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Deliverable 3.2 Update
Enrolment of 180 DCM Patients

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Abbreviations

DCM	Dilated Cardiomyopathies
CMP	Cardiomyopathies
EF	Ejection fraction

NCCP	Non-compaction cardiomyopathies

Disclaimer: This document is an update of D3.2 – Enrollment of 180 DCM Patients, submitted at M20 (November 2014). The updates are clearly highlighted in the document. The major updates are:

1) Increase the enrollment study time by six months. Accordingly, the revised study schedule plans to enroll patients up to month 30. The follow up examination will nonetheless be performed within month 36, with time between the examinations varying from 6 to 18 months. Clinical and technical partners agree that this will not jeopardize the study success as, given the rapid evolution of the disease, a follow-up time of six months will still be sufficient to identify clinical changes and corroborate the predictive mechanical models. Furthermore a significantly shorter follow-up time might provide a second set of data for patients collected before the event of cardiac failure, mechanical support and/or transplant, thus possibly enriching the quality and relevance of the data.
2) We decided to include in the study all dysfunctional non compaction cardiomyopathies since from a clinical and cardio-mechanical standpoint can be considered a specific type of dilated dysfunctional cardiomyopathy
3) We decided furthermore to include patients with dilated cardiomyopathy with age < 1 year and/or in acute phase. Clinical partners agree that this group of patients might add useful information to the study since from the acute onset phase significant changes in a short timeframe are expected, often developing into intractable heart failure needing mechanical support device implantation and/or cardiac transplant (i.e. both primary end-points of the study).

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Activity Performed

The WP3 activity in the first 6 months (M13-18) has focused on the completion of all clinical protocols approval as necessary precondition for the data collection. As soon as it could start, it has been progressing speedily, with the ambition of recuperating the lost time. The overall amount number of included patients is however still significantly lower than initially forecasted in the DoW, even though at least all the clinical data of the enrolled patients have been acquired according to the targets. The number of MRIs is still low, but expected to rise with the implementation of better defined inclusion criteria. Furthermore patients have been identified that fall into the disease group but show contraindications for a MRI study but with available genetic testing and partial retrospective data from imaging.

The main problems faced by WP3, which have led to the declared delay in the data collection, have concerned the unification of the clinical protocols, the definition of a multicentre agreement with regard to the specific MRI study protocol, taking into account the different machine brands and sequences implemented among the participating centres. OPBG has had its 1.5T Siemens MR scanner installed in March 2014, but due to a deferral in its implementation its operational usage within the MD-project could start only in July. UCL faced significant bureaucracy issues due initially to the delay of the ethical approval, and to the difficulty encountered in hiring an adequate research fellow to be dedicated to the study. Given the fact that DHZB officially joined the project only in January 2014 (entering as a substitute partner of John Hopkins University), DHZB could get its clearance from the Ethical Committee only in the Spring and could subsequently start the enrolment only in June.

Methodology and Selection Criteria

The Cardiomyopathy group is committed to perform an observational longitudinal cohort study in the three clinical centres, ensuring altogether the enrolment of 180 CM patients (60 per centre), with clinical, laboratory, bio-humoral, genetic and imaging data (Echocardiography and MRI), and to re-evaluate all patients after one year from the first visit, collecting the same data as at the baseline (but for genetics).

Current inclusion criteria

- Presence of biventricular heart physiology
- LV abnormal ejection fraction and/or fractional shortening, diagnosed by echocardiogram
- Increased left ventricular end-diastolic diameter >2 standard deviations from the expected normal limit

Current exclusion criteria

- Evidence of acute cardiomyopathy (signs or symptoms present <3 months), systemic hypertension (>95th percentile for age and height), persistent high rate supraventricular arrhythmia, pericardial disease (including restrictive and constrictive pericarditis), univentricular heart physiology, cor pulmonale.

