IDEA-FAST

Identifying Digital Endpoints to Assess FAtigue, Sleep and acTivities in daily living in Neurodegenerative disorders and Immune-mediated inflammatory diseases.

Grant Agreement No. 853981

WP6 – Clinical Validation Study Organisation and Management

D6.5: Mid-term recruitment report of the Clinical Observational Study

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1 Abstract

This deliverable reports on the recruitment situation of the 29-month IDEA-FAST Clinical Observational Study (COS, initially called Clinical Validation Study) after the first 6 months. Up to the date of submission, 265 participants have been recruited, which is encouraging given that circumstances such as different regulations and requirements of local ethics committees (concerning ethics applications) and legal departments (concerning site agreements) led to a delayed start of the COS. In addition, recruitment was markedly hampered by the Corona pandemic. Those teams that were able to recruit report feasible assessment across the visits. Participants are reporting back that the study is meaningful and future-oriented in their view. As far as can be judged with the current data and our own experience as sponsor / cohort leads, the compliance of the participants is excellent and there is a very good retention rate. Nevertheless, the current recruitment rate is still below our target recruitment rate. This is partly because it took considerably longer to implement the required site agreement at some of the recruiting sites due to slow responses from their legal teams. Until this agreement was in place, recruitment could not start at these sites. In order to overcome this slow start, the following adaptations to the initial COS strategy have been initiated: (i) facilitating recruitment of participants at the individual sites, (ii) adding more institutions to the recruiting centres, i.e. departments that are located at already recruiting sites, and (iii) supporting teams from local study sites and inform them as well as possible. With these adaptations, we are optimistic that we will still reach our final target of N=2000 in January 2025. This is supported by the enormous commitment of all people involved, including patients.

2 Introduction

This deliverable reports on the first 6 months of recruitment for the Clinical Observation Study (COS, formerly Clinical Validation Study). The study started in June 2022, a few months later than originally planned, and is scheduled to last 31 months. The current deliverable is due at the end of November 2022 (i.e. only 6 months into the study), whereas the actual mid-term of the COS will only be reached in September 2023. Nevertheless, the preparation of this deliverable and the associated structured review of the start of the study seems very useful to us in order to be able to take stock of the patient recruitment and other aspects of the COS at an early stage and discuss appropriate mitigation strategies where necessary.

The COS forms the core part of the IDEA-FAST project and aims to assess 2000 participants, four times each over 6 months for fatigue and sleep deficits using digital devices, and to compare the parameters extracted from these devices with common clinical parameters, including diary-extracted data. The aim of the study is to define digital parameters for the assessment of fatigue and sleep deficits in 6 different diseases, and preferably parameters that are applicable and valid across the different diseases. Table 1 shows the breakdown of the 2,000 participants into the various cohorts for different diseases and also healthy controls.

Table 1: Clinical Observation Study of IDEA-FAST: Number of planned control subjects and participants who have the diseases of interest.

Participants	n
Parkinson's Disease	500
Huntington's Disease	200
Rheumatoid Arthritis	200
Systemic Lupus Erythematosus	200
Primary Sjögren's Syndrome	200
Inflammatory Bowel Disease	500
Healthy Controls	200

3 Conduction of the COS and progress to date

The COS study started in June 2022, with initially only the sponsor site (Kiel) able to recruit. (See also deliverable D6.4 for details of the ethics approvals package). For all other sites, there were various reasons why site initiation and recruitment could only be achieved at a later date. The length of time it took between site agreement signature and the positive decision of the responsible ethics committee were obtained, the reasons for respective delays and the WP6 team's approach to the given circumstances are presented in this deliverable. The planned start of the COS was already postponed from February 2022 in order to allow further interaction between the IDEA-FAST consortium and EMA and to obtain a Qualification Advice for the COS assessment protocol. This process was interposed between the Feasibility Study phase and the COS phase, and led to a generally delayed start of the COS as the ethics application had to be adapted to the outcome of the EMA feedback. These latter aspects are not part of this deliverable.

3.1 Research Ethics Approvals

As of October 2022, the current study protocol version V2.0 has been approved by the ethics committees in all involved countries. Table 2 shows the ethics submissions and approvals in all participating countries.

Table 2: IDEA-FAST COS: Submission and approval dates of the local Ethics Committees.

