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Deliverable 3.3
Re-evaluation of all patients

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Abbreviations

DCM	Dilated Cardiomyopathies
CMP	Cardiomyopathies
EF	Ejection fraction
NCCP	Non-compaction cardiomyopathies

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1. Activity Performed

The WP3 activity in the latter 6 months (M30-36) has focused on completion of the data acquisition including follow up studies. The number of included patients is consistent with the forecast in the DoW with only minor deviations. The number of patients who have undergone at least one MRI has increased significantly and follow-up scanning is ongoing and close to completion. In addition, as agreed previously, some patients included in the study cannot undergo an MRI but their other data, such as genetic tests and other imaging modalities, will be analyzed.

WP3 had to overcome a number of challenges at the beginning of the study. These led to the declared delay in completing the data collection and 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 had its 1.5T Siemens MR scanner installed in March 2014 and it became available for use in MD-PAEDIGREE in July 2014. UCL experienced bureaucratic delays with ethical approval and hiring of clinical research staff. DHZB joined the project late (January 2014) to replace John Hopkins University. As a result, DHZB obtained ethical permission in the Spring of 2014 and began enrolment in June 2014.

1.1 Aims and Methodology

In WP3, the aim is to carry out an observational longitudinal cohort study in the three clinical centres, enrolling 180 cardiomyopathy patients (60 per centre), with clinical, laboratory, bio-humoral, genetic and imaging data (Echocardiography and MRI). The follow-up interval for all patients is 6 months to 18 months after the first visit, collecting the same data as at the baseline.

2.Clinical Data and Routine Laboratory Data Collection

2.1 Progress

The WP3 partners have defined a common set of parameters required for modeling cardiomyopathy in children. This included defining the measurement techniques, the units for the variables and how data will be coded. The methods for clinical evaluation have also been defined and a case report form has been produced to record the data. Data sharing and anonymisation is needed and some functional tools have been implemented by the technical partners but remain in development. The partners have decided to include 4D flow sequences in the imaging protocols when feasible, despite the extensive scanning time that these sequences require, because of the rich data that they provide for evaluation of the cardiac models such as fluid-solid interaction (FSI) models. Electromechanical models are also being produced by the technical partners and the clinical partners are acquiring additional ECG data in order to calibrate these models.

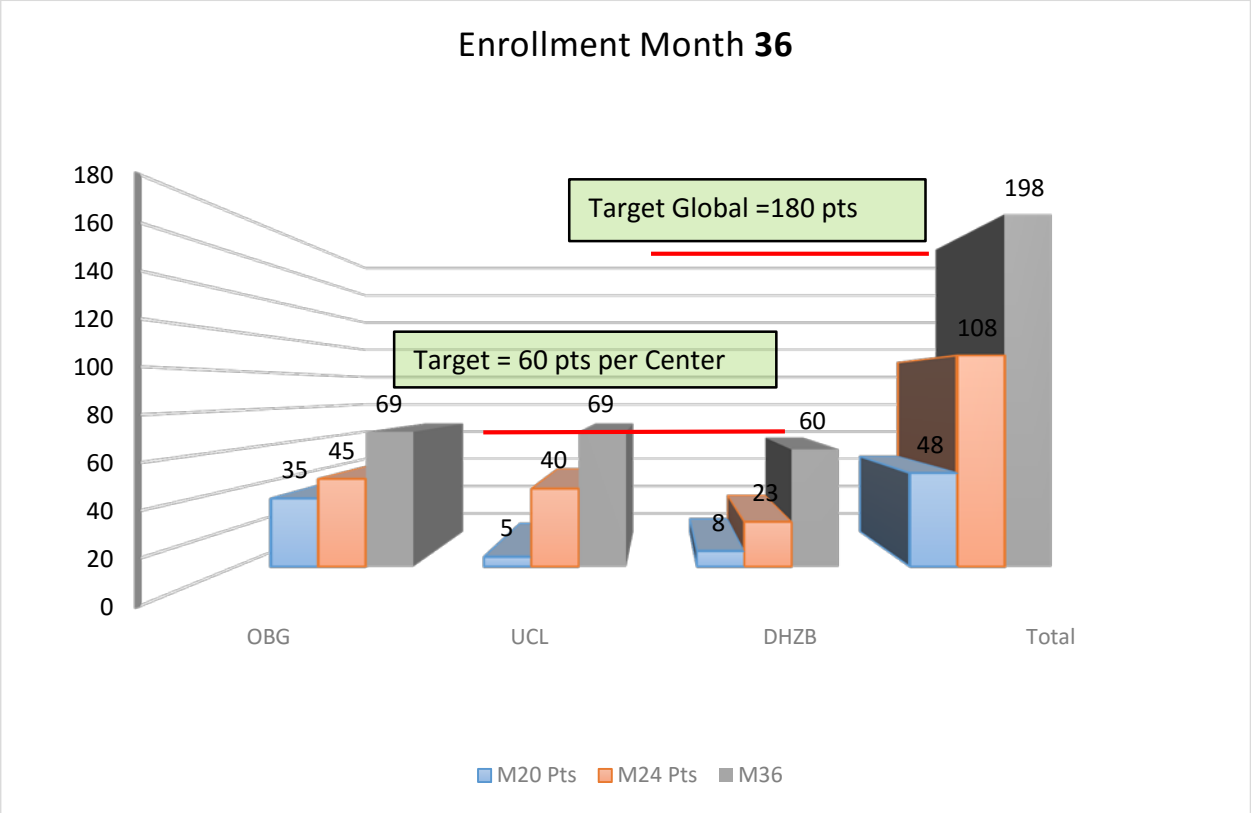
The partners have decided that intermediate imaging data (3D echo and/or MRI) between the baseline and follow-up visits will be useful for better definition of clinical progression of cardiomyopathy in each patient. In many cases, these data will be acquired routinely as part of the clinical follow-up that these patients undergo. Dynamic data from cardiopulmonary exercise (CPEX) will be used where available and acquired whenever possible to enrich the phenotyping of cardiac function in a subgroup of the cohort. CPEX will not be available for all cases because it is difficult to perform in younger patients and also because it is sometimes contraindicated. In cases where CPEX cannot be performed, the Six Minute Walk Test (6MWT) will be used.