T3.2 Clinical data & Routine laboratory test data collection

Progress

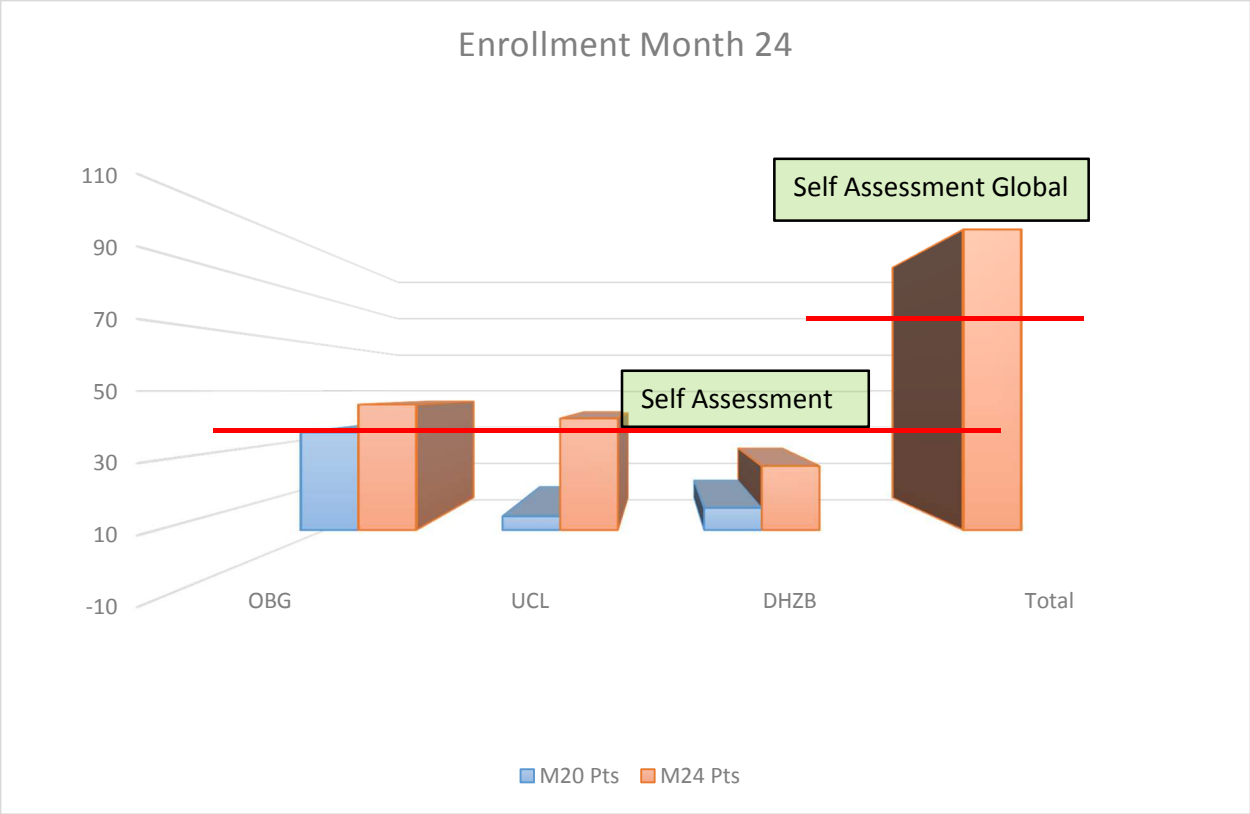
A general agreement on data collection needs for modelling (what data, which values, codification, etc.), with a complete clinical evaluation, was reached and case report forms were designed accordingly. Data sharing and the methods to anonymise data have been discussed with the technical partners and implemented. OPBG requested whether for MRI there was the need to provide a 2d or 4d flow, because for children both sequences are long to perform and difficult to sustain. The modelling partners eventually requested 4D flows, as better adequate for their needs.
Electrical axis parameters were also requested by the modelling partners for personalisation, and some ECG values were also deemed necessary for the validation. The agreed solution has been that clinicians will send the scanned ECG with already calculated time intervals to the technical partners.