Country	EC Submission	EC Approval
GER (Kiel)	20Oct2021: Submission of COS protocol V1.0 **24Apr2022: Submission of COS protocol V2.0**	03Nov2021: Favorable Opinion for COS V1.0 **26Apr2022: Favorable Opinion for COS V2.0**
GER (Münster)	21Jan2022: Submission of COS protocol V1.0 **23May2022: Submission of COS protocol V2.0**	18Feb2022: Favorable Opinion for COS V1.0 **03June2022: Favorable Opinion for COS V2.0**
NOR	11Jan2022: Submission of COS protocol V1.0 08Mar2022: Additional information provided to EC **06May2022: Resubmission of COS protocol V2.0**	28April2022: Favorable Opinion for COS V1.0 **25May2022: Favorable Opinion for COS V2.0**
AUT	19Jan2022: Submission of COS protocol V1.0 **13June2022: Resubmission of COS protocol V2.0** **22July2022: Resubmission**	10thFeb2022: EC provided preliminary vote for COS V1.0 with conditions precedent **EC response: mid of July 2022** **16Aug2022: Favorable Opinion for COS V2.0**
ITA	Jan28th: Submission of COS protocol V1.0 **12May2022: Resubmission of COS protocol V2.0**	31Mar2022: Favorable Opinion for COS V1.0 **07June2022: Favorable Opinion for COS V2.0**
IRE	07Feb2022: Submission of COS protocol V1.0 **02June2022: Submission of COS protocol V2.0**	22Feb2022: Favorable Opinion for COS V1.0 **25July2022: Favorable Opinion for COS V2.0**
GBR	18Feb2022: Submission of COS protocol V1.0 (assessed for REC proportionate review) **29Apr2022: Resubmission of COS protocol V2.0**	30Mar2022: Provisional Opinion for COS V1.0 **08June2022: Favorable Opinion for COS V2.0**
PRT	23Mar2022: Submission of COS protocol V1.0 **25July2022: Resubmission of COS protocol V2.0**	10May2022: Favorable Opinion for COS V1.0 **02Sep2022: Favorable Opinion for COS V2.0**
ESP	30Mar2022: Submission of COS protocol V1.0 **29Apr2022: Resubmission of COS protocol V2.0**	8Apr2022: EC was requesting further information **04May2022: Favorable Opinion for COS V2.0**
POL	31Mar2022: Submission of COS protocol V1.0 **11May2022: Resubmission of COS protocol V2.0**	04May2022: Favorable Opinion for COS V1.0 **13June2022: Favorable Opinion for COS V2.0**
NDL	**31May2022: Initial submission with COS V2.0** **12Aug2022: Resubmission to the EC queries** **23Sep2022: Resubmission to the EC queries**	14July2022: EC response with some queries 13September2022: EC response with some queries **17Oct2022: Favorable Opinion for COS V2.0**

The first ethical submission was performed with the study protocol V1.0 on 20th October 2021 in Kiel, Germany and the favourable approval was received on 3rd November 2021. Subsequently, submissions in the participating countries took place between January and May 2022, upon availability of all documents necessary to complete the submission packages. Although it had been planned to start the submissions in the UK and the Netherlands in December 2021 (due to the highest recruitment targets in these countries), the signature of the agreement between the Sponsor and ECRIN took longer than expected, which subsequently affected the contracting and starting the activities of the involved ECRIN partners. In the UK, the submission was performed on 18th February 2022. A provisional opinion on protocol V1.0 was given by the ethics committee in March 2022, requesting further modifications before a final opinion could be issued. The queries were addressed in close collaboration between the Sponsor, Principal Investigators (PIs) and Clinical Trial Units (CTU), and involved a transfer of the application to another ethics committee with earlier available meeting dates to expedite the review. The resubmission was performed on 29th April 2022 with the study protocol V2.0, and a favourable opinion was provided on 8th June 2022. In the Netherlands, due to pending documents and negotiations of the draft site agreement required for ethics submission, the initial submission was performed from the beginning with study protocol V2.0 on 31st May 2022. The first and second response from the ethics committee with substantial queries was received in July and September 2022, respectively, which were addressed in by the Sponsor, PIs and CTU. Finally, on 17th October 2022, a favourable opinion was provided, and consequently local approvals were received in November 2022.