The following data are being acquired to underpin the cardiovascular models:

- ECG

- Systemic BP (max, mean, min) acquired during Echo and MRI
- Echocardiography with 3D Scan
- MRI with 4D flow and 2D flow
- Cath data if taken for clinical reasons (e.g. cardiac transplant listing)
- Karto (electrophysiological mapping data) if collected for clinical reasons

The enrollment period has now ended. Patient enrolment is complete in all three centers. OPBG has enrolled 69 patients; UCL has enrolled 69 patients; DHZB has enrolled 60 patients. In total 198 patients have been enrolled (overrunning the expected target number of 180).



Enrollment Target achieved and overrun (target of 180 patients). Note the steady increase of patient enrollment in the past few months.

2.2 Significant Findings

One particular case in the population enrolled at OPBG deserves to be highlighted. The patient presented to the Emergency Room (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). There was no known cardiac disease and/or sudden death report in his family history. The patient was reported to be asymptomatic until September 2012 and performed regular physical activity (gym + swimming). There were no significant clinical events reported in his past medical history. In the three months prior to his 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 of 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 and a reduced cardiac ejection fraction (EF) and a dilated left ventricle (LV). An initial diagnosis of myocarditis / dilated cardiomyopathy was suspected.

During his hospitalization, the patient underwent detailed echocardiographic examination and markedly increased trabeculae of the left ventricular apical and lateral walls was found, 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 tests 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 clinic until January 2014 when, due to evidence of worsening clinical condition, he was hospitalized and entered onto the national heart transplant list. Accordingly, he underwent cardiac catheterization and, due to unstable haemodynamics, was implanted with temporary mechanical heart support (Jarvick). After two days, he underwent cardiac transplant and is now doing well at follow-up. Of note, his heart collected during transplant underwent pathology and histology testing at OPBG, which confirmed the diagnosis of idiopathic dilated cardiomyopathy.

2.3 Solved Issues

DHZB encountered difficulty in recruiting children with confirmed DCMP, that meet ethical criteria to undergo the study, 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 for undergoing MRI. The same could be true with other forms of cardiomyopathies such as non-compaction but little data exist to examine this possibility. DCMP patients at DHZB who have milder forms of the disease with almost normal or normalized LV function/dimensions may still meet 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 with genetic factors. Accordingly, revised inclusion criteria were agreed to include other primary and secondary cardiomyopathies as described in the original proposal, also allowing inclusion of patients that are already under treatment and thus might have a normal or normalized cardiac function. In addition, it was agreed to include patients with dilated cardiomyopathy with age < 1 year and also patients in the acute phase of their disease.

2.4 Corrective Actions Taken

The revised study schedule planned 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.

According to the technical partners, provided that at least 40% of the enrolled patients have an available complete dataset, the number of subjects in the study is quite sufficient to support the disease modeling. 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.

3. Imaging Acquisition and Data Processing

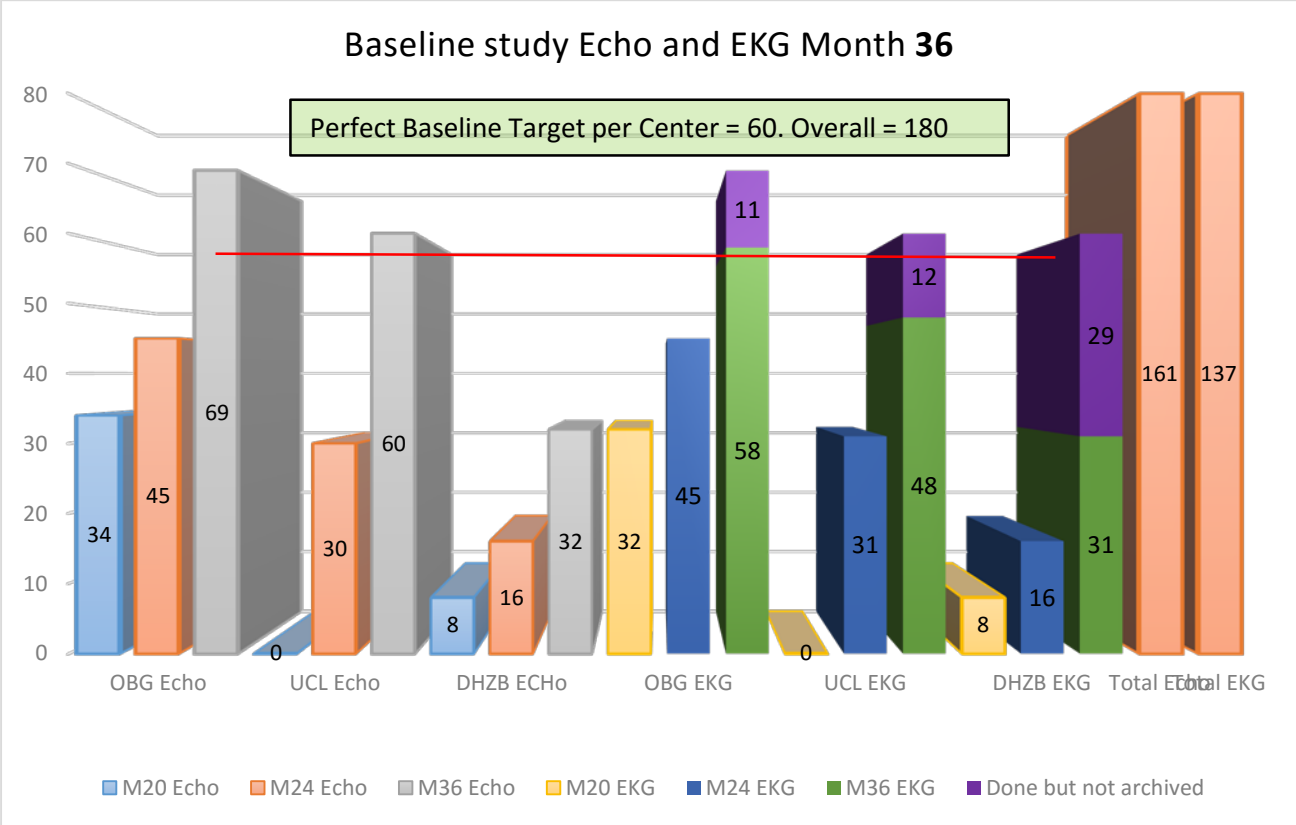
3.1 Progress

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 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 better evaluation and tweaking of the modeling pipeline for paediatric CMP cases.

