makes Good Clinical Practice (GPC) a legal requirement across 25 member states from May 2004 and it requires every state member to appoint a "competent authority" to ensure compliance with this directive.

What is Good Clinical Practice?

GCP is an International ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that the clinical trial data are credible.

Any kind of clinical trial must follow these principles with independency of the number of patients, the devices used, etc. to ensure the validity of the data obtained.

6.2.4.1 Certified Devices

6.2.4.1.1 Regular Usage

In this case there is no difference in the requirements for the trials organization whether the patient is healthy, at home or in the hospital as long as the usage of the device is the regular one. If it were not the regular one, the case of study would be the one described in chapter 3.4.1.2.

6.2.4.1.1.1 GENERAL REQUIREMENTS (ISO 14155-1)

Formal Agreements

There shall be agreements between the sponsor, the clinical investigators and other relevant parties which define their responsibilities. All formal agreements should be recorded in writing and signed by all parties involved.

Qualifications

All parties participating in the conduct of the clinical investigation shall be appropriately qualified by education and/or experience to perform their tasks.

Clinical Investigation Plan (Protocol)

A clinical investigation plan shall be compiled according to ISO 14155-2 (described in chapter 3.4.1.1.2)

Design of the clinical investigation

The clinical investigation shall be designed to evaluate weather the device is suitable for the purpose(s) and the population(s) for which it is intended. It shall be designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and will support the clinical investigation objectives.

Confidentiality

At all times throughout the clinical investigation confidentiality should be observed by all parties involved. All data shall be secured against unauthorized access.

Privacy and confidentiality of information about each subject shall be preserved in the reports and any publication of the clinical investigation data.

Lists of subjects' names and identifying information should, wherever possible, be maintained separately from case report forms.

Start of clinical investigation

No clinical investigation should start until:

A. A clinical investigation plan has been written and signed
B. The opinion and/or approval of the ethic(s) committee(s) has been obtained
C. Regulatory clearance or approval, if applicable, has been obtained.

Informed Consent

(described in chapter 3.4.1.1.3 and 3.4.1.1.4)

6.2.4.1.1.2 CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S) (ICH)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

General Information

1. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
2. Name and address of the sponsor and monitor (if other than the sponsor).
3. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
4. Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
5. Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
6. Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
7. Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

1. Name and description of the investigational product(s).
2. A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
3. Summary of the known and potential risks and benefits, if any, to human subjects.
4. Description of and justification for the route of administration, dosage, dosage, regimen, and treatment period(s).
5. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
6. Description of the population to be studied.
7. References to literature and data that are relevant to the trial, and that provide background for the trial.

Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

Trial Design

1. The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:
2. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
3. A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
4. A description of the measures taken to minimize/avoid bias, including:
   (a) Randomization.
   (b) Blinding.
5. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).
6. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
7. A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
8. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
9. Maintenance of trial treatment randomization codes and procedures for breaking codes.
10. The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

Selection and Withdrawal of Subjects

1. Subject inclusion criteria.
2. Subject exclusion criteria.
3. Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
   (a) When and how to withdraw subjects from the trial/ investigational product treatment.
   (b) The type and timing of the data to be collected for withdrawn subjects.
   (c) Whether and how subjects are to be replaced.
   (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

Treatment of Subjects

1. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment
2. Group/arm of the trial.
3. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
4. Procedures for monitoring subject compliance.

Assessment of Efficacy

1. Specification of the efficacy parameters.
2. Methods and timing for assessing, recording, and analyzing of efficacy parameters.

Assessment of Safety

1. Specification of safety parameters.
2. The methods and timing for assessing, recording, and analyzing safety parameters.
3. Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
4. The type and duration of the follow-up of subjects after adverse events.

Statistics

1. A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
2. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified.
3. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
4. The level of significance to be used.
5. Criteria for the termination of the trial.
6. Procedure for accounting for missing, unused, and spurious data.
7. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
8. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Quality Control and Quality Assurance

Ethics

Description of ethical considerations relating to the trial.

Data Handling and Record Keeping

Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

Depending on the type of “sponsor” (company, university, hospital) an insurance policy may be needed

Publication Policy

Publication policy, if not addressed in a separate agreement.

Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

6.2.4.1.1.3 INFORMED CONSENT OF TRIAL SUBJECTS - PIC (ICH)

Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

1. That the trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subject's responsibilities.
6. Those aspects of the trial that are experimental.
7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
10. The compensation and/or treatment available to the subject in the event of trial-related injury.
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. The anticipated expenses, if any, to the subject for participating in the trial.
13. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise
14. Entitled.
15. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
16. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.
17. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
18. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
19. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
20. The expected duration of the subject's participation in the trial.
21. The approximate number of subjects involved in the trial.

6.2.4.1.1.4 DATA USAGE CONSENT

In case it is not required to accomplish all the points considered in the PIC, it will be substituted by a data usage consent form.

Some countries have a data protection law that is a requirement when requesting data from individuals (like clinical studies). Normally in the PIC there should be a paragraph reflecting this.

When recollecting data from patients, data use consents should be use in any circumstances (integrated in the PIC or stand alone)

6.2.4.1.2 New Usage Indications

When performing clinical trials in patients in with new indication or usage different from the intended use specified in the label (approved by CE) an approval of the Ministry of Health is needed in some countries. (This will add an extra 60days minimum to the timelines).

UNE-EN ISO 14155 will be applied in any case.

6.2.4.2 Not certified Devices

In the case of not certified devices, small test can be carried out without the CE Mark certification but certain regulation must be followed in order to validate the usage of the device and accomplish the requirements needed to get the right certifications afterwards.

This regulation will depend on the kind of device that will be used in the trial, according to the Council Directive 93/42/EEC by the European Union (EU) and European Free Trade Association (EFTA) (see ANEX 1 and 2). WP6 will assist any trial responsible in order to make sure the device under test has been properly set within the corresponding category and, according to it, will provide the regulation and guidelines to follow.

EU standards for trials with investigational medicinal products are:

- ICH E6 document → Scientific guideline that must be taken into account
- EU Directive (2001/20/EC) → Directive across 25 members that accomplishes ICH-GCP.
- EU Directive (2005/28/EC) → European Commission directive regarding investigational medicinal devices for human use.
- National laws → National Law transposed from the EU directive that each member state should follow.

6.2.4.2.1 Medical Device Classification

The classification of medical devices in the European Union is outlined in Annex IX of the Council Directive 93/42/EEC. There are basically four classes, ranging from low risk to high risk.

- Class I (including Is & Im)
- Class IIa
- Class IIb
- Class III

The authorization of medical devices is guaranteed by a Declaration of Conformity. This declaration is issued by the manufacturer itself, but for products in Class Is, Im, IIa, IIb or III, it should be backed by a Certificate of Conformity of so-called Notified Body, i.e. an organization accredited to validate the compliance of the device to the European Directive. Medical devices that pertain to class I (on condition they do not need to be sterilized or are not used to measure a function) can be put on the market purely by self-certification.

The European classification depends on rules that involve the medical device's duration of body contact, its invasive character, its use of an energy source, its effect on the central circulation or nervous system, its diagnostic impact or its incorporation of a medicinal product.

Taking into account the different monitoring sensors that will be included in this project, a complete evaluation of each of the devices will be carried out by WP6 according to the informational form provided by the partner responsible of the trial. Therefore, a specific guideline will be provided for each study, in case it is necessary.