With regard to the other participating countries, based on the final submission strategy and after having received favourable opinion for study protocol V1.0 in Kiel, the submission started in all participating countries with the protocol V1.0, followed by an amendment submission after having received and

implemented the EMA feedback. Initial submissions in Spain, Poland and Portugal were performed in March 2022, upon availability of all documents necessary to complete the submission packages. Protocol V1.0 was approved by the ethics committees in Germany, Ireland, Italy, Poland, Portugal and Norway (after provision of additional documents) between November 2021 and May 2022. In Spain and in Austria, after receiving the first feedback from the ethics committee, the resubmission was performed with study protocol V2.0. In countries where a favourable opinion for study protocol V1.0 was available, an amendment submission/resubmission was necessary to obtain approval for the study protocol V2.0.

3.2 Site Agreements

In November 2021, a first draft of the site agreement was sent out from the Sponsor to the study sites. It was revised in March 2022 (the financial part was elaborated and some more details added) and sent out again. Starting from there, reminders were regularly sent out to the sites asking for feedback. The negotiation process went quite smoothly for most sites. However, some sites had queries regarding the indemnity allowance, and after that they requested the Controller Processor Agreement to be in place (currently in signature process). Other sites had requests regarding data protection and wanted to have paragraphs added from an agreement that is usually used in their country. The communication was very tedious because e-mails were often only answered with much delay.

The negotiation process with some UK sites was also difficult at the beginning as they were only able to review the site agreements after confirmation of approval from the UK Research Ethics Committee and the UK Human Research Authority (HRA) approval, which was obtained on 8th June 2022 (the official study start was on 1st June 2022). There were also requests to see the IRAS full Ethics Submission package and they had several questions regarding a specific document called SoECAT which is not in use for IDEA-FAST because the funding arrangement required a tri-partite site agreement between the Coordinator, Sponsor and the study site. As tri-partite site agreements are not the “standard” practice, many R&D departments of the UK study site were unfamiliar with it.

Another issue was the slow response of some legal teams coupled with staff turnover at a few sites during the negotiation process, with little or even no information communicated to the new staff member.

Despite these difficulties, 16 out of 19 planned sites have now signed the site agreement, not counting Kiel (UKSH) for whom a site agreement is not required. These are as follows:

- Münster, Germany
- Newcastle (UNEW), UK
- London (Queen Mary, QMUL), UK
- London (St, Marks), UK
- Leeds, UK
- Devon & Exeter, UK
- Manchester (Northern Care Alliance NHs Foundation Trust), UK
- Glasgow, UK
- Rotterdam (EMC), Netherlands
- Leiden (LUMC), Netherlands
- Stavanger, Norway
- Innsbruck, Austria
- Madrid, Spain
- Warsaw, Poland
- Lisbon, Portugal
- Brescia, Italy

Two of the remaining sites should be completed shortly, while for the third, the partner concerned has changed to a different local recruitment site, requiring negotiations of the site agreement to be restarted.

3.3 Recruitment according to the batch principle

The recruitment was planned according to a "batch" principle. This has the advantage of requiring 20% fewer reusable digital devices used for the individual assessment. The device package for each participant costs around 2,000 Euros and consists of a bed sensor, a smartphone and a wearable motion sensor). The batch principle envisaged that study participants are recruited and then measured in three discrete batches. Each recruitment period would occur within a defined period of 3-5 months, with the participant being provided with the devices and instructions during a first visit and then assessed over a follow-up period of 24 weeks (Figure 1).

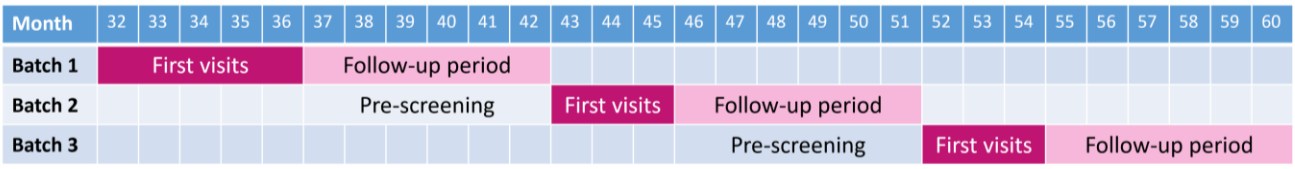

Figure 1: Recruitment strategy of the IDEA-FAST COS according to the batch principle.

Since it is planned to have three batches, and each centre must recruit around one third of the targeted local study population per batch. This has worked well in some study centres (e.g. Kiel, Brescia, Stavanger). At other study centres, however, it has been shown that this strategy is difficult to implement, especially when they were affected by a delayed start (see above). Both the accelerated recruitment in a short period of time, as well as the lack of possibility to continue recruiting afterwards during a phase of 6 months, have been perceived by these centres as an obstacle to successful recruitment.