Furthermore it has been agreed that some intermediate scans (echo 3D and/or MRI) will be useful to build the model also in-between the baseline and the follow-up control. During examinations it has been observed that CPX is difficult to perform in younger patients, and therefore only in a subgroup this test will be performed in the course of the study (allowing the clinical PMs allocated for such tasks to be transferred to other task or aspects of the project). A standard set of parameters for the Six Minute Walk Test (6MWT) has been identified, reflecting the functional exercise level for daily physical activities, and is routinely ongoing within the Data collection. For the modelling needs, the following activities will be performed on most patients:

-Scanned ECG
-Systemic BP (max,mean,min) taken at time of Echo and MRI SCAN
-Echocardiography with 3D Scan
- MRI with 4D Flows, 2D Flow and 3D Flow
-Cath data, when taken for clinical reasons (TX listing)
-Karto data, if collected for clinical reasons

Updates at Month 24

Patient enrolment is steadily ongoing in all three centers. OPBG has enrolled 45 patients so far (45 Echos, 22 MRI, 45 ECG); UCL has enrolled 34 patients (21 Echo, 32 MRI, 23 ECG); DHZB has enrolled 24 patients (16 echo, 15 MRI, 16 ECG). In total 103 patients have been enrolled so far. General enrollment is thus globally on time, despite a significant delay in DHZB.



Overall Self-Assessment plan minimum Target achieved (90 patients overall cut off, 30 for each Center reached only for OBG and UCL). The new self-assessment plan is the same as the old one. Note the increase of patients enrolled since October 2014.

Significant Findings

One particular outcome in the population enrolled so far at OPBG deserves to be highlighted. The case reported presented at the ER of OPBG in December 2012, and was assigned the study patient ID OPBG 010. OPBG 010 is an adolescent male, 16 years old (Height 155, weight 46kg). In his family history there was no known cardiac disease and/or sudden death report. The patient was reported to be asymptomatic until September 2012 and was used to perform regular physical activity (gym+swimming). In his past history there were no significant clinical events reported. During three months prior to hospitalization he experienced increasing tiredness and reduced exercise tolerance, associated with moderate weight loss, despite no change in eating habits. Thus in November 2012 he underwent nutritional screening which identified evidence of gluten intolerance. Between November and December 2012 one episode on flu-like illness was reported, lasting three to four days. Due to acute and increasing chest pain and dyspnoea, he was admitted to the ER in Dec 2012. Cardiology screening was performed with evidence of reduced EF and dilated LV. A first diagnosis of myocarditis vs dilated cardiomyopathy was suspected.

During hospitalization the patient underwent detailed echocardiographic examination with evidence of markedly increased trabeculae of the left ventricular apical e and lateral walls, possibly suggesting the presence of left ventricular non-compaction. The patient underwent standard in-hospital care and was discharged from the hospital in stable NYHA II/III. In march 2013, as per study protocol, the patient was readmitted to the hospital to be enrolled in the MD-Paedigree WP-3 study and underwent: laboratory testing, genetic testing, 3D echocardiography and cardiac MRI. Preliminary genetic testing were negative (study sample is currently undergoing exome sequencing at OPBG), while echocardiography confirmed the probable diagnosis of left ventricular non-compaction. However, the MRI study, although confirming the presence of a markedly dilated and dysfunctional left ventricle, did not confirm the diagnosis of left ventricular non compaction while suggesting a possible case of idiopathic dilated cardiomyopathy.
OPBG 010 was followed up in the heart failure outpatient and clinic until January 2014 when due to the evidence of worsening clinical conditions, the patient was hospitalized and entered national heart transplant list. Accordingly the patient underwent cardiac catheterization and due to unstable haemodynamics was implanted a temporary mechanical heart support (Jarvick). After two days, the patient underwent cardiac transplant and is now doing well at follow-up. Of note, the patient's heart collected during transplant underwent pathology and histology testing at OPBG, which confirmed the diagnosis of idiopathic dilated cardiomyopathy.

Open Issues

DHZB encountered difficulty in recruiting children with confirmed DCMP, that meet ethical criteria to undergo the study, and and EF <50%, notwithstanding its very large patient population (one of the largest in Germany). This raised the possibility that there might be some epidemiological differences between the populations studied in the three clinical centers. DCMP could be more frequent in Italy, while more German children with chronic forms of DCMP were registered – who have typically an EF>50%. Other more functionally impaired patients have been the subject of various therapeutic approaches including medication, ICD/Pacemaker implantation and heart transplantation, and may have contraindications to undergo MRI. The same could be true with other forms of cardiomyopathies such as non-compaction, but not much data exists. DCMP patients at DHZB who have milder forms of the disease with almost normal or normalized LV function/dimensions may stillmeet the inclusion criteria. However, DCMP reflects only one entity of cardiomyopathies that are only incompletely understood. Other forms of cardiomyopathy including non-compaction cardiomyopathies (NCCP), Hypertrophic cardiomyopathy (HCM or HOCM), Arrhythmogenic right ventricular cardiomyopathy (ARVC), Restrictive Cardiomyopathy (RCM) are common within the patient population of cardiomyopathies and also show an association to a genetic basis.