6.3 CE Certification Introduction

One of the goals of the European Economic Community is the constitution of an Internal Market. The internal Market is “an area without internal frontiers in which the free movement of goods, people, services and capital is ensured”. Whereas the content and scope of the laws, regulations and administrative provisions in force in the Member States with regard to the safety, health protection and performance characteristics of medical devices are different, whereas the certification and inspection procedures for such devices differ from one Member State to another, whereas such disparities constitute barriers to trade within the Community, there must be a supranational set of directives to harmonize these National provision in order to guarantee the free movement of such devices within the internal market. These rules must then be absorbed by each Member State in its Legal System.

The 93/42/EEC Directive applies to medical devices, defined as:

'medical device' *means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:*
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

One of its essential objectives is to “provide patients, users and third parties with a high level of protection and attain the performance levels attributed to them by the manufacturer”, taking account “of technology and practice existing at the time of design and of technical and economical considerations compatible with a high level of protection of health and safety”.

It is composed by 25 articles and 13 annexes containing general principles and conformity assessment procedures to make a product bear the CE mark and enable it to move freely within the Community and to be put into service in accordance with its intended purpose.

6.3.1 Some useful definitions

In Article 1, a proper terminology is defined to deal with medical devices. Here is a little excerpt concerning “HEARTCYCLE telecare” certification.

- ***'accessory'*** *means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device;*
- ***'custom-made device'*** *means any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient.*
- *The abovementioned prescription may also be made out by any other person authorized by virtue of his professional qualifications to do so.*
  Mass-produced devices which need to be adapted to meet the specific requirements of the medical practitioner or any other professional user are not considered to be custom-made devices;
- ***'device intended for clinical investigation'*** *means any device intended for use by a duly qualified medical practitioner when conducting investigations as referred to in … Annex X in an adequate human clinical environment.*
  For the purpose of conducting clinical investigation, any other person who, by virtue of his professional qualifications, is authorized to carry out such investigation shall be accepted as equivalent to a duly qualified medical practitioner;
- ***'manufacturer'*** *means the natural or legal person with responsibility for the design, manufacture, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party.*

The obligations of this Directive to be met by manufacturers also apply to the natural or legal person who assembles, packages, processes, fully refurbishes and/or labels one or more ready-made products and/or assigns to them their intended purpose as a device with a view to their being placed on the market under his own name

- ***'intended purpose'** means the use for which the device is intended according to the data supplied by the manufacturer on the labelling, in the instructions and/or in promotional materials;*
- ***'placing on the market'** means the first making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view to distribution and/or use on the Community market, regardless of whether it is new or fully refurbished*
- ***'putting into service'** means the stage at which a device is ready for use on the Community market for the first time for its intended purpose*

A more detailed definition of every kind of medical device, aimed to device classification is done in Annex IX and will be treated afterwards.

6.3.2 A brief description of certification workflow

First of all we have to mention that the 93/42 Directive divides medical devices into four categories, called Classes. The classes are I, IIa, IIb, III, and correspond to their level of potential risk for the patient. Thus, for instance, class I devices represent the lower risk for the user or patient, class IIa are generally connected to an energy source (and then associated with a raised hazard), class IIb are devices interacting with the human body and class III correspond to critical devices such as implantable or invasive devices, whose malfunction is normally cause of serious damage or death for the patient. Before getting into more detail in the certification study, we'll propose a simple sequence of steps (procedures described in the Directive's annexes) to obtain certification.

1. **Essential requirements** - Article 3: The devices must meet the essential requirements set out in *Annex I* which apply to them, taking account of the intended purpose of the devices concerned.
2. **Device Classification** – Article 9(.1): Devices shall be divided into Classes I, IIa, IIb and III. Classification shall be carried out in accordance with Annex IX.
3. **Designation of notified body** – (Annex XII where necessary). The conformity assessment procedures for Class I devices can be carried out, as a general rule, under the sole responsibility of the manufacturers in view of the low level of vulnerability associated with these products. For Class IIa devices, the intervention of a notified body should be compulsory at the production stage, for devices falling within Classes IIb and III which constitute a high risk potential, inspection by a notified body is required with regard to the design and manufacture of the devices. Class III is set aside for the most critical devices for which explicit prior authorization with regard to conformity is required for them to be placed on the market
4. **Declaration of Conformity** - Article 11, Annexes: II, III, IV, V, VI, VII, fulfilling different procedural requirement according to device class.
5. **CE Marking** - Annex XII

Article 12: Particular procedure for systems and procedure packs

Since the composite nature of the HEARTCYCLE, Article 12 deserves a particular interest in our treatment: it establishes how to deal with systems of medical devices.

…

Any natural or legal person who puts devices bearing the CE marking together within their intended purpose and within the limits of use specified by their manufacturers, in order to place them on the market as a system or procedure pack, shall draw up a declaration by which he states that:
(a) he has verified the mutual compatibility of the devices in accordance with the manufacturers' instructions and has carried out his operations in accordance with these instructions; and

(b) he has packaged the system or procedure pack and supplied relevant information to users incorporating relevant instructions from the manufacturers; and
(c) the whole activity is subjected to appropriate methods of internal control and inspection.
Where the conditions above are not met, as in cases where the system or procedure pack incorporate devices which do not bear a CE marking or where the chosen combination of devices is not compatible in view of their original intended use, the system or procedure pack shall be treated as a device in its own right and as such be subjected to the relevant procedure pursuant to Article 11.

Any natural or legal person who sterilized, for the purpose of placing on the market, systems or procedure packs referred to in the previous paragraph or other CE-marked medical devices designed by their manufacturers to be sterilized before use, shall, at his choice, follow one of the procedures referred to in Annex IV, V or VI. The application of the abovementioned Annexes and the intervention of the notified body are limited to the aspects of the procedure relating to the obtaining of sterility. The person shall draw up a declaration stating that sterilization has been carried out in accordance with the manufacturer's instructions.
…
The products … themselves shall not bear an additional CE marking. They shall be accompanied by the information referred to in (point 13 of) Annex I which includes, where appropriate, the information supplied by the manufacturers of the devices which have been put together. The declaration referred to in these paragraphs above shall be kept at the disposal of competent authorities for a period of five years.

Generally, when a device is connected to one or more medical devices, its conformity to the essential requirements must be verified working connected at least with one of the devices it is intended to.

Notified Body

Where the conformity assessment procedure involves the intervention of a notified body, the manufacturer, or his authorized representative established in the Community, may apply to a body of his choice within the framework of the tasks for which the body has been notified.

Annex XI describes CRITERIA TO BE MET FOR THE DESIGNATION OF NOTIFIED BODIES:

1. The notified body, its Director and the assessment and verification staff shall not be the designer, manufacturer, supplier, installer or user of the devices which they inspect, nor the authorized representative of any of these persons. They may not be directly involved in the design, construction, marketing or maintenance of the devices, nor represent the parties engaged in these activities. This in no way precludes the possibility of exchanges of technical information between the manufacturer and the body.
2. The notified body and its staff must carry out the assessment and verification operations with the highest degree of professional integrity and the requisite competence in the field of medical devices and must be free from all pressures and inducements, particularly financial, which might influence their judgment or the results of the inspection, especially from persons or groups of persons with an interest in the results of the verifications…

Shortly the Notified body should not be in any way implied in any step of the design and production of the device and is its concern to evaluate the concordance with the Directive.

