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# Deliverable 5.2

# Report on baseline data collection status

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**Abbreviations**

ANA, antinuclear antibodies;
CHAQ, childhood health assessment questionnaire;
CRP, C-reactive protein;
ESR, erythrocyte sedimentation rate;
HLA, human leukocyte antigen;
IQR, interquartile range;
JADAS, juvenile arthritis disease activity score;
JIA, juvenile idiopathic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs;
PGA, physician's global assessment of disease activity on a 0-10 scale.

## Table of Contents

# Overall summary

- Ethical approval of the clinical protocols has been acquired in all three centres.
- The number of included patients is a bit lower than expected.
- All clinical data has been acquired in the enrolled patients according to the targets.
- The number of MRIs and CGAs is still low, but expected to rise due to a modification to the clinical protocol.

# Task T 5.1: Data Collection Protocols and Informed Consent (M1-3)

## Progress

Data collection protocols and informed consent forms have been finalized, approved and implemented in all three centres. This task is completed.

# Task T 5.2: Clinical Data Collection (M4-40)

## Progress

A general agreement on data collection (what data, which values, codification, etc.) was reached and case report forms were designed accordingly. Data sharing and the methods to make the data anonymous have been discussed with IT partners, OPBG, IGG, UMCU, USFD, URLS and Fraunhofer.

Patient enrolment started in October 2013 for both OPBG and IGG and in March 2014 for UMCU.

## Significant Results

In total, 52 patients have been enrolled (IGG: 27; OPBG: 21; UMCU: 4). Furthermore, there are four eligible patients at OPBG, whose consent will be asked in the following weeks, when they will have their visit at the outpatient department. Baseline data for 46 patients are summarized in table 1.

**Table 1. Baseline data**

| | ***N*=46** |
|---|---|
| **Centre** | |
| IGG, *n* (%) | 25 (54.3) |
| OPBG, *n* (%) | 19 (41.3) |
| UMCU, *n* (%) | 2 (4.3) |
| **Demographics** | |
| Female, *n* (%) | 39 (84.8) |
| Age at onset (y), median (IQR) | 4.04 (2.68-7.59) |
| Age at diagnosis (y), median (IQR) | 4.27 (3.05-8.06) |
| **JIA category** | |
| Oligoarticular onset, *n* (%) | 34 (73.9) |
| Polyarticular onset, *n* (%) | 9 (19.6) |
| Systemic onset, *n* (%) | 0 (0) |
| Psoriatic arthritis, *n* (%) | 2 (4.4) |
| Enthesitis-related arthritis, *n* (%) | 0 (0) |
| Undifferentiated arthritis | 0 (0) |
| **Disease characteristics** | |
| ANA positive, *n* (%) | 24 (52.2) |
| Rheumatoid factor positive, *n* (%) | 0 (0) |
| HLA-B27 positive, *n* (%) | 0 (0) |
| Uveitis, *n* (%) | 4 (8.7) |
| Morning stiffness, *n* (%) | 25 (54.4) |
| **Disease activity** | |
| Active joints (*n*), median (IQR) | 2 (1-4) |
| Limited joints (*n*), median (IQR) | 1 (1-3) |
| PGA, median (IQR) | 6.0 (4.0-7.5) |
| Parent/patient assessment of pain, median (IQR) | 3.3 (0.8-6.0) |
| Parent/patient assessment of well-being, median (IQR) | 3.6 (1.0-5.3) |
| CHAQ score, median (IQR) | 0.50 (0.13-0.84) |
| JADAS-10, median (IQR) | 12.0 (9.0-18.3) |
| **Laboratory** | |
| White blood cells, median (IQR) | 9.5 (7.4-11.5) |
| Neutrophils, median (IQR) | 4.7 (3.6-6.1) |
| Lymphocytes, median (IQR) | 3.1 (2.6-3.9) |
| Haemoglobin, median (IQR) | 12.2 (11.5-13.2) |

| | |
|---|---|
| Platelets, median (IQR) | 391 (294.5-483) |
| ESR, median (IQR) | 20 (12-44) |
| CRP, median (IQR) | 0.45 (0.45-1.8) |
| | |
| **Medication** | |
| Use of NSAIDs, *n* (%) | 34 (73.9) |
| Use of other drugs, *n* (%) | 7 (15.2) |

### Explanation of reasons for failing to achieve critical objectives and its impact

Overall, 52 patients have been enrolled in eight months (month 8-15). This is slightly below what was expected when writing the 1st annual report (60 patients). This is partly due to the delay at UMCU in getting ethical approval, but also because five patients in Genoa, four patients in Rome and one patient in Utrecht were eligible but were not willing to participate for various reasons, e.g. language barrier, people living far from the hospital, people who thought it too much hassle to participate, etc. Finally, there were only two months between the annual report and the current deliverable and we have been unlucky in that not many new-onset patients visited our centres during these months. Consequently, we could not enrol as many patients as we expected.

### Reasons for deviations from the DoW

Delay at UMCU in data collection due to delay of ethical approval, patients declining participation and slightly smaller than expected number of eligible patients.