Corrective actions

Update at month 24

The Partners involved in this study have identified the following corrective actions:
1) Inclusion of patients with contraindication to MRI.
2) Increasing the inclusion of other primary and secondary cardiomyopathyies as described in the original proposal, also allowing to include patients that are already under treatment and thus might have a normal or normalized cardiac function.
3) Continue patient recruitment until M30

Increase the enrollment study time by six months. Accordingly, the revised study schedule plans to enroll patients up to month 30. The follow up examination will nonetheless be performed within month 36, with time between the examinations now varying from 6 to 18 months. Clinical and technical partners agree that this will not jeopardize the study success as, given the rapid evolution of the disease, a follow-up time of six months will still be sufficient to identify clinical changes and corroborate the predictive mechanical models. Furthermore a significantly shorter follow-up time might provide a second set of data for patients collected before the event of cardiac failure, mechanical support and/or transplant, thus possibly enriching the quality and relevance of the data.

So far, comprising the three study centers one hundred and three patients have been enrolled in the study. According to the technical partners, provided that at least 40% of the enroll patients have an available complete dataset, the reached number of subjects is already sufficient to provide sufficient data for the disease modelling requested. It should be noted that in clinical studies a number of drop out and incomplete datasets are to be expected, thus it has been agreed with the technical reviewers that a number of 30 to 40 baseline studies would be sufficient to deliver the models. This aspect has also been evaluated by the D12.1. Regardless of this, granted the increased time allocated for enrollment, we plan to complete the whole study sample of 180 patients, even if DHZB (who has so far shown more delay in the enrollment) will not reach the prospected sample of 60 patients, as this lack could be filled in by OPBG and UCL during the upcoming months.

Many discussions have been made among the clinical partners regarding whether to include noncompaction (NCCP) as secondary type of cardiomyopathies, given discording guidelines on this disease. However, as shown at the half-yearly meeting in Utrecht in September 2014, when found at a dilated and dysfunctional stage, LV NCCP is not always easily distinguishable from DCM. In detail, a patient with heart failure was shown, in whom diagnosis of non-compaction was suspected at echocardiography, and no clear diagnosis could be made on MRI (DCM vs LV non-compaction). However as the patient had undergone cardiac transplant clinicians were able to analyse the actual heart specimen, and diagnosis of primary DCM was made by the pathologist.
Therefore, we decided to include in the study all dysfunctional non compaction cardiomyopathies since from a clinical and cardio-mechanical standpoint can be considered a specific type of dilated dysfunctional cardiomyopathy.