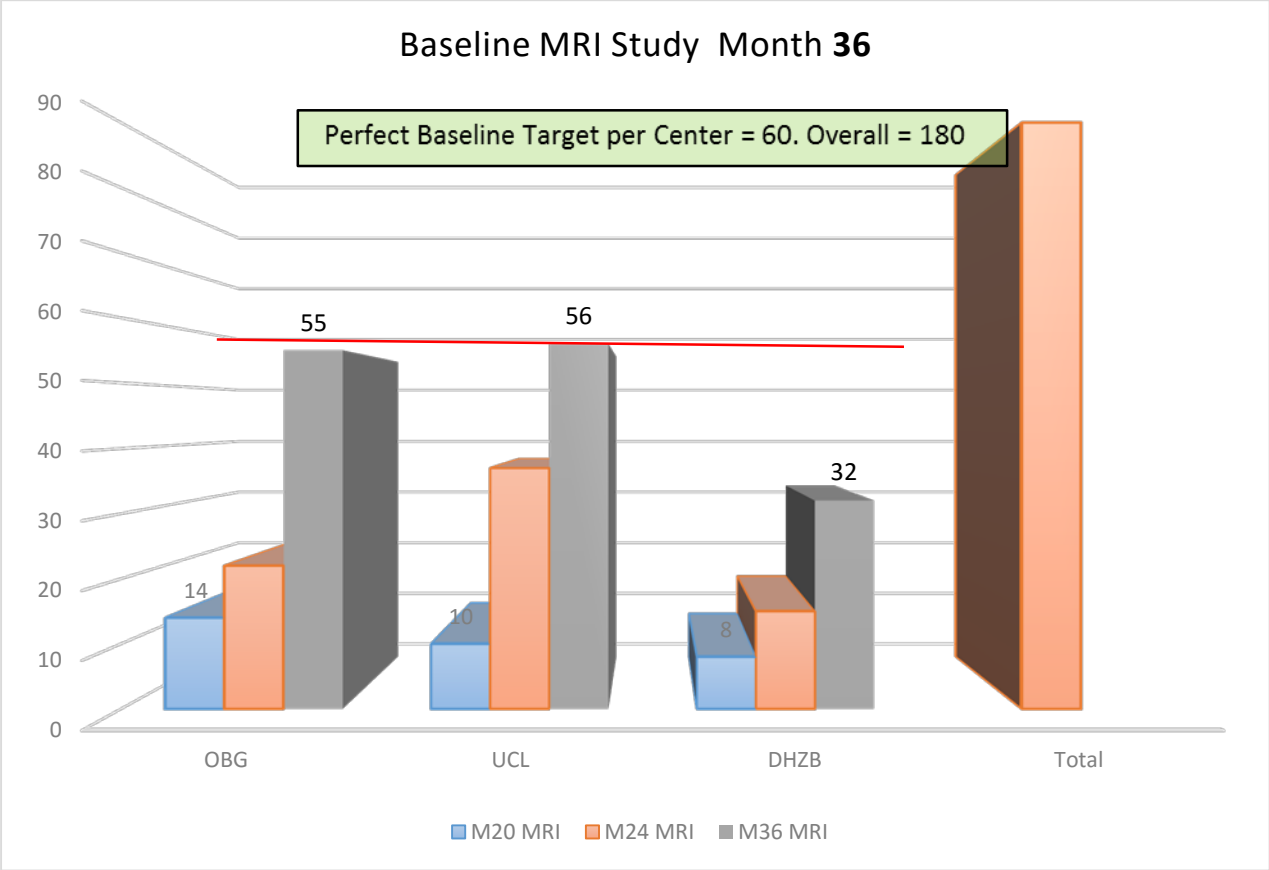
3.2 Baseline Study

Despite the slow start linked to the problems listed in the previous deliverables and to the fact that Berlin joined the study late in the baseline study has basically reached the expected target. There were made 161 echocardiograms (69 OBG, 60 UCL and 32 Berlin) of the theoretical baseline number of 180 (60 per center). About the EKG although they are not all uploaded in the coming weeks should be gathered from the patient files considering that these patients are checked frequently and an EKG is usually performed during clinical controls.

Despite our pessimistic estimates regarding the total number of “realistic performable” MRI, baseline reached MRI number was very good, accomplished in 143 patients (55 OBG, 56 UCL,32 Berlin) out of the theoretical number of 180 (60 per center). Our fears were linked to the following reasons: 1) The number of patients requiring anesthesia is above the number expected at the beginning of the study. 2) Parents’ reluctance for their children to undergo MRI under general anesthesia (i.e. not signing consent) has been more common than expected. 3) Patients unable to undergo an MRI study due to claustrophobia have been more common than expected 4) Lack of economic support for covering family travel to the hospital to perform the additional examinations



All centers have completed or nearly completed the expected amount of ECHO and EKG (60 per center, 180 overall). The number of ECHO performed overall was 161/180 (89%). The majority of EKGs were performed but are not counted in this graph (purple area) because they still have to be scanned and uploaded from the patients file. The target is achieved for Rome and London with Berlin with a quite delay, however, part of this delay is accounted for by their late entry to the project



The number of MRI studies has increased rapidly in the last few months. At the end of the enrollment phase, the target is substantially achieved for Rome and London with Berlin a little behind; however, part of this delay is accounted for by their late entry to the project. Anyway, the overall baseline MRI number (143) is higher than expected showing that the majority of patients enrolled (80%) had an MRI study.