Essential Requirements

In this Section we'll focus on requirements directly concerning the HEARTCYCLE certification study, for a complete list of requirements please read the entire Directive text.

6.3.2.1 GENERAL REQUIREMENTS

The devices must be designed and manufactured in such a way that, when used under the conditions and for the intended purposes, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, providing that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.

More in detail this document focuses on the solutions adopted by the manufacturer to reduce the risk for anyone involved in using the concerned device.

The manufacturer must apply the following principles in the following order:
- eliminate or reduce risks as far as possible (inherently safe design and construction);
- where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated;
- inform users of the residual risks due to any shortcomings of the protection measures adopted.

Moreover, the device must be designed, manufactured and packaged in such a way that its characteristics and performances will not be adversely affected by transport and stress conditions.

Shortly, every risk has to be reduced with the available technology at its least; if there's a risk condition that cannot be avoided at all, the user has to be informed.

6.3.2.2 REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION

In this section are exploited those design characteristics of a medical device relevant for the HEARTCYCLE system:

- *Devices with a measuring function*: Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device.

- *Requirements for medical devices connected to or equipped with an energy source*: Devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to the intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.
  Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.
  Moreover, has to be granted: Protection against electrical risks, protection against mechanical and thermal risks, protection against the risks posed to the patient by energy supplies or substances

To fulfil these requirements, the manufacturer must supply (and include in the packaging for every device) a set of documents:

A **Label** bearing the following particulars:
(a) *the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or instructions for use, shall contain in addition the name and address of either the person responsible … or of the authorized representative of the manufacturer established within the Community or of the importer established within the Community, as appropriate;*
(b) *the details strictly necessary for the user to identify the device and the contents of the packaging;*
(c) *where appropriate, the batch code, preceded by the word 'LOT', or the serial number;*
(d) *where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month;*
(e) *where appropriate, an indication that the device is for single use;*
(f) *if the device is custom-made, the words 'custom-made device';*
(g) *if the device is intended for clinical investigations, the words 'exclusively for clinical investigations';*
(h) *any special storage and/or handling conditions;*
(i) *any special operating instructions;*
(j) *any warnings and/or precautions to take;*
(k) *year of manufacture for active devices other than those covered by (e). This indication may be included in the batch or serial number;*
(l) *where applicable, method of sterilization.*

Device Instructions

(a) the details referred to in the Label, with the exception of (d) and (e);
(b) the performances …and any undesirable side-effects;
(c) if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;
(d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;
(e) where appropriate, information to avoid certain risks in connection with implantation of the device;
(f) information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;
(g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of ri-sterilization;
(h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilization of the device to be resterilized, and any restriction on the number of reuses.
Where devices are supplied with the intention that they be sterilized before use, the instructions for cleaning and sterilization must be such that, if correctly followed, the device will still comply with the general requirements;
(i) details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.);
(j) in the case of devices emitting radiation for medical purposes, details of the nature, type, intensity and distribution of this radiation.

The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular:
(k) precautions to be taken in the event of changes in the performance of the device;
(l) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.;
(m) adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;
(n) precautions to be taken against any special, unusual risks related to the disposal of the device;
(o) medicinal substances incorporated into the device as an integral part …
(p) degree of accuracy claimed for devices with a measuring function.

6.3.3 How to classify a device

This chapter is developed as a set of rules intended to classify the device into one of the two classes foreseen to be used within HEARTCYCLE.

- ***Active medical device*** *Any medical device operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy. Medical devices intended to transmit energy, substances or other elements between an active medical device and the patient, without any significant change, are not considered to be active medical devices.*
- ***Active device for diagnosis*** *Any active medical device, whether used alone or in combination with other medical devices, to supply information for detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities.*

Implementing rules

If the device is intended to be used in **combination with another device**, the classification rules shall apply separately to each of the devices. Accessories are classified in their own right separately from the device with which they are used

Note

Standalone software, e.g. software which is used for image enhancement is regarded as driving or influencing the use of a device and so falls automatically into the same class. Other standalone software, which is not regarded as driving or influencing the use of a device, is classified in its own right.

Classification: (invasive devices will not be analyzed since they are out of the scope of this project)

Non-invasive devices

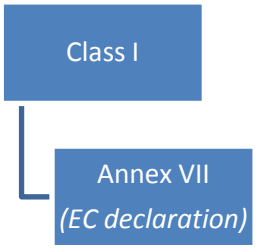
- ***Rule 1:*** *Every non-invasive devices are in Class I, unless one of the rules set out hereinafter applies.*
- ***Rule 10:*** *Active devices intended for diagnosis are in Class IIa:*
  - if they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum,
  - if they are intended to image in vivo distribution of radiopharmaceuticals,
  - if they are intended to allow direct diagnosis or monitoring of vital physiological processes, unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS (Central Nervous System) in which case they are in Class IIb.
  Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class IIb.

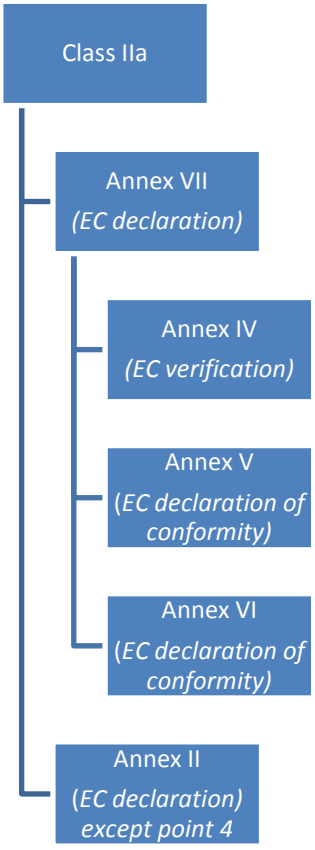
According to this analysis, so far HEARTCYCLE devices are expected to be ClassI, ClassIIa or ClassIIb.

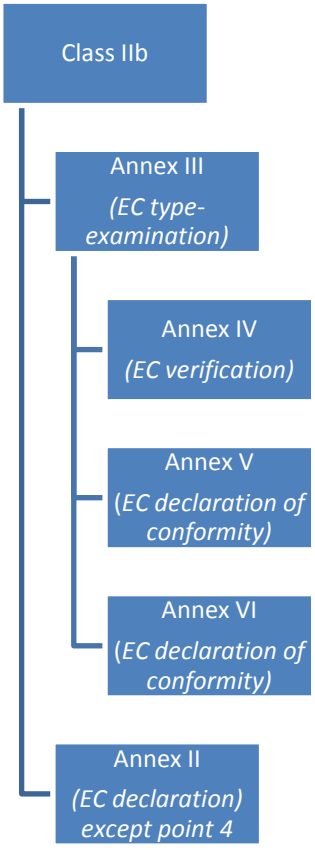
6.4 Certification Procedures: Class I, IIa, IIb

6.4.1 Visual representation: an overview

This is a visual representation of what has to be done to obtain each level of certification, to accomplish the Directive's requirements it is necessary to follow only one path from right to left.