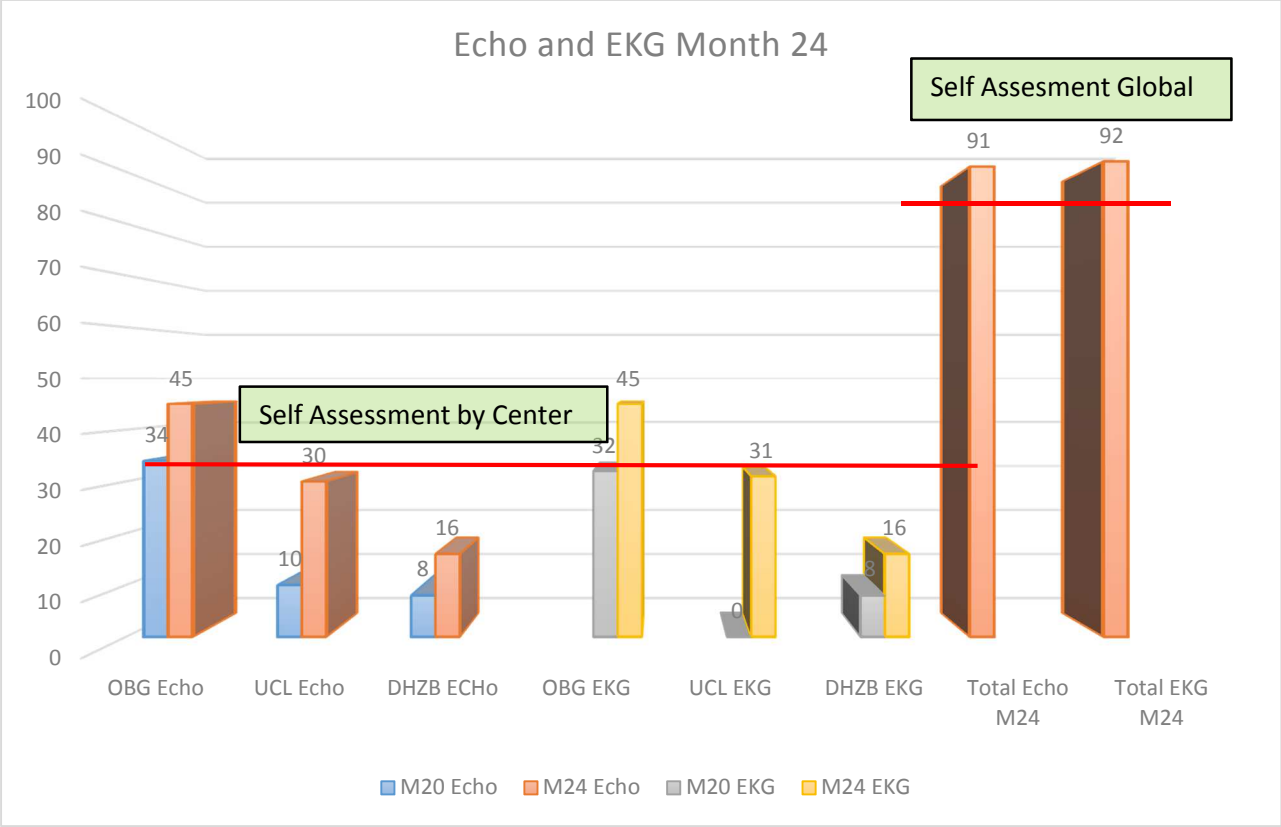
We decided furthermore to include patients with dilated cardiomyopathy with age < 1 year and also in acute phase. Clinical partners agree that this group of patients might add very interesting information to the study since from the acute onset phase, significant changes in short period of time are expected often developing into intractable heart failure needing mechanical support device implantation and/or cardiac transplant (i.e. both primary hard end points of the study). It should be also considered that in pediatric cardiology there are no clear cut-offs on the exact timing for which chronic cardiomyopathy can be defined (general assumption is 1- 3 months after the first diagnosis of dysfunction to define eligibility criteria for the study according with ad hoc literature).
As a further mitigation plan, we have decided to evaluate the possibility to include different forms of cardiomyopathy, which could also represent an ancillary aim to evaluate the validity of the derived model in different cardiac dysfunctional diseases. Anyway, the main aim of the study remains the dilated cardiomyopathies

We believe that the sum of these corrective actions will allow all three centres to speed up data collection and comply with the Self- Assessment Plan and the DoW objectives (i.e. within month 36, with follow up examinations). See new self assessment plan below