3.3 Re-evaluation Study (Follow up)

Follow up examinations are ongoing and the number is rapidly increasing. The follow up study has some delay due to the general delay that the study suffered at the beginning of the study. Furthermore a significant amount of patients reached study end point or were lost to follow-up. Overall, 67 patients (33%) do not have a complete follow-up complete dataset.

Among these 67, however only 29 (14% overall) were lost at follow up while in the remaining 38 (19% overall) a clinical end point was reached before study end (see graph below). There were four clinical end points:

1) death, which occurred in 3 pts

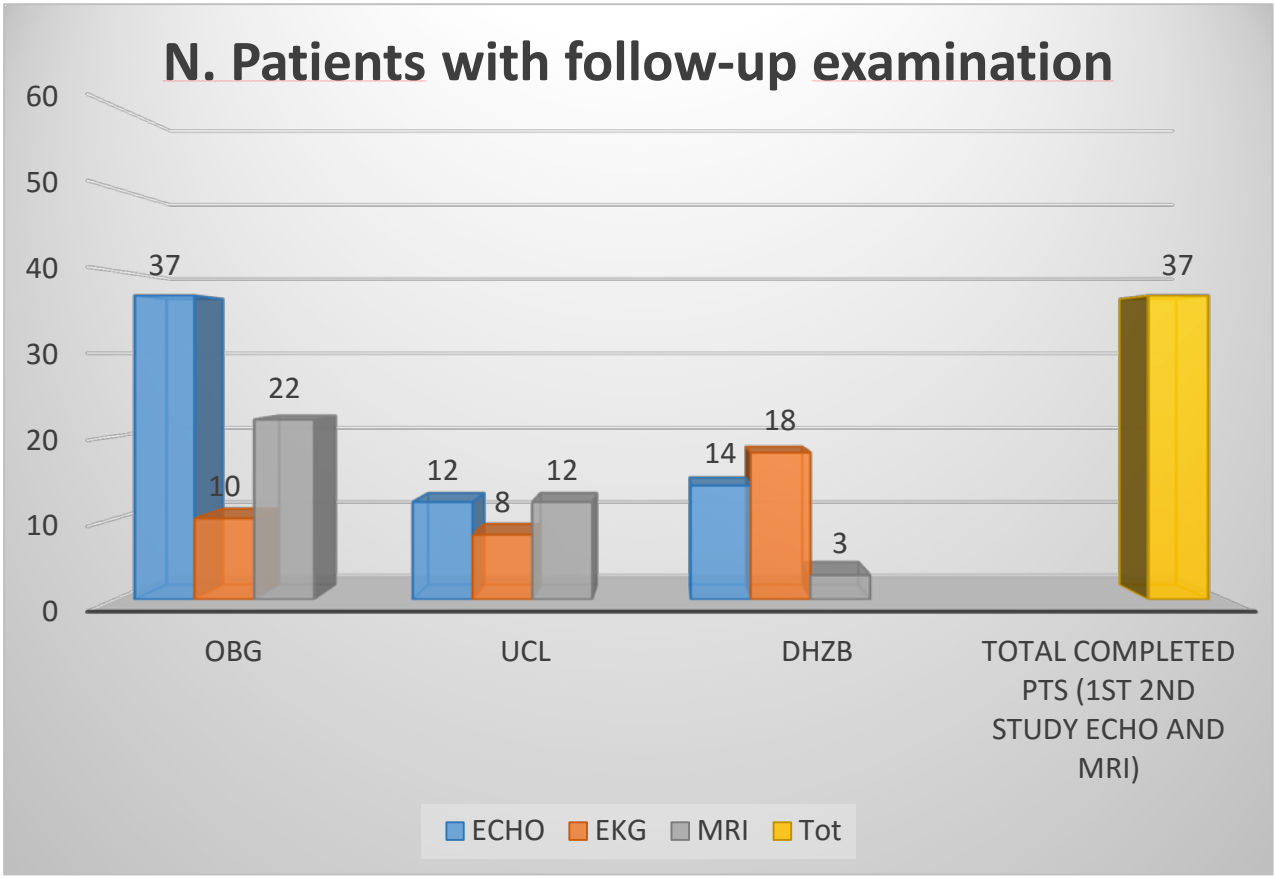
2) transplanted patient (19 pts)

3) patient waiting transplant (8 pts)

4) Patient that had a pacemaker implantation (8 pts) and cannot have a MRI performed.

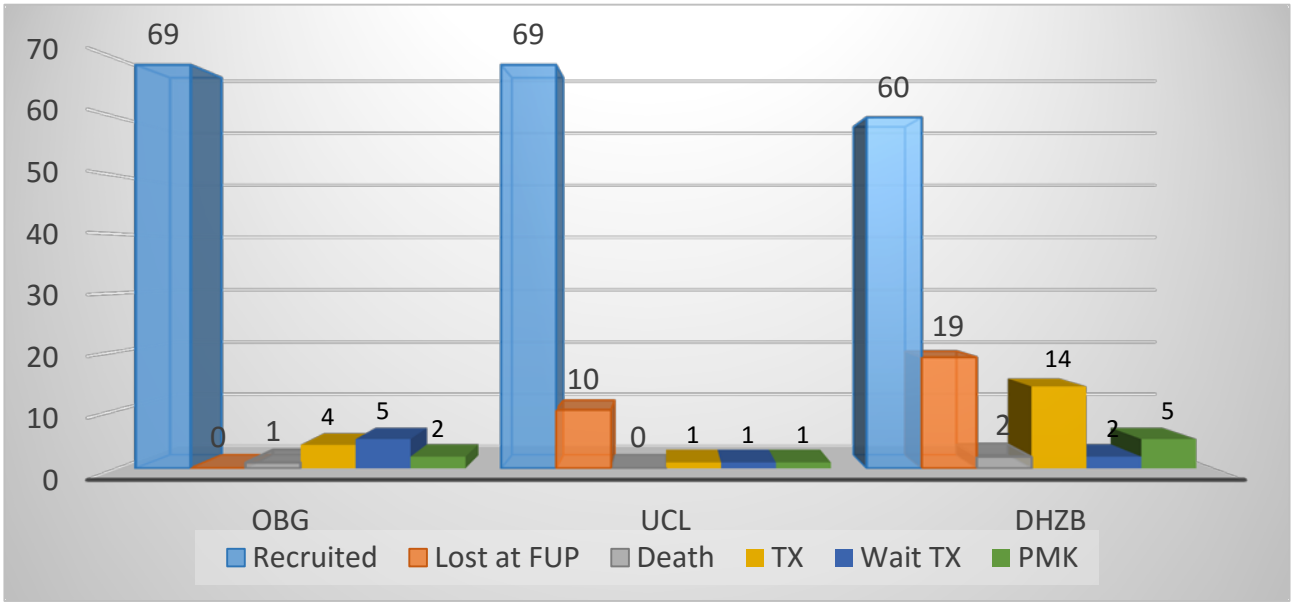
Therefore, we outline that the number of follow up MRI will be significantly lower than the baseline study for the following reason: 1) lost at follow up in less than 15% of the study population. 2) Expected and generic difficulties to perform a MRI in child as described in the chapter of baseline study. 3) MRI not clinically justifiable if performed under general anesthesia (i.e. the risk associated with the procedure overcomes the benefits provided by the examination). 4) Reaching study endpoint.

