D4.2 Ethical approval including all amendments

Mobilise-D

Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement

Grant Agreement No. 820820

[WP4 – Definition and validation of digital mobility outcomes against clinical endpoints]

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1 Abstract

This document addresses the status of ethical approval and amendments for the **clinical validation study (CVS)** within Mobilise-D. Partner 01 (UNEW), as the principal sponsor, submitted their ethical application on Nov. 12th 2020 and received provisional approval after minor changes on Dec. 16th 2020, (IRAS 289543). This ethical approval applies to all UK sites (Newcastle, Sheffield, London). In line with the project plans the other sites are now asked to submit their local proposals in an identical format.

The other Non-UK sites either have submitted in December (Stuttgart, Kiel, Trondheim) or will submit their proposals early in January 2021 (Erlangen, Großhansdorf, Zürich, Athens, Milano, Leuven, Barcelona, Montpellier, Tel Aviv).

The Ethics Committee of the Medical Faculty, Kiel University approved the study on the 20th December 2020.

Individual requirements of the local ethical commissions (LECs) at the sites are addressed by the sites individually. All applications are uploaded to the project file store. Information on the current submission status of each sites is detailed in the attached spreadsheet.

Individual submission schedules of the sites allow real time feedback and are expected by Feb 2021 based on prior submissions.

Possible amendments will be presented to LECs in Feb 2021 or March 21. Currently this information is being collected, e.g. planned embedded PhD projects.

Based on the ethical approval for the Technical Validation Study (TVS), no major risks for the planned study start are expected.

The publication of the study protocol as an open access publication is in preparation.

2 Introduction

The Mobilise-D consortium has developed and is planning to implement a long-term digital mobility assessment in several cohorts of patients suffering from chronic diseases.

The aim is to demonstrate that the measurement of digital mobility outcomes (DMOs) is feasible and acceptable for patients. The DMOs are expected to allow a valid and clinically relevant **monitoring** of patients detecting clinically meaningful change across the differing cohorts covering a broad age range.

The monitoring in representative patient populations is relevant to describe trajectories of change such as spontaneous improvement or more frequent mobility decline. This is a ground truth needed to interpret changes induced by pharmacological interventions.

The consortium is expecting that DMOs will not replace current standards of supervised clinical outcome assessments (COAs) and patient reported outcomes (PROs). DMOs are a unique method to assess physical mobility and physical activity in patients, which currently are based on subjective report that is often influenced by reporting and recall bias.

Furthermore, it is expected that DMOs can successfully **predict** relevant clinical events such as falls, hospital and care home admissions.

Secondary relevant aspects are the exploratory analysis of DMOs for future stratification of subgroups, prognostic tools and safety monitoring of pharmacological and non-pharmacological interventions.

Ultimately, it is expected that DMOs provide a more accurate method to develop, assess and qualify new medicines or repurpose existing treatments.

The first stage of this project was the **technical validation study (TVS)** of a device-algorithm pair to measure real-world walking speed, walking bout duration and distribution, walking distance, uptime and other DMOs such as variability and other qualitative parameters of walking. The TVS was also an investigation into the usability and acceptability of the device and the data collection methods from the perspective of the participants and researchers.

The second stage of the project–the CVS–aims to use this technically validated device-algorithm pair to link DMOs to clinical endpoints for regulatory approval and clinical endorsement.

Four clinical cohorts which represent conditions that are common in high income countries are among the most prevalent conditions for life expectancy with considerable disability and thereby reduce the health span of many European citizens. The aim of the consortium is to recruit representative clinical populations suffering from a common neurodegenerative condition affecting mobility (PD), the most prevalent chronic respiratory disease (COPD), the most prevalent neuro-inflammatory condition (MS) and the most severe fall related injury of older persons (PFF). Sarcopenia and frailty will be studied in subgroups of the cohorts mentioned above.

Clinical sites are distributed across regions from ten different countries (Belgium, France, Germany, Greece, Italy, Spain, UK, Switzerland, Norway, Israel). They represent not only different geographical areas but also different health care systems such as NHS and non-NHS systems.

The academic clinical sites have been selected based on their pre-existing and sustained expertise in recruiting, assessing and following patients in the diseases that are examined. All sites have a track-record of conducting observational studies. They have participated in pharmaceutical and non-pharmaceutical intervention trials. Most sites also have extensive experience with sensor-based assessments of mobility.

As another dimension, all sites have a key interest in the involvement of patient and family carers in study design and conduct. They have been involved in public debates of resource allocation, balanced patient advocacy and ethical discourse with political planners and health care funders.

This deliverable covers the process rationale and status of ethical applications across sites.

3 Results

The current status of ethical applications is shown in Appendix A. After submission of the ethical application for all UK sites led by UNEW, all other non-UK sites have submitted or will submit their ethical application with reference to this first application, using the same protocol. The main ethical application by UNEW has been approved provisionally by the responsible LEC on 16.12.2020. In addition, all sites include their cohort-specific assessment procedures into their application.

The Ethics Committee of the Medical Faculty, Kiel University approved the study on the 20th December 2020, see Appendix B.