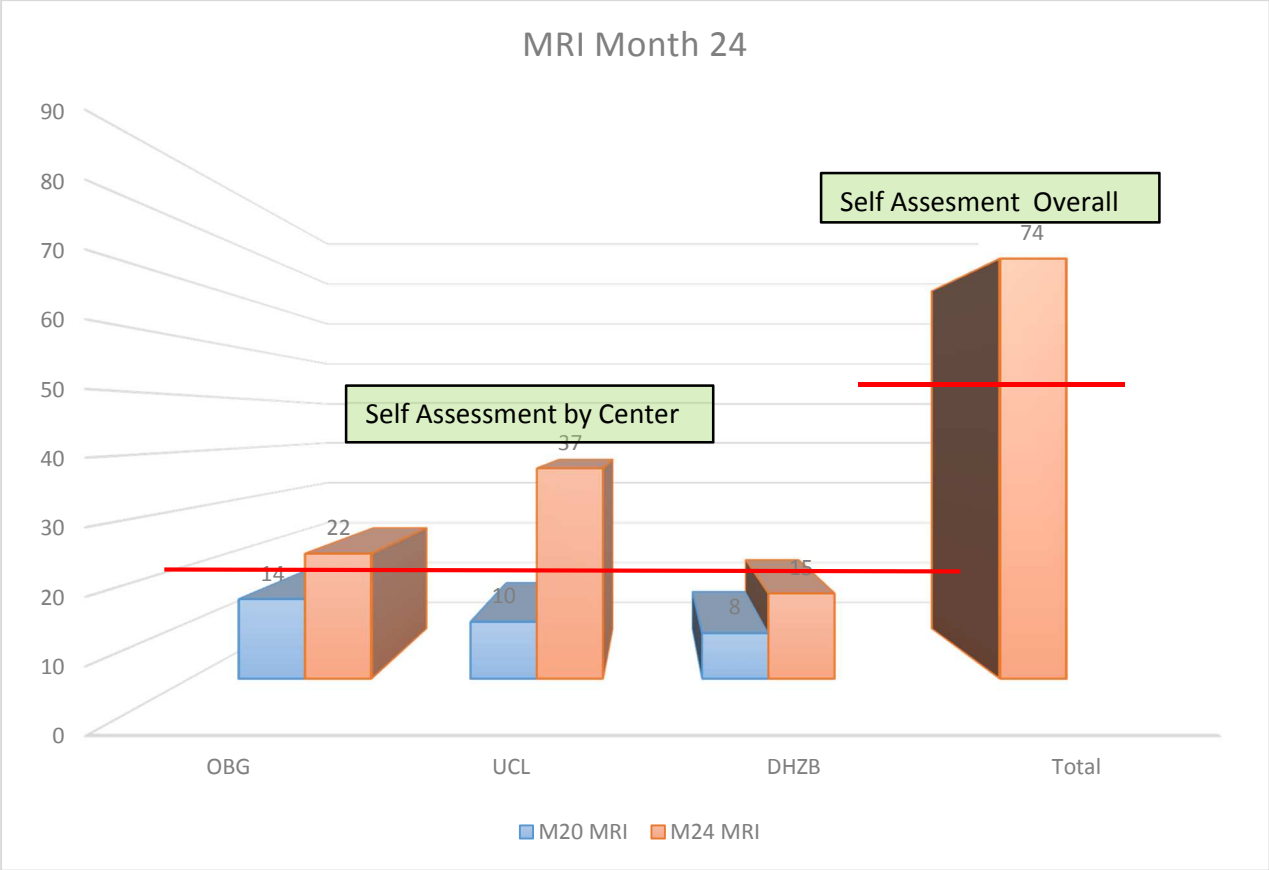
T3.4 Imaging Acquisition and data processing

Progress

An agreement concerning the standard to export 3D data has been reached. In terms of providing Retrospective Data, there were some issues regarding the sharing (non-disclosure) agreement with the technical partners. GNÚBILA and VPH-Share have set up an uploading and anonymisation system which is now operational. Both OBPG and UCL have provided basis examples of short axis stacks and flow sequences allowing their comparison with each other, leaving to Siemens the decision on how to parameterise the data. In order to achieve higher accuracy for data with breathing artefacts, a method to automatically align short axis stacks, making use of existing mesh models in combination with a slice registration algorithm has been implemented. As data acquisition is spinning up at the different clinical centers, larger amounts of data will be made available for the technical partners in the coming months, allowing to better evaluate and tweak the modelling pipeline to paediatric CMP cases.



Overall target of 90 patients (30 for each Center) has not yet been reached, apart from OBG.
The new self-assessment plan has not changed as compared to the previous released version. It should be noted that that as all the enrolled patients will have an echocardiogram examination performed, the acquisition of data will be on schedule. Thus the target will be easily achieved in a short timeframe.