It is worth to highlight that despite not providing complete datasets, the 38 patients reaching study endpoint represent a source of highly significant data, to both evaluate and validate the mechanical models.

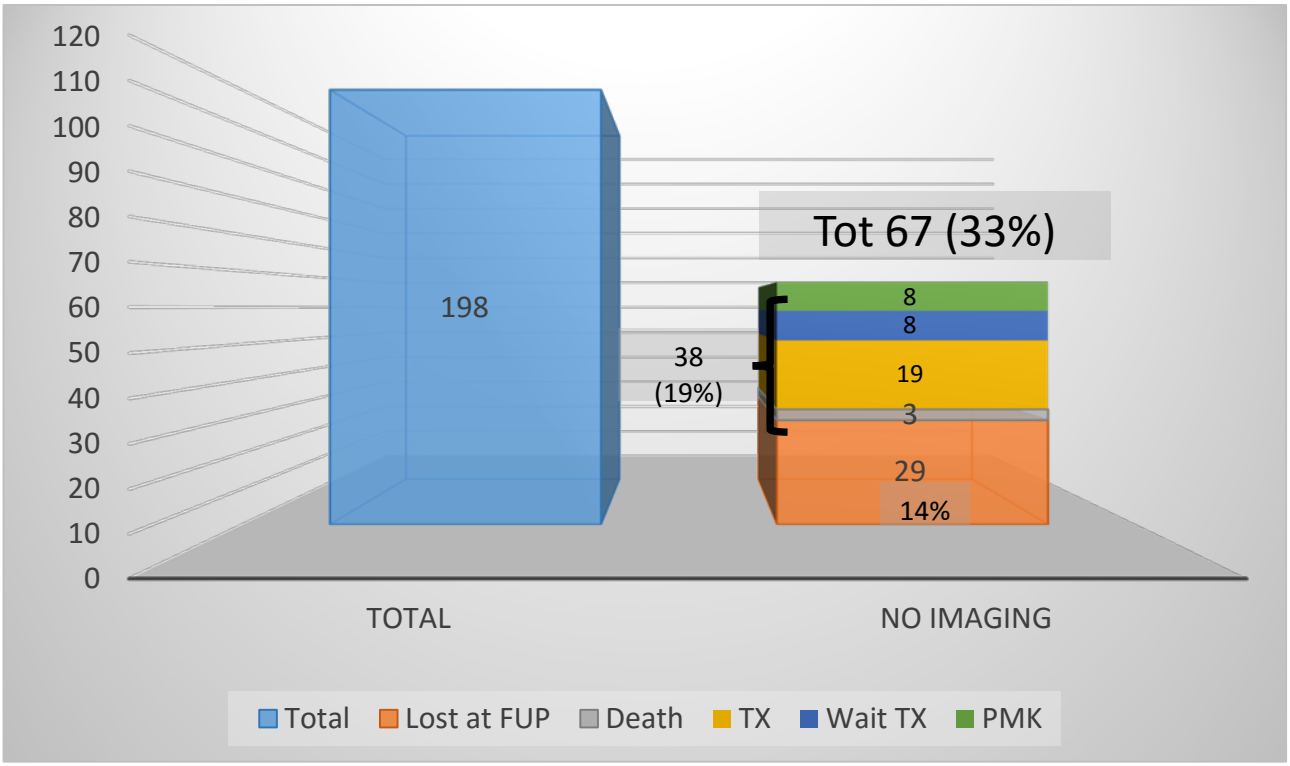


Number of follow up studies in the 3 Centers showing a good progression of follow up study. Up to now there are 37 patients that do have a complete examination (baseline and follow up with echocardiography and MRI)

Lost at Follow up, Death, Transplanted (TX), Waiting TX, PMK implantation



Status by center representing the number of patients that do not have, due to a premature end point, a re-evaluation study. TX = Transplanted, PMK = Pacemaker implantation (patients with PMK cannot have a MRI scan for technical reason)