Class IIa
Annex VII
(EC declaration)
Annex IV
(EC verification)
Annex V
(EC declaration of conformity)
Annex VI
(EC declaration of conformity)
Annex II
(EC declaration) except point 4


Class IIb
Annex III
(EC type-examination)
Annex IV
(EC verification)
Annex V
(EC declaration of conformity)
Annex VI
(EC declaration of conformity)
Annex II
(EC declaration) except point 4

6.4.2 Medical devices: CE Mark

6.4.2.1 Class I

For Class I devices, as we mentioned, it is not necessary the intervention of a notified body unless the device falls in one of two particular conditions.

Class I devices can be certified by the manufacturer: *In the case of devices falling within Class I, other than devices which are custom-made or intended for clinical investigations, the manufacturer shall, in order to affix the CE marking, follow the procedure referred to in Annex VII and draw up the EC declaration of conformity required before placing the device on the market*

6.4.2.2 Class IIa

The manufacturer shall follow

- the procedure relating to the EC declaration of conformity set out in Annex VII, coupled with either (only one of these):
    - the procedure relating to the EC verification set out in Annex IV or
    - the procedure relating to the EC declaration of conformity set out in Annex V (production quality assurance) or
    - the procedure relating to the EC declaration of conformity set out in Annex VI (product quality assurance)
- Instead of applying these procedures, the manufacturer may also follow the procedure referred to in Annex II (full quality assurance), with the exclusion of point 4 (that is the "Examination of the design project" by the notified body)

6.4.2.3 Class IIb

In the case of devices falling within Class IIb, other than devices which are custom-made or intended for clinical investigations, the manufacturer shall, in order to affix the CE marking, either:

- *follow the procedure relating to the EC declaration of conformity set out in Annex II (full quality assurance); in this case, point 4 of Annex II is not applicable; or*
- *follow the procedure relating to the EC type-examination set out in Annex III, coupled with:*
    - *the procedure relating to the EC verification set out in Annex IV; or*
    - *the procedure relating to the EC declaration of conformity set out in Annex V (production quality assurance); or*
    - *the procedure relating to the EC declaration of conformity set out in Annex VI (product quality assurance).*

6.4.2.4 Annexes of Interest

The steps for the Conformity assessment procedures depend on the device class and can vary, according to manufacturer's choice within a few alternative certification paths contained in this Directive.

Before considering each case in detail, it is very useful to analyse the "operative annexes" of this Directive which means the chapter containing the effective procedure step to be followed during the assessment. These are Annexes II, III, IV, V, VI and VII.

Despite the appearance and the initial complexity deriving from the necessity of completeness in the requirements of this Directive, there are a few main concepts to learn to disentangle.

6.4.2.4.1 Introducing the Declaration of conformity

A few more words should be spent introducing Annexes II, VII, V and VI.

First of all, the 93/42/EEC Directive splits the process of making a product available to market in three phases: design, production (in terms of manufacturing), post-production.

The above-mentioned chapters contain similar procedures, all specific to the EC Declaration Of Conformity, they only differ in what phase these procedures must be applied. The EC declaration of conformity is the procedure whereby the manufacturer or his authorized representative (established in

the Community who fulfils the obligations imposed)… ensures and declares that the products concerned meet the provisions of this Directive which apply to them.

6.4.2.4.2 Annex II

Here, the notified body is involved in every step of the production, that's why it refers to a "Full quality assurance system". The requirements in this section are so detailed and complete that Annex II is often enough to certify a "high" class device, but this will be covered later. Thus, *the manufacturer must ensure application of the quality system approved for the design, manufacture and final inspection of the concerned products.*

The whole Annex is focused on the definition of a Quality system and the procedure to assess its conformity to the Directive requirements, in all the three phases.

Quality System

The declaration of conformity is the procedure whereby the manufacturer who fulfils the obligations imposed by Section 1 ensures and declares that the products concerned meet the provisions of this Directive which apply to them.
The manufacturer must affix the CE marking … and draw up a written declaration of conformity. This declaration must cover a given number of the products manufactured and be kept by the manufacturer

The manufacturer must lodge an application for assessment of his quality system with a notified body. Some details of the requirements for a quality system will be omitted, please refer to the complete 93/42/EEC Directive text. In this deliverable we'll only cover the aspects concerning the HEARTCYCLE telecare system.

The application must include:

- *the name and address of the manufacturer and any additional manufacturing site covered by the quality system;*
- *all the relevant information on the product or product category covered by the procedure;*
- *a written declaration that no application has been lodged with any other notified body for the same product-related quality system;*
- *the documentation on the quality system;*
- *an undertaking by the manufacturer to fulfil the obligations imposed by the quality system approved;*
- *an undertaking by the manufacturer to keep the approved quality system adequate and efficacious;*
- ***an undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective action**. This undertaking must include an obligation for the manufacturer to notify the competent authorities of the following incidents immediately on learning of them:*
  - (i) any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;
  - (ii) any technical or medical reason connected with the characteristics or performance of a device leading for the reasons referred to in subparagraph (i) to systematic recall of devices of the same type by the manufacturer.

***Application of the quality system must ensure that the products conform to the provisions of this Directive which apply to them at every stage, from design to final inspection**. All the elements, requirements and provisions adopted by the manufacturer for his quality system must be documented in a systematic and orderly manner in the form of written policies and procedures such as quality programmes, quality plans, quality manuals and quality records.*
It shall include in particular an adequate description of:
(a) the manufacturer's quality objectives;
(b) the organization of the business and in particular:
- the organizational structures, the responsibilities of the managerial staff and their organizational authority where quality of design and manufacture of the products is concerned,

- the methods of monitoring the efficient operation of the quality system and in particular its ability to achieve the desired quality of design and of product, including control of products which fail to conform;

(c) the procedures for monitoring and verifying the design of the products and in particular:
- a general description of the product, including any variants planned,
- the design specifications, including the standards which will be applied and the results of the risk analysis, and also a description of the solutions adopted to fulfil the essential requirements which apply to the products if the standards referred to in Article 5 are not applied in full,
- the techniques used to control and verify the design and the processes and systematic measures which will be used when the products are being designed,
- if the device is to be connected to other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when connected to any such device(s) having the characteristics specified by the manufacturer,
…
- the clinical data referred to in Annex X,
- the draft label and, where appropriate, instructions for use;

(d) the inspection and quality assurance techniques at the manufacturing stage and in particular:
- the processes and procedures which will be used, particularly as regards sterilization, purchasing and the relevant documents,
- the product identification procedures drawn up and kept up to date from drawings, specifications or other relevant documents at every stage of manufacture;

(e) the appropriate tests and trials which will be carried out before, during and after manufacture, the frequency with which they will take place, and the test equipment used; it must be possible to trace back the calibration of the test equipment adequately.

The notified body must audit the quality system to determine whether it meets the requirements … The assessment team must include at least one number with past experience of assessments of the technology concerned. The assessment procedure must include an inspection on the manufacturer's premises and, in duly substantiated cases, on the premises of the manufacturer's suppliers and/or subcontractors to inspect the manufacturing processes.
The decision is notified to the manufacturer. It must contain the conclusions of the inspection and a reasoned assessment.

The manufacturer must inform the notified body which approved the quality system of any plan for substantial changes to the quality system or the product-range covered.

In addition, the manufacturer must lodge with the notified body an application for examination of the design dossier relating to the product (describing the design, manufacture and performances of the product in question). The notified body must examine the application and, if the product conforms to the relevant provisions of this Directive, issue the application with an EC design-examination certificate.

