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Report on baseline and intermediate follow-up data collection status

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Abbreviations

IGG	Istituto Giannina Gaslini
JIA	Juvenile idiopathic arthritis
OPBG	Ospedale Pediatrico Bambino Gesù
UMCU	University Medical Centre Utrecht
USFD	University of Sheffield

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Introduction

This deliverable is a follow up on deliverable 5.2 and describes the enrolment of patients with juvenile idiopathic arthritis (JIA), baseline data collection, which was completed as per 31 December 2015, and the intermediate follow up of patients enrolled, which is still ongoing.

Baseline data collection

Patient enrolment was started in October 2013 for clinical partners IGG and OPBG, and, due to delays in the obtaining of ethical approval, in March 2014 for clinical partner UMCU. According to the DOW, enrolment should have ended in June 2015, but because the expected number of enrolled patients was not attained yet at that moment, it was decided to postpone the end of the enrolment period until December 2015. In all three centres together, 169 patients have been enrolled (IGG: 74, OPBG: 64, UMCU: 31). At the time of writing of this deliverable, clinical data was available of 165 patients (summarized in Table 1). All numbers and percentages in this deliverable are based on those 165 patients and are therefore subject to minor changes.

Table 1. Baseline data

	***N*=165**
Centre	
IGG, *n* (%)	74 (44.8)
OPBG, *n* (%)	64 (38.8)
UMCU, *n* (%)	27 (16.3)
Demographics	
Female, *n* (%)	123 (74.6)
Age at onset (y), median (IQR)	4.12 (2.28-7.88)
Age at diagnosis (y), median (IQR)	4.43 (2.46-8.23)
JIA onset	
Oligoarticular onset, *n* (%)	112 (67.9)
Polyarticular onset, *n* (%)	44 (26.7)
Psoriatic arthritis, *n* (%)	5 (3.0)
Enthesitis-related arthritis, *n* (%)	2 (1.2)
Undifferentiated arthritis	2 (1.2)
Disease characteristics	
ANA positive, *n* (%)	103 (62.4)
Rheumatoid factor positive, *n* (%)	0 (0)
HLA-B27 positive, *n* (%)	4 (2.4)
Uveitis, *n* (%)	11 (6.7)
Morning stiffness, *n* (%)	93 (56.4)

Disease activity	
Active joints (*n*), median (IQR)	2 (1-5)
Limited joints (*n*), median (IQR)	2 (1-3)
PGA, median (IQR)	5.0 (3.0-7.5)
Parent/patient assessment of pain, median (IQR)	3.4 (1.0-6.0)
Parent/patient assessment of well-being, median (IQR)	3.4 (1.0-5.7)
CHAQ score, median (IQR)	0.5 (0.1-1.0)
JADAS-71, median (IQR)	12.5 (7.9-18.3)
Laboratory	
White blood cells, median (IQR)	8.7 (7.0-11.1)
Neutrophils, median (IQR)	4.5 (3.5-5.5)
Lymphocytes, median (IQR)	3.0 (2.3-4.2)
Haemoglobin, median (IQR)	12.0 (11.4-12.7)
Platelets, median (IQR)	372 (299-467)
ESR, median (IQR)	23 (13-43)
CRP, median (IQR)	0.62 (0.45-2.0)
Medication	
Use of NSAIDs, *n* (%)	120 (72.7)
Use of other drugs, *n* (%)	32 (19.4)

Abbreviations: ANA, antinuclear antibodies; CHAQ, childhood health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IGG, Istituto Giannina Gaslini; IQR, interquartile range; JADAS, juvenile arthritis disease activity score; JIA, juvenile idiopathic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; OPBG, Ospedale Pediatrico Bambino Gesù; PGA, physician's global assessment of disease activity on a 0-10 scale; UMCU, University Medical Centre Utrecht; y, year.

Baseline data collection consists in the collection of clinical data, such as demographics and disease characteristics, which has been collected of all enrolled patients. Likewise, blood samples for routine laboratory examinations (see Table 1) have been collected of all enrolled patients. Furthermore, additional blood samples and, if available, synovial fluid samples are collected for Luminex® analysis. This has been done in 131 (79%) and 56 (34%) patients at baseline, respectively. Next, stool samples are being collected for the analysis of gut microbiota. In all, 116 samples (70% of patients) have been collected at baseline. Additionally, an extensive joint ultrasound was performed in 152 (92%) enrolled patients at baseline. Finally, imaging for the development of the biomechanical ankle model, i.e. MRI and CGA, was only performed in patients with ankle involvement at baseline and above 6 years of age. Since the number of patients satisfying these criteria remained too low, it was decided to start including patients with long-term involvement of the ankle as well. Currently, 26 patients have performed an MRI of the ankle at baseline (14

new-onset patients and 12 patients with long-term involvement of the ankle) and 24 of those have performed a CGA as well. The difference of two patients is due to the fact that no CGAs are performed at UMCU, due to unsurmountable differences in the equipment used at UMCU on the one hand, and IGG and OPBG on the other hand.