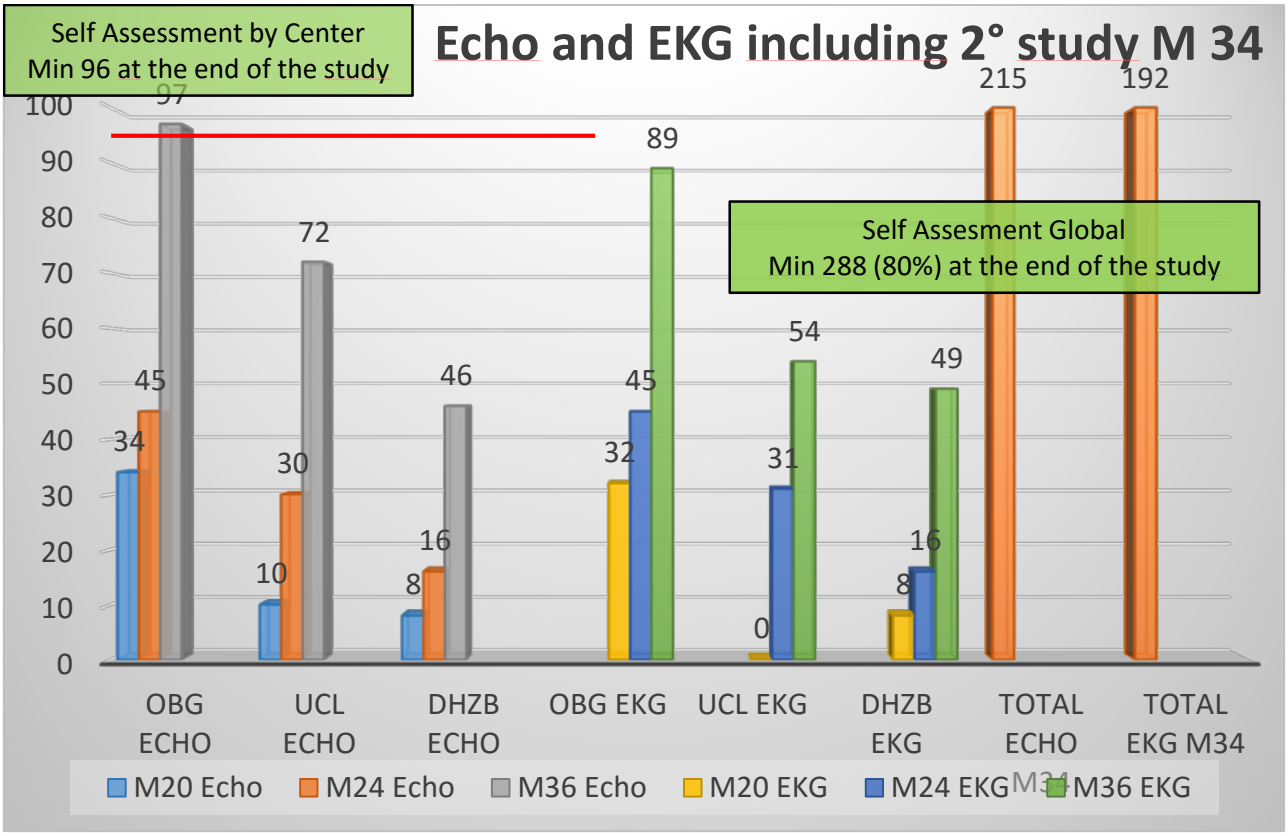


Overall out of 198 enrolled patients, 67 pts (33%) have no follow-up imaging data, of these:
29 pts (14%) were lost at follow up and we do not have any clinical information after the baseline study.
38 pts (19%) reached clinical end point: 3 death, 19 were transplanted, 8 are waiting transplant and 8 had PMK implantation

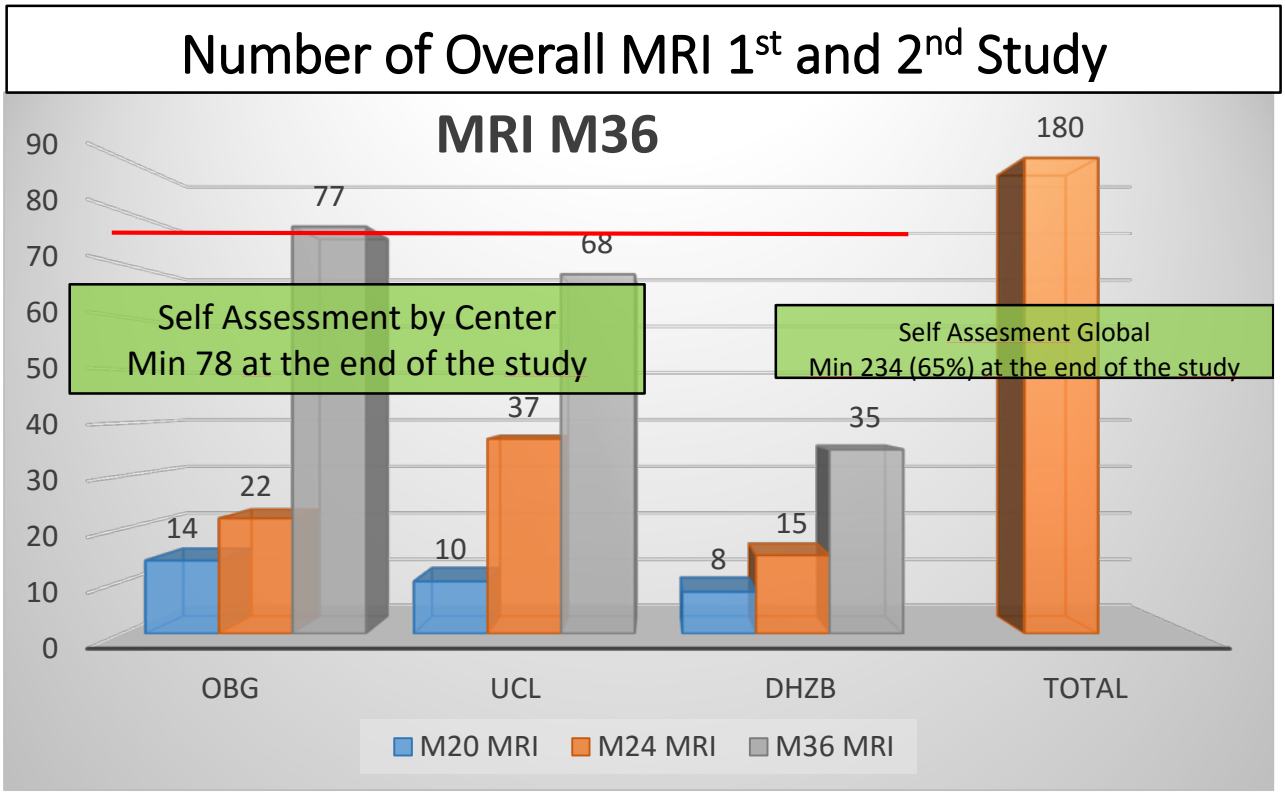
Considering the total number of examination study (first + second) we performed overall 215 echocardiograms (97 OBG, 72 UCL, 46 DHZB). Including patients who reached study endpoint, this number should be increased to 253. We stated in our self-assessment plan that at month 36 we should have a minimum of 96 echocardiographic study per center with a overall target of 288 studies. We are not too far from the target and we believe that by the end of April we will reach and overrun easily the targeted number of missing echocardiograms (i.e. 35).