6.4.2.4.3 Annex III

EC TYPE-EXAMINATION 1. EC type-examination is the procedure whereby a notified body ascertains and certifies that a representative sample of the production covered fulfils the relevant provisions of this Directive. The word “TYPE” means a representative sample of the production in question.

The notified body must include these documents:

- *the name and address of the manufacturer and the name and address of the authorized representative if the application is lodged by the representative;*
- *a general description of the type, including any variants planned;*
- *design drawings, methods of manufacture envisaged, in particular as regards sterilization, and diagrams of components, sub-assemblies, circuits, etc.;*
- *the descriptions and explanations necessary to understand the abovementioned drawings and diagrams and the operation of the product;*

- *a list of the standards referred to in Article 5, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements if the standards referred to in Article 5 have not been applied in full;*
- *the results of the design calculations, risk analysis, investigations, technical tests, etc. carried out;*
- *a statement indicating whether or not the device incorporates, as an integral part, a substance as referred to in … Annex I and data on the tests conducted in this connection;*
- *the clinical data referred to in Annex X;*
- *the draft label and, where appropriate, instructions for use;*
- *a written declaration that no application has been lodged with any other notified body for the same type.*

The notified body must then:

- examine and assess the documentation and verify that the type has been manufactured in conformity with that documentation
- carry out or arrange for the appropriate inspections and the tests necessary to verify whether the solutions adopted by the manufacturer meet the essential requirements of this Directive
- If the type conforms to the provisions of this Directive, the notified body issues the applicant with an EC type-examination certificate

6.4.2.4.4 Annex IV

EC VERIFICATION

EC verification is the procedure whereby the manufacturer or his authorized representative established in the Community ensures and declares that the products which have been subject to the verification procedure is conform to the type described in the EC type-examination certificate and meet the requirements of this Directive which apply to them.

Shortly, this Annex logically follows Annex III (which is indispensable for applying this one). Again, the manufacturer must set up a procedure to gain feedback experience from post-production phase (it is literally the same paragraph we just found at the end of Annex VII).

The notified body must carry out the appropriate examinations and tests in order to verify the conformity of the product with the requirements of the Directive either by examining and testing every product or by examining and testing products on a statistical basis as specified, as the manufacturer decides. We'll omit the statistical percentage for sampling acceptance, non-conformity, adding that they refer to harmonized standards

6.4.2.4.5 Annex V and VI

These two sections of the Directive are really similar, speaking in terms of procedures, just like Annex II and VII they are meant for the EC Declaration of Conformity, they both must follow Annex III and they share a lot of documentation to draw up; however they largely differ in terms of application phases.

Annex V is the *Production quality assurance*, that means that the notified body examines and certifies the production system for the concerned device, while annex VI is the *Product quality assurance,* where the notified body certifies the device after testing the final production and the products ready to be marketed.

This is the documentation shared between the two annexes.

The manufacturer must lodge an application for assessment of his quality system with a notified body

This procedure is nearly identical to the one we found in Annex II, the main difference is that here the quality system is certified only for one phase of the production (manufacturing – final test).

Just for completeness' sake, we'll highlight a paragraph we can find in each of the three annexes to see the abovementioned difference.

- Annex II – "Application of the quality system must ensure that the products conform to the provisions of this Directive which apply to them at every stage, from design to final inspection"

- Annex V – “Application of the quality system must ensure that the products conform to the type described in the EC type-examination certificate”
- Annex VI – “Under the quality system, each product or a representative sample of each batch is examined and the appropriate tests defined in the relevant standard(s) … or equivalent tests are carried out to ensure that the products conform to the type described in the EC type-examination certificate and fulfil the provisions of this Directive which apply to them”

Also the auditing, testing and surveillance procedures for the notified body are very similar, so please refer to the Directive for the details.

6.4.2.4.6 Annex VII

This is another section concerning the assessment for the EC Declaration of conformity, but only the manufacturer or his representative is involved. **This Annex is very important because it is often sufficient to certify a Class I device.**

The manufacturer must prepare the following technical documentation.

The manufacturer or his authorized representative established in the Community must make this documentation, including the declaration of conformity, available to the national authorities for inspection purposes for a period ending at least five years after the last product has been manufactured.

Also in the case where there is a product from another initiative (e.g. the belt and the vest in MyHeart) that is useful for the HEARTCYCLE system the technical documentation related to these products is highly desired.

Where neither the manufacturer nor his authorized representative are established in the Community, this obligation to keep the technical documentation available must fall to the person(s) who place(s) the product on the Community market.

The technical documentation must allow assessment of the conformity of the product with the requirements of the Directive. It must include in particular:
- a general description of the product, including any variants planned,
- design drawings, methods of manufacture envisaged and diagrams of components, sub-assemblies, circuits, etc.,
- the descriptions and explanations necessary to understand the abovementioned drawings and diagrams and the operations of the product,
- the results of the risk analysis and a list of the standards …, applied in full or in part, and descriptions of the solutions adopted to meet the essential requirements of the Directive if the standards … have not been applied in full,
- in the case of products placed on the market in a sterile condition, description of the methods used,
- the results of the design calculations and of the inspections carried out, etc.; if the device is to be connected to other device(s) in order to operate as intended, proof must be provided that it conforms to the essential requirements when connected to any such device(s) having the characteristics specified by the manufacturer,
- the test reports and, where appropriate, clinical data in accordance with Annex X,
- the label and instructions for use.
…
The manufacturer shall institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective actions, taking account of the nature and risks in relation to the product. He shall notify the competent authorities of the following incidents immediately on learning of them:

- *Any malfunction or deterioration in the characteristics and/or performance of a device*
- *Any technical or medical reason leading to systematic recall of devices of the same type by the manufacturer.*

6.4.3 Some further explanation: **Rule 10 in detail**

Since some devices composing the HEARTCYCLE fall in this rule, make some examples of its application are shown in the table below.

RULE 10	**EXAMPLES**
Active devices intended for diagnosis are in Class IIa:	
- if they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum,	- Magnetic resonance equipment, pulp testers, evoked response stimulators, diagnostic ultrasound.
- if they are intended to image in vivo distribution of radiopharmaceuticals,	- Gamma cameras, positron emission tomography and single photon emission computer tomography.
- ***if they are intended to allow direct diagnosis or monitoring of vital physiological processes*** [1]***,***	- ***Electrocardiographs, electroencephalographs, cardioscopes with or without pacing pulse indicators - Electronic thermometers - Electronic stethoscopes*** ***- Electronic blood pressure measuring equipment***
unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS in which case they are in Class IIb	- ***Intensive care monitoring and alarm devices (for e.g. blood pressure, temperature, oxygen saturation), biological sensors, blood gas analysers used in open heart surgery, cardioscopes and apnea monitors, including apnea monitors in home care***
Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class II B.	- Diagnostic X-ray sources.

Note

Vital physiological processes and parameters include for example respiration, heart rate, cerebral functions, blood gases, blood pressure and body temperature. Medical devices intended to be used for continuous surveillance of vital physiological processes in anaesthesia, intensive care or emergency care are in Class IIB, whilst medical devices intended to be used to obtain readings of vital physiological signals in routine check ups and in self- monitoring are in Class IIA. A thermal imaging device intended to monitor blood flow is not considered to be a temperature measuring device.