Overall minimum SAP target of 54 patients has been reached globally, and almost so by each center (i.e. 18 patients per Center). The new self-assessment plan (regarding MRI) has been subject to minor changes from the previous version. See new self-assessment plan below

Update at month 24

Overall echocardiographic examinations aquired so far are slightly below what requested by the Self Assesment Plan, despite one of the centers (OBG) has already reached the target. In contrast MRI aquisition presents a more significant backlog, apart from UCL, for which MRI aquisition more closely follows patient enrollment. As previosuly stated, delay in MRI aquisition for OBG is the result of a delay in MRI machine availability and to the delay in hospital approval for exams performed in anesthesia (which represent a significant proportion of the children enrolled at OBG. For both echocardiographic exams and MRI exams, DHZ is in significant delay, however it should be noted that DHZ has joined the consortium at a later time, given the unexpected drop out of John's Hopkins Hospital.

Significant Results

UCL has provided tetralogy of Fallot shapes on which the software for the statistical estimation of a heart shape remodelling model from a cross-sectional database of images was completely reengineered. Moreover UCL is willing to acquire DTI images in the future.

Corrective actions

Update at month 24

The number of echocardiographic examinations available will increase quickly once UCL will start uploading the already performed echo examinations, thus at present we believe that at current, patient enrollment and echocardiographic examination are close to the target of 90 datasets. This is also due to the higher number of patients enrolled at both OBG and UCL, which have fulfilled the current lack in enrollment at DHZ.
We foresee that the number of available MRI studies will be slightly lower as compared to the target for a number of unexpected clinical and ethical reasons:

1) *The number of patients requiring anesthesia is above the number prospected at the beginning of the study.*
2) *Follow up MRI might not be clinically justifiable especially if performed in general anesthesia (i.e. the risk associate with the procedure overcomes the benefit provided by the examination.)*
3) *Parents' low compliance on performing MRI in general anesthesia (i.e. not signing consent)*
4) *Patients unable to perform MRI study due to claustrophobia*
5) *Lack of economic support for covering family travel to the hospital to perform the additional examinations*

In conclusion, after thorough discussion with our technical partners, it has been agreed that the minimum number of complete datasets to perform an adequate modelling tool needs to be around 30 to 40 baseline patients, being significantly lower that what initially prospected. Thus, we believe that despite the delay in patient enrollment, the data acquired will be more than sufficient to develop the modelling tool requested. Nonetheless, applying the corrective actions here proposed, we believe that the total number of patients can actually be reached, thus giving us enough data to not only develop the tool, but also to perform initial clinical validation of the models.

For modelling the data received from the clinical partners, the only adaptation needed was to rescale the adult model to fit the paediatric population. A general understanding has been reached about the fact that the CaseReasoner should in principle be fed also with other basic data (e.g. blood tests...), and that its appropriate adaptation will occur over time, in parallel to the project's developments. Both OBPG and UCL have provided basis examples of short axis stack and flow sequences allowing their comparison with each other (UCL's are faster) leaving to Siemens the decision on how to parameterize the data.

Updated Self-assessment Plan (variations compared to the previous self-assessment plan are highlighted in red)

WP3							
Relevant task(s)	Objective description	Measurement process / Unit	Indicator (M24)		Indicator (M36)		
			Lower	Higher	Lower	Higher	
T.3.2	Clinical data & Routine laboratory test Data collection (including ECG)	Percentage of overall studies on 180 patient studied twice = 360 studies 180 for each center	25% (90 studies, 30 per center)	50% (180 studies, 60 per center)	90 % (324 studies, 108 per center)	100% (360 studies, 120 per center)	
T3.3.1	Imaging Acquisition (Echo) Acquisition at month	Percentage of overall studies on 180 patient studied twice = 360 studies 180 for each center	25% (90 studies, 30 per center)	50% (180 studies, 60 per center)	80 % (288 studies, 96 per center)	100% (360 studies, 120 per center)	
T3.3.2	Imaging (MRI) Acquisition at month	Percentage of overall studies on 180 patient studied twice = 360 studies 180 for each center	15% (54 studies, 18 per center)	35% (126 studies, 42 per center)	65% (234 studies, 78 per center)	85 % (306 studies, 102 per center)	
T3.5	Quality and usability of collected data	Percentage of overall studies on 180 patient studied twice = 360 studies 180 for each center	90% of data usable for modeling	90% of data usable for modeling	90% of data usable for modeling	90% of data usable for modeling	