We performed overall 180 MRI (77 OBG, 68 UCL, 35 DHZB). Including patients who reached study endpoint, this number should be increased to 219. We stated in our self-assessment plan that at month 36 we should have a minimum of 78 MRI study per center with an overall target of 234 studies. The number considering the patients with premature end points is fair good OBG and UCL are almost in target just Berlin has some kind of delay. In UCL and OBG from now to the end of April are already scheduled fair good number of follow up scan (see graph below). Considering this projection at the end of April we plan to have 199 MRI perfomed, with a total of follow-up data for 237.

Number of Overall ECHO and EKG 1st and 2nd Study

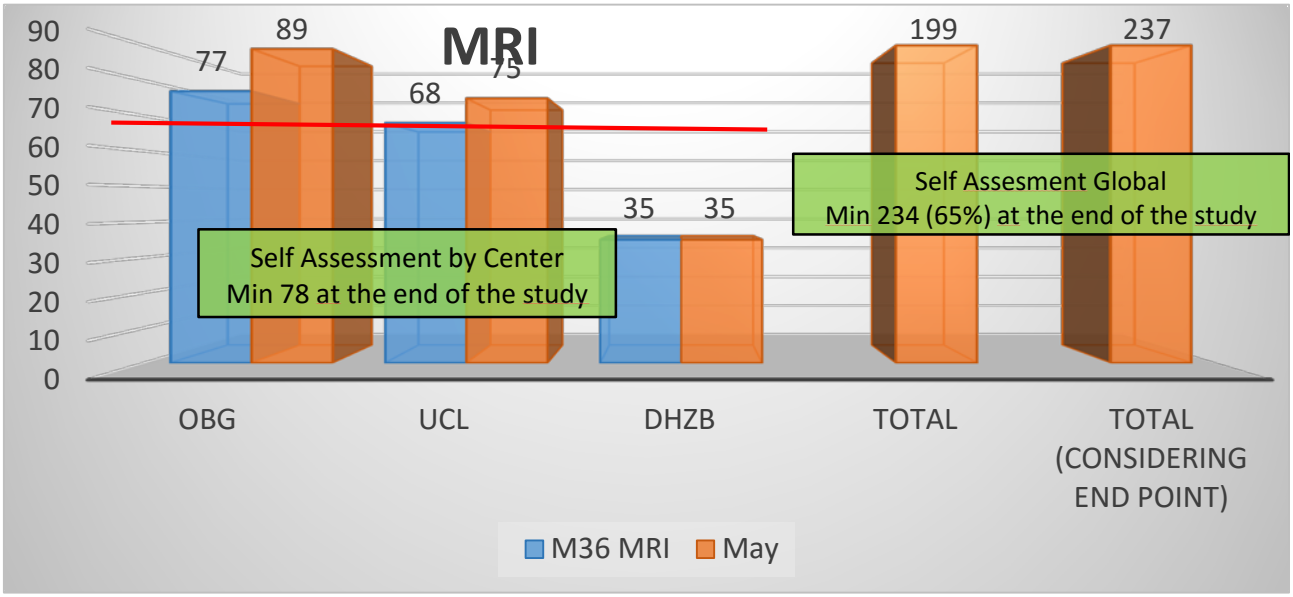


Overall, 215 Echocardiographic studies have been done (97 OBG, 72 UCL, 46 DHZB) and we are not far from the target of our self-assessment plan of 288 (96 per center). The number of echocardiographic examination is increasing fast and by the end of April, we should easily reach the expected number



Overall, 180 MRI studies have been done (77 OBG, 68 UCL, 35 DHZB and we not so far from the target of our self-assessment plan of 234 (78 per center). Considering that 67 patients cannot have a follow up MRI because they reached a premature end point (lost at follow up, death, transplantation, waiting transplant and PMK implantation) the overall number of MRI is quite good

Projection up to May 2016 (already scheduled patients)