6.4.4 Certifying the HEARTCYCLE system

One point to focus on is the diversity of the modules embedded in the HEARTCYCLE. Medical devices involved in this architecture have diverse nature and origin and thus require their own certification process. HEARTCYCLE contains among others:

- Software modules
- Sensor module

It is important to take into account that any certified medical device, i.e. electronic blood pressure meter, could become a topic of certification in this context if it is possible for a program to automatically access its memory and extract or send directly the measurements to the HEARTCYCLE system, or if it can use a software module from the HEARTCYCLE system to perform artifact rejection or a specialised analysis of the recorded data. On the other side if the patient is responsible to send the measurement inserting them by manually typing on a telephone or computer keyboard, the source of these measurements is indifferent. On the other hand, if the measurement is sent to the HEARTCYCLE contact center automatically via the device, and the measurement is immediately assessed by the HEARTCYCLE software modules, then another procedure should be followed for the certification process. Other devices, like the ECG recorder, although they need manufacturer's certification, they are considered as being directly connected with HEARTCYCLE modules.

6.4.4.1 Software Certifying

The HEARTCYCLE telecare system is composed by software modules structured medical knowledge and various types of medical services and medical assistive modules such as decision support systems for example. Taking into account thus the above mentioned HEARTCYCLE structure, and the fact that we approach the HEARTCYCLE product as an MDD we can analyze how directive 93/42 handles this kind of medical devices.

First of all it must be said that the Directive, and this is intentional, does not treat specifically the process of certifying any category of devices. That is because this supranational directive is just a guideline that traces the essential requirements for the safety of patients and users. This is not a detailed workflow to obtain a certification.

Moreover, software medical devices are maybe the newest and atypical kind of devices, compared for example with "classical" medical devices such as a syringe, an ECG or a pacemaker.

The definition of a medical device explicitly includes software components, but it considers software more as driving another medical device than a stand alone unit. The directive mostly refers to software in combination with other devices. The only point where we can find a precise mention is:

Standalone software, e.g. software which is used for image enhancement is regarded as driving or influencing the use of a device and so falls automatically into the same class. Other standalone software, which is not regarded as driving or influencing the use of a device, is classified in its own right.

Considering whether software is active or not we should focus on the definition. Software depends for its functioning *on a source of electrical energy or any source of power other than that directly generated by the human body.*

If this interpretation is not enough, Article 12 of the directive should be considered, taking software as part of a system composed among the others, by a personal computer which is connected to an electrical source. This system is "active" so, being said that the whole system and each component has to fulfil the essential requirements, the software has to be verified as an active device.

Certification is also needed for the hardware (that is normally a personal computer or similar) the software runs on. Indeed, the hardware-software system must be connected to energy sources and other devices respecting the essential requirements for the user safety. Just like for the software, the directive compels the manufacturer to verify that the device or system used for its intended purpose is neither dangerous for the user nor compromising in any way patient's health. Again it has to be faced the lack of precise values or definitions of levels of danger or at least practical and systematic ways to define when a risk is acceptable or not. In the case of the HEARTCYCLE system, the hardware is

composed by monitoring devices which are mostly certified by their manufacturer, by the telematics infrastructure, which as an architecture should be certified, and by the driving modules and hardware components of the home based telematics stations.

To render certification more compliant in terms of effective quantitative rules that need to be followed, a technical standard should be applied instead of trying to fulfil qualitative methods.

6.4.4.1.1 Harmonized Standards

As already mentioned , the Medical Devices Directive is the instrument that all the EU states have decided to adopt to establish the Essential Requirements of Safety and Health that Medical Devices must meet so that they may be placed on the market of the European Union.

These requirements are high-level, essential and unavoidable; they must be met in compliance with the technological state of the art that evolves over time and that therefore is not established by the Directive.

A new division of tasks and responsibilities governs the relations between legislation and standardization: the Community institutions only harmonize, through directives, the Essential Requirements relating to the health and safety of the citizens, consumer protection and environmental protection. The European standardization institutes--CEN, CENELEC and ETSI--have the task of adopting the procedures that define the technical specifications operators need to design and manufacture products that conform to the essential demands of the directives.

Therefore, "harmonized standards", developed by the European standardization bodies on the basis of a mandate from the Commission of the European Communities, set the generic requirements of the directives. These standards must compulsorily be translated into national technical standards, and any conflicting standards must be eliminated.

The harmonized standards, however, as well as the national standards that implement them, are not obligatory: each manufacturer, in fact, is free to produce on the basis of different specifications. In that case, however, he must prove that the product conforms to the requirements of the directives. On the other hand, a product manufactured on the basis of the harmonized standards benefits from a presumption of conformity with the essential requirements of the directives.

Note, however, that for the presumption of conformity to be effective, the reference to the harmonized standard must be published in the Official Gazette of the European Community and the harmonized standard ratified at the national level.

In the absence of harmonized standards, and transitionally, the member states are required to accept as conforming to the essential requirements any product manufactured according to the purely national standards, which have been subject to a special recognition procedure by the Commission.

The harmonized standard taken in exam in the following section is:

CEI EN 60601-1 (general standard)

Medical electrical equipment

Part 1: General requirements for safety

A general standard is normally completed (in terms of details and real procedures) by its collateral standards. A complete discussion of this topic, however, would be too wide and a bit off-topic.

Those that are more linked to the HEARTCYCLE are:

CEI EN 60601-1-1/A1

Medical electrical equipment

Part 1: General requirements for safety

1. Collateral Standard: Safety requirements for medical electrical systems

CEI EN 60601-1-4

Medical electrical equipment

Part 1: General requirements for safety

4. Collateral Standard: Programmable electrical medical systems

The first collateral standard mainly refers to the environmental safety of an electrical medical system. Its intent is to define quantitatively some otherwise vague terms concerning safety, such as for example “patient area”, and to propose a standard way to connect medical devices and other devices to electrical sources. This is accomplished through multiple taps and coupling methods to avoid shock hazard to users and patients (e.g. avoiding leakage currents).

This standard should be certainly applied certifying the HEARTCYCLE but since it is of more interest in the deployment phase, when it will be chosen in detail the physical structure to implement (that is the model of personal device, the connections and the position of the hardware related to the patient and user, etc.), it will not be treated in this deliverable.

On the contrary CEI EN 60601-1-4 is related to the development life cycle of a programmable medical device and so it is the perfect supplement for the 93/42 Directive in relation with the process of certifying a software module or a system containing programmable interfaces. This requires then a short summary of the concepts and definitions it exposes which will be later used throughout the deliverable to study the certification process of a telemedicine system.

6.4.4.1.2 CEI EN 60601-1-4

Computers are increasingly used in Medical Electrical Equipment, often in critical-safety roles. The use of computing technologies introduces a level of complexity which is exceeded only by the biological systems of the patients they are intended to diagnose or treat. This complexity means that systematic failures can escape practical accepted limits of testing. Accordingly, this safety standard goes beyond traditional testing and assessment of the finished Medical Electrical Equipment and includes requirements for the process by which they are developed. That’s because testing of the finished product is no more, by itself adequate to address safety of complex medical equipment.

The CEI EN 60601-1-4 collateral standard applies to the safety of medical electrical equipments and medical electrical systems incorporating programmable electronic subsystems (PESS). These will be called Programmable Electrical Medical Systems (PEMS).