3.4 COS communication organigram and focus

During the conduct of IDEA-FAST COS we have established 4 working groups to facilitate effective execution of the study, which all advance the processes within the assigned COS aspects:

- COS daily business management and trouble-shooting (Team B, lead Kiel (Sponsor))
- Data management and analysis (Team C, lead WP4, 5 and 7)
- Cohort internal communication (Team D, lead respective cohort leads)
- COS formal study management (Team E, lead ECRIN and Kiel CTU)

In addition, the leads of these task forces are part of the COS Oversight Team (Team A), which meets at monthly intervals. This makes it possible to discuss important results, questions and challenges from teams B to E in the overall context. In our experience so far, the structure works extremely well. Important insights have been drawn from it, which are reflected in the mitigation strategies proposed below (see discussion part).

4 Recruitment over the last 6 months

Figure 2 and Table 3 provide detailed information on the recruitment progress to date. Based on the batch principle, in order to be on track to meet our target, we would expect to have recruited 550 study participants into the IDEA-FAST COS up to 30th November 2022 (red line in Figure 2). In fact, 265 participants have been included in the study up to the cut-off date.

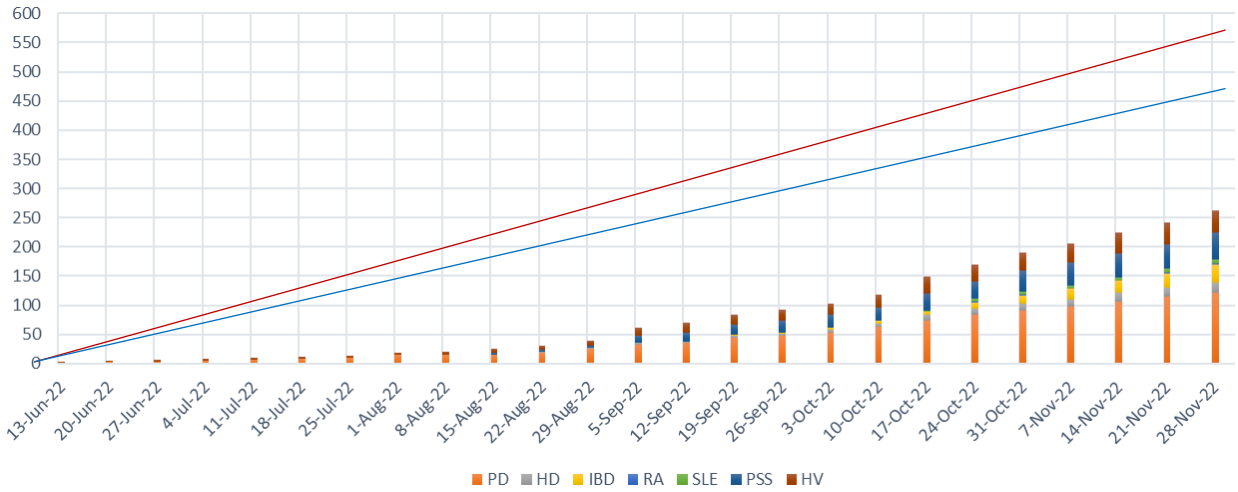

Figure 2: Recruitment progress of the IDEA-FAST COS over the course of the first 6 months, broken down by single cohorts (different colours). The red diagonal line shows expected recruitment based on batch strategy with expected N=550 at end of Nov 2022. The blue diagonal line shows expected recruitment based on continuous recruitment strategy (see section 5) with expected N=453 at end of Nov 2022.

Table 3: Clinical Observation Study of IDEA-FAST as of 30th November 2022: Number of already recruited control subjects and participants who have the diseases of interest.

Participants	n
Parkinson's Disease	121
Huntington's Disease	17
Rheumatoid Arthritis	1
Systemic Lupus Erythematosus	7
Primary Sjögren's Syndrome	48
Inflammatory Bowel Disease	32
Healthy Controls	39
Total	**265**

5 Discussion, including mitigation strategies

Six months after the start of the IDEA-FAST COS, we have been able to recruit 265 study participants in 11 study centres despite difficult circumstances (delayed start while awaiting EMA qualification advice and implementation of this in the current COS study protocol; slow progress on finalising some site agreements; marked restrictions due to the COVID-19 pandemic; and other reasons described below). All study centres now have positive ethical approval, and only 3 site agreements are still outstanding. Some study centres were able to recruit more than expected over the first 6 months. The general feedback from the study centres regarding the complexity of the assessment is consistently positive: the participants find the content of the study meaningful and forward-looking, and can tolerate the number of visits and assessments well. The devices used in the study are well accepted by the study participants, and minor side effects occur only very rarely (e.g. skin irritation with the move monitor attached to the lower back).