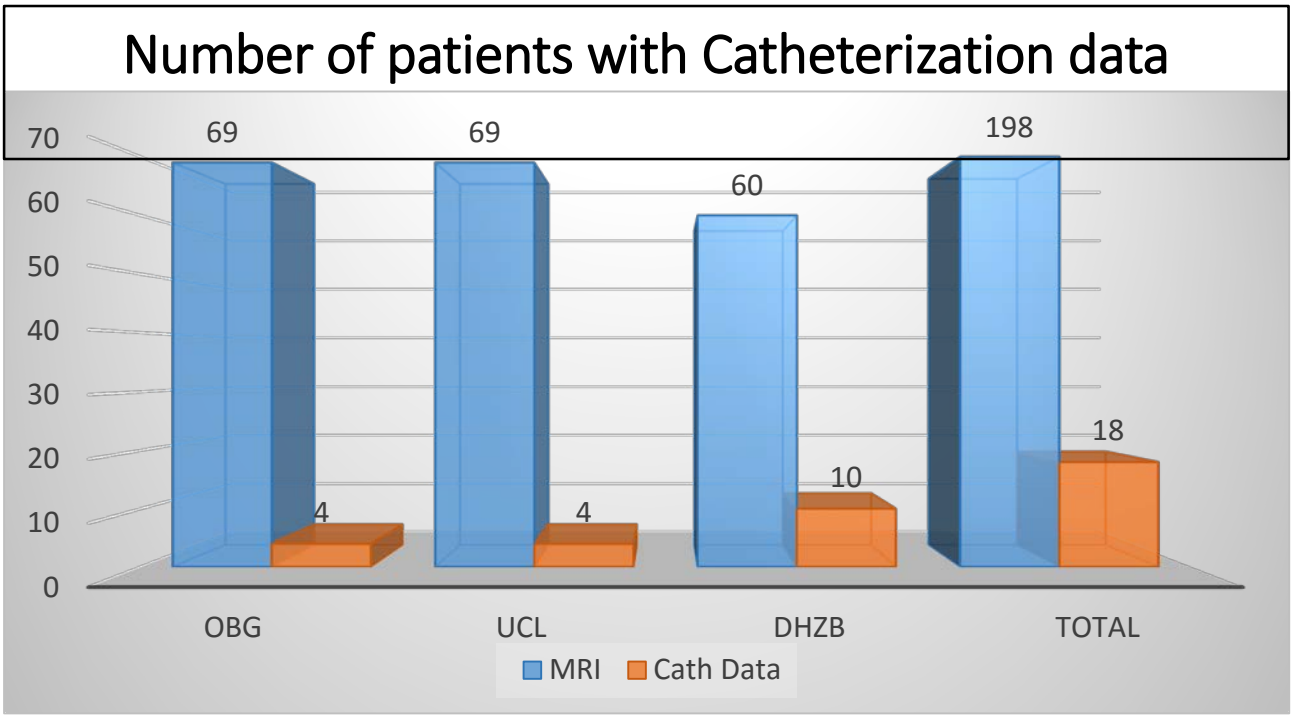


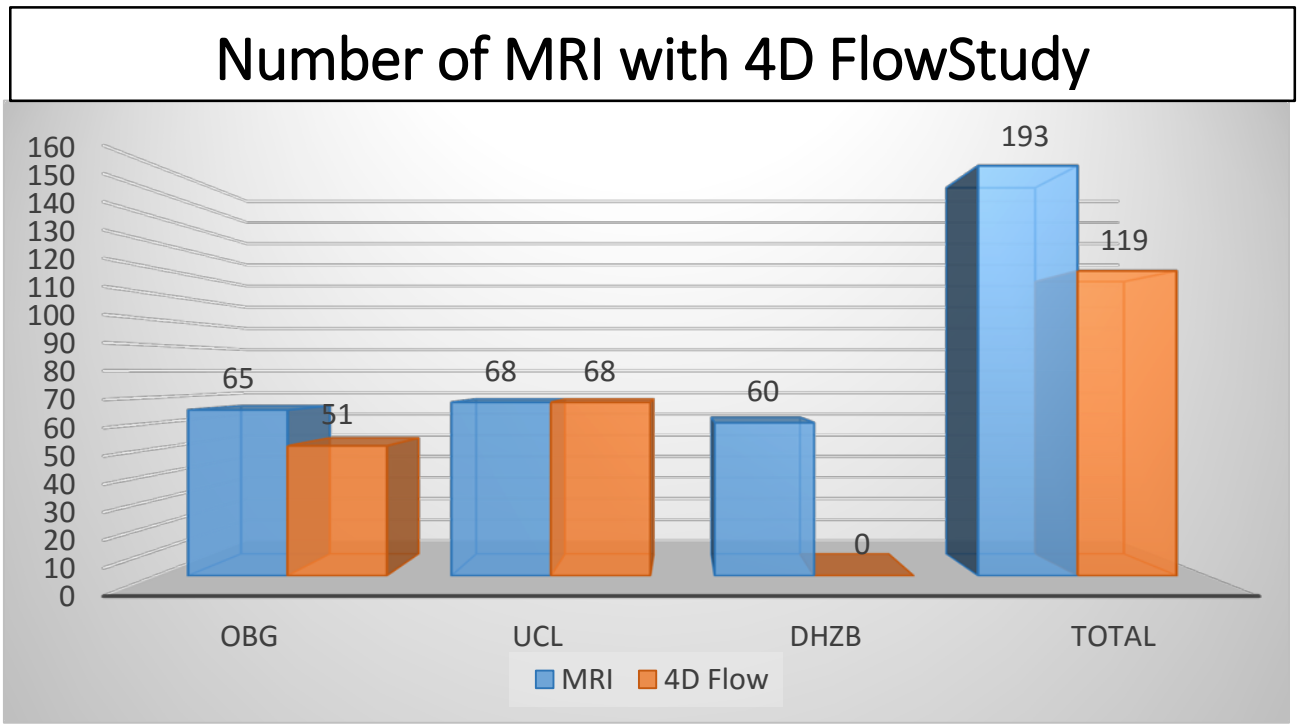
Projection of MRI that will be done up to May 2016. We expect to have a minimum of 199 MRI performed by the end of April.

3.4 Highlights of the study

In our series we have catheterization data of 18 patients (pressure measured directly inside the heart) that are very useful to our technical partners (WP8) to build the hemodynamic modeling of the heart.

Furthermore, since now we have 119 MRI with 4dflow that are essential to our technical partners (WP8) to build the hemodynamic and fluid structure interactions.





4. Data upload and integration into the infostructure [M24 - M36]:

All data have been uploaded in the sharing facilities supplied by infostructure.

The self assessment plan with the lower indicator in red. Task 3.2 is achieved. Task 3.3.1 (echocardiography) is not far from the target and will be reached and overrun by next May. Task 3.3.2 (MRI) the target is almost reached and will be reached by the end of April considering the already scheduled MRI.

WP3 Self-assessment Plan							
Relevant task(s)	Objective description	Measurement process / Unit	Indicator (M24)		Indicator (M36)		**Status**
			Lower	Higher	Lower	Higher	
T.3.2	Clinical data & Routine laboratory test Data collection	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)	**93 %**
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)	**70%** **> 80% up to May 2016**
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)	**60%** **65 % up to May 2016**