Some systems which incorporate software and are used for medical purpose fall outside the scope of this standard, e.g. many medical informatics systems. The definitions to be satisfied are:

Medical Electrical Equipment: Any electrical equipment providing no more than one connection to a main power supply which is dedicated to diagnosis ,treatment, monitoring of a patient under medical supervision, having a physical or electrical contact with the patient and/or transferring energy to or from the patient and/or recording energy to or from the patient. (2.2.15 of IEC 601-1)

Medical Electrical System: combination of more medical electrical equipments or of a medical electrical equipment with a non medical electrical equipment, having a specified purpose and connected by coupling and/or a portable multiple tap.

Before starting the analysis of this standard we must claim that this is not a complete treatment of it and that this is only intended to highlight the aspects of this collateral standard which apply to the HEARTCYCLE telecare system.

Some terminology

DEVELOPMENT LIFE CYCLE: Necessary activities occurring during a period of time that starts at the concept phase of a project and finishes when VALIDATION of the PEMS is complete

HAZARD ANALYSIS: Identification of HAZARDS and their initiating causes.

Note: The quantification of HAZARD is not a part of the HAZARD ANALYSIS.

MAXIMUM TOLERABLE RISK: Value of RISK which is specified as the maximum which may be permitted.

Note: The value may be specified for the PEMS as a whole or for a particular HAZARD.

PROGRAMMABLE ELECTRICAL MEDICAL SYSTEM (PEMS): MEDICAL ELECTRICAL EQUIPMENT or MEDICAL ELECTRICAL SYSTEM containing one or more PROGRAMMABLE ELECTRONIC SUBSYSTEM.

PROGRAMMABLE ELECTRONIC SUBSYSTEM (PESS): System based on one or more central processing units, including their software and interfaces.

RESIDUAL RISK: RISK identified by HAZARD ANALYSIS which remains after RISK management has been completed.

RISK: Probable rate of occurrence of a HAZARD causing harm, and the degree of SEVERITY of the harm.

RISK MANAGEMENT FILE: That part of the quality records required by this standard.

RISK MANAGEMENT SUMMARY: Document, which provides traceability for each HAZARD and each cause of the HAZARD to the RISK analysis and to the VERIFICATION that the RISK of the HAZARD is controlled.

Note This document may be held on paper or on electronic media.

SAFETY: Freedom from unacceptable RISK.

SAFETY HAZARD(hereinafter referred to as hazard): Potentially detrimental effect on the PATIENT, other persons, animals, or the surroundings, arising directly from MEDICAL ELECTRICAL EQUIPMENT.

SAFETY INTEGRITY: Likelihood of a safety-related system satisfactorily performing the required SAFETY functions under all the stated conditions within a stated period of time.

SEVERITY: Qualitative measure of the possible consequences of a HAZARD

VALIDATION: Process of evaluating a PEMS or a component of a PEMS during or at the end of the development process, to determine whether it satisfies the requirements for its intended use

VERIFICATION: Process of evaluating a PEMS or a component of a PEMS to determine whether the products of a given development phase satisfy the specified requirements imposed at the start of that phase

Documentation to be produced

These documents, herein referred to as RISK MANAGEMENT FILE are:

1. RISK MANAGEMENT SUMMARY

Developed throughout the DEVELOPMENT LIFE-CYCLE, containing:

a) identified HAZARDS and their initiating causes;
b) estimation of RISK
c) reference to the SAFETY measures, including their required SAFETY INTEGRITY, used to eliminate or control the RISK of the HAZARD;
d) evaluation of effectiveness of RISK control;
e) reference to VERIFICATION

2. RISK MANAGEMENT PLAN

The manufacturer shall prepare a risk management plan including:

a) scope of the plan, defining the project or product and the DEVELOPMENT LIFE-CYCLE phases for which the plan is applicable;
b) the DEVELOPMENT LIFE-CYCLE to be applied, including a VERIFICATION plan and a VALIDATION plan;

It shall be defined for the design and development phase and shall be divided into phases and tasks, with a well defined input, output and activity for each. The plan shall also include processes for risk management and documentation requirements

c) management responsibilities (in accordance with ISO 9001)
d) risk management process, (explained below)
e) requirements for reviews

3. RISK MANAGEMENT PROCESS

This should be composed by:

- **Risk analysis:**
  - *HAZARD analysis:*

    HAZARDS shall be identified for all reasonably foreseeable circumstances including:
    - NORMAL USE
    - INCORRECT USE

    The HAZARDS considered shall include, as appropriate:
    - HAZARDS to PATIENTS;
    - HAZARDS to OPERATORS;
    - HAZARDS to service personnel;
    - HAZARDS to bystanders;
    - HAZARDS to the environment.

    Reasonably foreseeable sequences of events, which may result in a HAZARD, shall be considered.

    Initiating causes considered shall include, as appropriate:
    - human factors;
    - hardware faults;
    - software faults;
    - integration errors;
    - environmental conditions.

    Matters considered shall include, as appropriate:
    - compatibility of the system components, including hardware and software;
    - user interface, including command language, warning and error messages;
    - accuracy of translation of text used in the user interface and INSTRUCTIONS FOR USE;
    - data protection from human intentional or unintentional causes;
    - RISK/benefit criteria;
    - third party software.
  - *RISK ESTIMATION*:

    For each identified HAZARD the RISK shall be estimated, this estimation shall be based on an estimation of the likelihood of each HAZARD and/or the SEVERITY of the consequences of each HAZARD
- **Risk control:**

  RISK shall be controlled so that the estimated RISK of each identified HAZARD is made acceptable.

  A RISK is acceptable if the RISK is less than or equal to the MAXIMUM TOLERABLE RISK and the RISK is made as low as reasonably practicable.

  Methods of RISK control shall reduce the likelihood of the HAZARD or reduce the SEVERITY of the HAZARD or both.

  RISK control methods shall be directed at the cause of the HAZARD (e.g. by reducing its likelihood) or by introducing protective measures which operate when the cause of the HAZARD is present, or both, using the following priority:
  - inherent safe design;
  - protective measures including alarms;
  - adequate USER information on the RESIDUAL RISK.

  An evaluation of RISK CONTROL effectiveness should be recorded in the RISK MANAGEMENT SUMMARY. This can be done with a CAPA (corrective and preventive

actions) document, illustrating in a schematic way the action taken to prevent or react to a risk condition.

(throughout this section, every classification, categorization or estimation method used (e.g. level of severity) should be recorded in the RISK MANAGEMENT FILE)

4. REQUIREMENT SPECIFICATIONS

For the PEMS and each of its subsystems (e.g. for a PESS) there shall be a requirement specification.

The requirement specification shall detail the functions that are RISK-related. This includes functions that control RISKS arising from

- causes arising from environmental conditions;
- causes elsewhere in the PEMS;
- possible malfunctions.

For each of these functions, the requirement specification shall give the level of SAFETY INTEGRITY necessary to control the RISKS.

5. ARCHITECTURE

The architecture shall satisfy the requirement specification.

For the PEMS and each of its subsystems, an architecture shall be specified.

Where appropriate the specification shall include requirements for:

a) allocation of RISK control measures to subsystems and components of the PEMS;
b) redundancy;
c) diversity;
d) failure rates and modes of components;
e) diagnostic coverage;
f) common cause failures;
g) systematic failures;
h) test interval and duration;
i) maintainability;
j) protection from human intentional or unintentional causes.