### Proposed corrective actions

The delay in patient enrolment is expected to be substantially solved during the course of the second year of patient enrolment, because UMCU is now enrolling patients as well. From now on, it will therefore be possible to make use of maximal capacity to enrol patients at all three of these large European paediatric rheumatology centres. We are therefore justified to believe that more patients can be enrolled in the next period.

The number of eligible patients and the number of patients declining participation are beyond our influence and may vary over time.

## Task T 5.3: Routine Laboratory tests (M4-40)

### Progress

Routine blood examination is performed according to the physician's opinion, but always contains a standard set. OPBG, IGG and UMCU discussed which exams from this standard package would be collected for the study and drafted case report forms accordingly.

### Significant Results

Routine blood examination was performed in 97.8% of the enrolled patients. This is above the target of 65%. See table 1 for routine blood examination results.

## Task T5.4: Synovial and Blood Cytokine and inflammatory mediators profile (M4-40)

### Progress

Luminex protocols have been developed, tested and approved by laboratory staff of UMCU and implemented by all three centres. Luminex test batches have been successfully run by UMCU laboratory staff.

As described in the annual report, it was decided to analyse all samples at the same time and end of the study, in order to reduce the inter-test variability. Therefore, no cytokine profile has been made yet. Since Luminex is a semi-automatic test, it is feasible to analyse all samples at once at the end of the study.

Potential cytokines to be analysed in our study, will be drawn from: (a) previous results in JIA patients – this is possible thanks to UMCU's considerable experience with Luminex; (b) the literature; (c) mechanism of action of the cytokines with respect to the pathophysiology of JIA.

### Significant Results

According to the protocol, a Luminex blood sample should be collected at baseline. Synovial fluid is only available if the treating physician decides to perform a joint injection. Overall, blood was collected in 73.9% and synovial fluid in 34.8% of enrolled patients. This is above the target of 50%.

## Task T 5.5: Metagenomic data analysis (M4-40)

### Progress

Stool sample protocols regarding collection, storage and shipment have been developed and approved by laboratory staff at OPBG and implemented by all three centres. Twenty-eight faecal samples from OPBG (11) and IGG (17) patients at the onset of the disease have been collected and stored at -80°C in OPBG's bio-bank. All DNA has been extracted, consistent with metagenomic analysis protocols. The samples have been included into a DNA subset, also including DNA extracted from 29 healthy children, used as controls (OPBG bio-bank) in an age-matched case-control design.

### Significant Results

The faecal samples have been collected, from 28 IGG and OPBG patients. 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 29 "healthy" children, used as controls (OPBG bio-bank) in age-matched case-control 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. The JIA microbiota type has been compared to healthy and obese types.

In total, 30 stool samples have been collected: 65.2% of enrolled patients. This is above the target of 50%.

## Task T 5.6: Image acquisition and clinical annotation (M4-40)

### Progress

The radiologists of OPBG, IGG and UMCU, together with researchers from USFD, URLS and Fraunhofer have discussed, approved and implemented the protocols for MRI, clinical gait analysis (CGA) and ultrasound. Ultrasound has to be performed in all patients, whereas MRI and CGA (see task 5.7) only have to be performed in patients with ankle involvement at baseline.

### Significant Results

Overall, ultrasound has been performed in 91% of patients (above the target of 65%). In total, 3 MRIs have been performed.

### Explanation of reasons for failing to achieve critical objectives and its impact

The number of MRIs and CGAs is lower than the expected number. This is because most of the patients with ankle involvement (indeed, most of all patients) were younger than 5 years and could therefore not perform MRI and CGA. In the annual report we proposed a modification to the clinical protocol to augment the number of eligible patients for the biomechanical ankle model development. This modification has received ethical approval at OPBG and will hopefully receive approval at IGG soon. As soon as it is approved, some more datasets for the biomechanical ankle model will be available.

### Reasons for deviations from the DoW

In the annual report, we already mentioned the fact that dual X-ray absorptiometry has been replaced by an MRI scan of the lower limb.

The low number of patients for the biomechanical ankle model is due to the young age of patients who are consequently unable to perform CGA and MRI.

### Proposed corrective actions

A modification to the clinical protocol was written and already approved at OPBG. It will receive approval at IGG soon.

## Task T 5.7: Clinical gait analysis (M4-40)

### Progress

CGA protocols have been prepared and reviewed by all partners involved (URLS, USFD, IGG and OPBG). The first CGA studies have been performed.

### Significant Results

In total, 3 CGAs have been performed.

### Explanation of reasons for failing to achieve critical objectives and its impact

See task 5.6.

## Reasons for deviations from the DoW

UMCU will not enrol patients for CGA, because the equipment at UMCU turned out to differ from that used at OPBG and IGG in such a way that standardisation was not feasible. However, the expected number of patients enrolled at IGG and OPBG (40 to 60 in total) is deemed sufficient for USFD to prepare the personalised biomechanical models (taking into account what has been described under task 5.6 – corrective actions).

## Proposed corrective actions

The corrective action for task 5.6 is equally applicable for task 5.7.