Follow up data

According to the protocol, patients need to be followed up every 6 months for 2 years after enrolment. Additional visits are performed if a patient presents with a disease flare. At the time of writing of the report, the first enrolled patients have already completed the protocol.

More specifically, the 6 months follow up visit has been performed for 127 (77%) patients, the 12 month visit for 81 (49%) patients, the 18 month visit for 40 (24%) patients and the 24 month visit for 14 (8%) patients. Additionally, 17 (10%) patients presented with a disease flare.

At each follow up visit, disease status is monitored with respect to a) disease activity according to the internationally accepted and validated Wallace criteria, b) damage according to the juvenile arthritis damage index (JADI) and c) functional ability according to the childhood health assessment questionnaire (CHAQ). Disease status is summarized in Table 2.

Table 2. Disease outcome

	6 months (N=127)	12 months (N=81)	18 months (N=40)	24 months (N=14)
Clinical inactive disease	74 (58%)	56 (69%)	33 (83%)	9 (64%)
No functional limitations	86 (68%)	63 (78%)	36 (90%)	12 (86%)
No damage	117 (92%)	72 (89%)	39 (98%)	12 (86%)

Follow up data collection consists in the collection of clinical data, such as disease characteristics and outcome data (Table 2). Ultrasound needs to be performed at 6 months of all joints that were involved at baseline, and at 12, 18 and 24 months only of the ankles if they were involved at baseline. Blood and synovial fluid for Luminex® and stools for microbiota analysis have to be collected if a patient presents with clinical inactive disease, or a disease flare. CGA has to be performed at 6 and 12 months of those patients with ankle involvement and aged more than 6 years at baseline, whereas the ankle MRI is repeated at 12 and 24 months. Additionally, a lower limb MRI is performed at 6 months. See Table 3 for follow up data collection and Table 4 for the performance of MRI and CGA.

Table 3. Follow up data collection

	6 months (N=127)	12 months (N=81)	18 months (N=40)	24 months (N=14)
Blood sample	49 (39)	50 (62)	20 (50)	6 (43)
Synovial fluid sample	10 (8)	3 (4)	1 (3)	2 (14)
Stool sample	47 (37)	29 (36)	9 (23)	8 (57)

Ultrasound	106 (83)	46 (57)	19 (48)	6 (43)

Table 4. MRI and CGA

	New-onset		Long-term		Total	
	MRI	CGA	MRI	CGA	MRI	CGA
6 months	9	9	10	10	19	19
12 months	7	6	0	0	7	6
24 months	1	-	0	-	1	-

Data processing and analysis

Collected baseline and follow up data are currently being processed and analyzed in various ways. First, the majority of stool samples have been sent to Rome (Lorenza Putignani, WP7). DNA was extracted and qualitatively and quantitatively characterized for next generation sequencing (NGS) gene-targeted metagenomics. DNA has been stored into the OPBG bio-bank. The samples have been included into a DNA subset, also including DNA extracted from healthy children, used as controls (OPBG bio-bank) in an age and gender-matched case-control design. Due to expected difference between Italian and Dutch children, UMCU collected healthy-control stool samples in a 1:1 age and gender-matched design.

In order to analyse the operational taxonomic unit (OTU) content of JIA patients, a targeted approach based on pyrosequencing of the variable regions V1 and V3 of the 16S rRNA locus have been performed. Qualitative and quantitative metagenomic analyses of gut microbiota OTUs at Phylum and Order level have been provided, including the bioinformatic elaborations of JIA gut microbiota type, described by weighted/unweighted UNIFRAC and Bray Curtis algorithms.

At the time of writing, the first analysis aimed at characterizing the JIA samples and confronting them with age and gender-matched healthy controls is under way and will be published as soon as possible.

Next, all CGAs and MRIs have been anonymized and uploaded to the platform. These are currently being elaborated by USFD (WP10) for the biomechanical ankle development and Fraunhofer (WP10) for the automated MRI segmentation tool.

Finally, it was decided that all blood and synovial fluid samples would be analysed at the same time, to reduce the inter-test variability. The first batch of samples will be sent from IGG to UMCU shortly.

Conclusion

Data collection for WP5 is well on its way. Patient enrolment has ended as per 31 December 2015. In all, 169 patients have been enrolled, which is slightly less than expected. However, a further extension of the enrolment period was impossible, since this would provide too short a follow up period for patients enrolled after December 2015. Data of enrolled patients has been collected according to the protocol, meeting the targets set in the revised self-assessment plan. The first data analysis has commenced and more will be executed in the next reporting period, while clinical follow up will continue.