Nevertheless, we are behind expectations in terms of recruitment figures. Therefore, in order to overcome this shortfall and minimise any further risks during the remainder of the COS, we plan to incorporate the following modifications concerning our COS recruitment strategy:

1. From January 2023, the sites will be free to recruit according to either the batch principle or continuously, as they prefer. The Steering Committee has already agreed to the purchase of 30 additional device packages that are necessary to cover the need for additional device packages for this strategy, and the order has been placed. With continuous recruitment, the target rate over the first 6 months is decreased (as shown by the blue line in Figure 2) since recruitment is not halted for a period of time, as with the batch recruitment. Our calculations show that, based on continuous recruitment - and sufficient device packages - the target of 2000 participants by January 2025 is well within reach. Of course, a number of variables have to be taken into account, e.g. that the sites that are currently recruiting well will potentially reach their target earlier and that other sites will also have to recruit continuously and consistently.
2. As it turned out during the first months, recruitment within a cohort works particularly well when the cohort lead organises at least one short meeting every 2 weeks to discuss the respective situation at the local sites, so that cohort-specific issues can be addressed directly and without complications. Therefore, all cohort leads have been encouraged to hold cohort meetings at an appropriate frequency.
3. Discussions with the local study teams have shown that prompt feedback to the participants on the quantity and quality of the data collected is perceived as motivating. This could therefore have a positive effect on recruitment numbers. We therefore assume that a detailed discussion in the area of data check is required, and we have started an intense discussion about this with WPs 3, 4 and 7. It turned out that this process is particularly complex, as on the one hand different types of data are collected (clinical, patient-reported, sensor-derived passively and actively collected digital parameters), and on the other hand the feed of the data into the final database is done via different pipelines, which all have to fulfil different requirements. From our side, the urgency of solving this problem as soon as possible has been communicated and we will conclude this process with the other WPs as quickly as possible.
4. We are looking for additional departments that could recruit, in a first step within the institutions that are already recruiting as sites for the IDEA-FAST COS (e.g. rheumatology departments of sites that so far “only” recruit IBD patients. Contacts have been established already (e.g. in UKSH Kiel / Lübeck and in Brescia). If such departments show interest, they could start recruiting in an uncomplicated way in due course (since no additional site agreement will be required).

5. The COS support and trouble-shooting meetings (Team B, see above) have proved to be very well received. They enable the teams of the local sites to share practical questions that more or less necessarily arise during the assessment of the first study participants with the investigators on the sponsor site and other sites in an uncomplicated way, and to come to efficient solutions. We will continue to offer this service and encourage all new sites that are starting recruitment to participate in this exchange on a regular basis.
6. In the UK, the IDEA-FAST COS has been adopted into the NIHR portfolio (https://id.nihr.ac.uk/). This makes it easier to open new sites within the UK.

6 Conclusions

This deliverable reports on the recruitment situation of the 29-month IDEA-FAST COS after the first 6 months have been completed. Despite difficult circumstances and a not yet full complement of recruiting centres, it has been possible to recruit 265 participants during this period. The recruiting study teams report basically “easy-to-perform” assessment across all visits. The participants assess the study as meaningful and future-oriented, carry out the assessments conscientiously - as far as can be seen at present - and a good compliance over the entire individual course of the study as well as a good retention rate are apparent. Nevertheless, the required recruitment rate is higher than the current recruitment rate. We have therefore initiated a number of adaptations to the initial COS strategy, that aim at: (i) facilitating recruitment of participants at the individual sites (continuous instead of “batch” recruitment); (ii) adding more institutions to the recruiting centres, i.e. departments that are located at already recruiting sites; and (iii) supporting teams from local study sites and informing them as well as possible (e.g. through high frequency meetings with the cohort leads, and prompt feedback of uploaded data quality). We will consistently monitor the effect of these steps, also in connection with future recruitment figures, over the course of the next few months, and will evaluate in the meantime further strategies to improve the recruitment situation if the actual ones are not as effective as expected. It remains to be said, however, that we are very positive about the future of IDEA-FAST COS due to the experiences we were able to gather in the first six months from local study teams, from our participants, but also from other stakeholders in the wider circle of the organisation of this study.