6. DESIGN AND IMPLEMENTATION

Where appropriate, the design shall be decomposed into subsystems, each having a design and test specification.

Where appropriate, requirements shall be specified for:

a) software development methods;
b) electronic hardware;
c) computer aided software engineering (CASE) tools;
d) sensors;
e) actuators;
f) human-PEMS interface;
g) energy sources;
h) environmental conditions;
programming language;
third party software.

7. VERIFICATION

VERIFICATION of the implementation of SAFETY requirements shall be carried out.

A VERIFICATION plan shall be produced to show how the SAFETY requirements for each DEVELOPMENT LIFE-CYCLE phase will be verified.

8. MODIFICATION

If any or all of a design results from a modification of an earlier design then either all of this standard applies as if it was a new design or the continued validity of any previous design documentation shall be assessed under a modification/change procedure

9. ASSESSMENT

Assessment shall be carried out to ensure that the PEMS has been developed in accordance with the requirements of this standard and recorded in the RISK MANAGEMENT FILE. This may be carried out by internal audit.

The concept of RISK

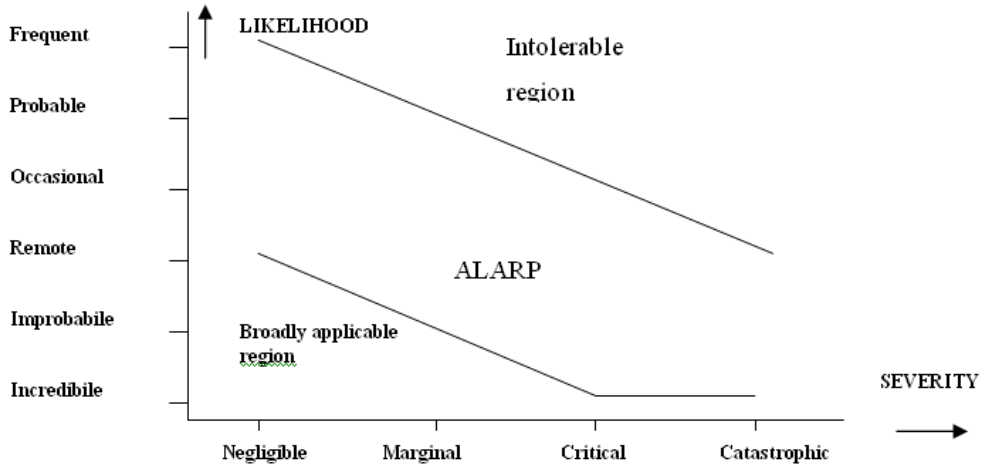
Software and other systematic failures do not fit into the concept of likelihood or probability as events in themselves. A major objective of this standard is to reduce likelihood of systematic errors being presents. Risk estimation is a necessary step both in determining where to focus design effort and in judging results.

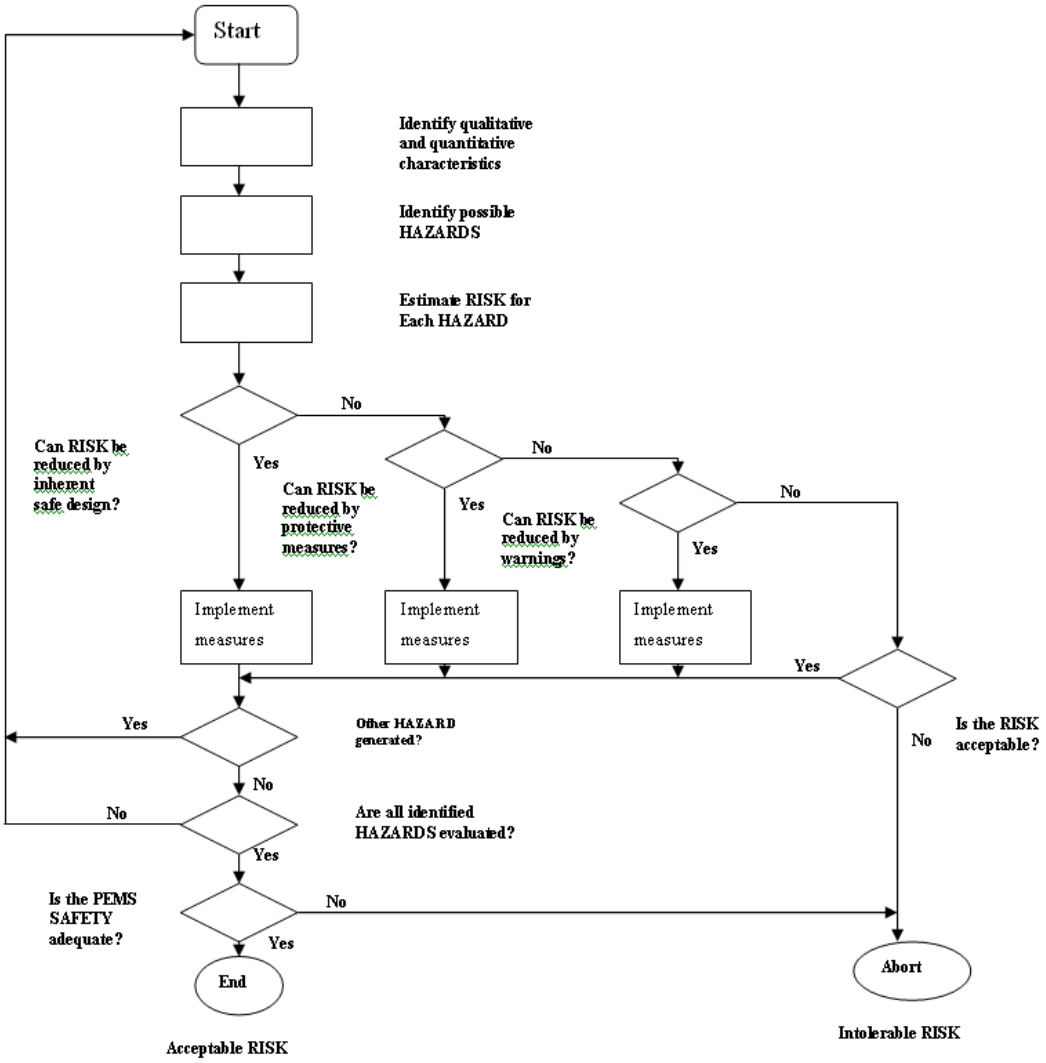
The concept of risk has two elements:

- Likelihood of hazardous event
- Severity of the consequences of the hazardous event

So risk can be categorized into three regions:

- Intolerable
- As Low As Reasonably Practicable
- Broadly acceptable





A hazardous event can result from the failure of a system. There are two types of possible failure:

- Random failures: e.g. the probability of failure of an electronic assembly
- Systematic failures: due to errors in any development life-cycle activity, like an incorrect limit in a database which permitted a hazardous condition. The likelihood of this kind of event is difficult to predict. There is, however, a relationship between the quality of the processes used during the development life-cycle and the likelihood of the fault being introduced or remaining undetected.

Safety Integrity

There are two principal concerns:

- Does the system provide all the necessary functions to control the risk?
- Will the system be operational when called on to carry out these functions?

Safety integrity is divided into:

- Hardware integrity (with regard to random failures)
- Systematic integrity (including hardware and software): architecture, project management, development.