As of Dec 30th 2021, not all sites have submitted their applications due to the necessity for some sites of including a sponsor agreement to their submission. This agreement is still processed with legal offices at most sites. Some sites require the agreement to be signed

prior to submission to ethics. The status of BREXIT also has an implication for the implementation of the CVS and may impact on the site agreements required.

4 Discussion

The study protocol and manual were refined and finalized in September 2020. The structure, timeline, inclusion and exclusion criteria and most of the assessments were confirmed with the original version submitted with the DoA. There were some changes resulting from the interactions with the different bodies of the European Medicines Agency (EMA), the advisory board and some changes resulted from internal discussion to streamline the process after piloting the baseline assessment to avoid overburdening of participants. Major changes were consented within and between the cohorts. The scoping review and regulatory review (see D 4.1.) was used to confirm and consolidate the planning process.

The Minimum Data Set (MDS) had only minor changes such as the introduction of the Groll Functional Comorbidity Index instead of the Charleston Comorbidity Index as it is superior for the identification of conditions leading to mobility disability (vs. mortality). The use of assessment tools for co-variates / confounders was minimized to avoid overburdening and fatigue during the assessment process. Examples are the use of validated short forms to assess fear of falling, depression and cognitive deficits. For some cohorts the full instruments were moved to the cohort specific assessments.

The discussion with the Scientific Advisory Working Party of the EMA led to a number of refinements that has major influence on the protocol. Based on ongoing and future drug development it was decided to adjust the inclusion criteria of three of the four cohorts.

For the **MS** cohort it was decided to now include relapsing and (primary and secondary) chronic progressive forms to capture the mobility trajectories for both forms and the transitions of relapsing trajectories to secondary progressive courses in particular.

For the **PD** cohort it was decided to include Hoehn and Yahr stages 1-3 (instead of 2-4). This is meant to monitor patients that might be eligible for disease modifying drug trials in the future. H+Y 4 were considered to be mostly influenced by compensating strategies and non-pharmacological treatment influencing mobility problems.

For the **PFF** cohort the main endpoint after 6 months was modified to care home admission (instead of mortality) as it is very common and the worst case endpoint emphasized by patients and patient representatives. This led to a shift in the inclusion time point as early as the first postoperative week. The time window will now allow the monitoring of the recovery and subsequent decline phase for future drug developments.

The **COPD** cohort maintained their timelines and inclusion criteria based on prior experience with the ProActive project. Discussions with EMA focus on the definitions of exacerbations and the additional collection of environmental data such as air pollution to study the influence of pollutants on mobility.

An ongoing discussion with EMA remains on the use and the test measurement properties of the LLFDI (Late Life Functional Disability Index) as an overarching construct to measure disability and disability mobility in particular. While no discussant offered an evidence based alternative it was raised that the LLFDI has not been properly tested in younger participants. Some cohorts such as PD and MS have so far limited data on validity and reliability and it was suggested to collect more information over the upcoming years. It should be acknowledged that the EMA up to now is rarely if ever considering disability as

an outcome in drug approval but acknowledges that upcoming studies on medication that might influence the molecular ageing process will need new assessment approaches. The current QoL instruments such as EQ-5D lack the sensitivity to detect meaningful change.

Due to the unforeseen COVID 19 pandemic some changes to the study protocol had to be introduced. While baseline assessments will have to be administered as an in-house visit, the follow-up visits might be administered as home visits to keep participants in the study. With the 7-day sensor based measurements being the central part of the assessment we aim to keep the participants in the study even when they are not willing or capable to visit the study day clinics or gait laboratories. With the vaccination programs starting in EU-27, UK, Israel and Norway these days we expect that a significant number of the target population will be vaccinated during the first six months until October 2021. Nonetheless we have decided that the study will need an extended timeline for recruitment of the first patient in until the last patient will enter. This now pre-planned time window was decided to be 12 instead of 6 months.

COVID 19 mitigation planning will include remote training of assessment teams via webinars, online tutorials and a blended approach; remote monitoring will be installed. All local sites have defined rules for involving study participants including the use of hygiene standards.

Inclusiveness of enrolment will be monitored including approaching participants in rural regions. Accessibility of study centres is granted by transport support.

A continuous participant and public involvement and engagement (PPIE) strategy has been developed. This involves all sites and cohorts. Participants will receive feedback and are encouraged in co-designing the ongoing study process.

Further amendments are expected over the upcoming months and will be reported. It is expected that all studies will have accompanying students and PhD candidates involved. This information is currently collected and will be updated in real-time. All sites are informed that projects that are directly or indirectly linked to Mobilise-D will have to be reported and possible positive or negative interactions will have to be analysed and require acceptance by the study monitoring board.

In summary, ethical applications of Non-UK sites are either submitted or in the process of being submitted in January 2021 at the latest. All sites had been visited virtually until mid-December and have expressed their confidence in a timely approval of their applications by their LECs based on previous experience and close contact with LECs.

In case amendments affecting the baseline assessment are required prior to study start, these will need to be submitted at the end of January 2021 at the latest in order to avoid delay of study start at sites.

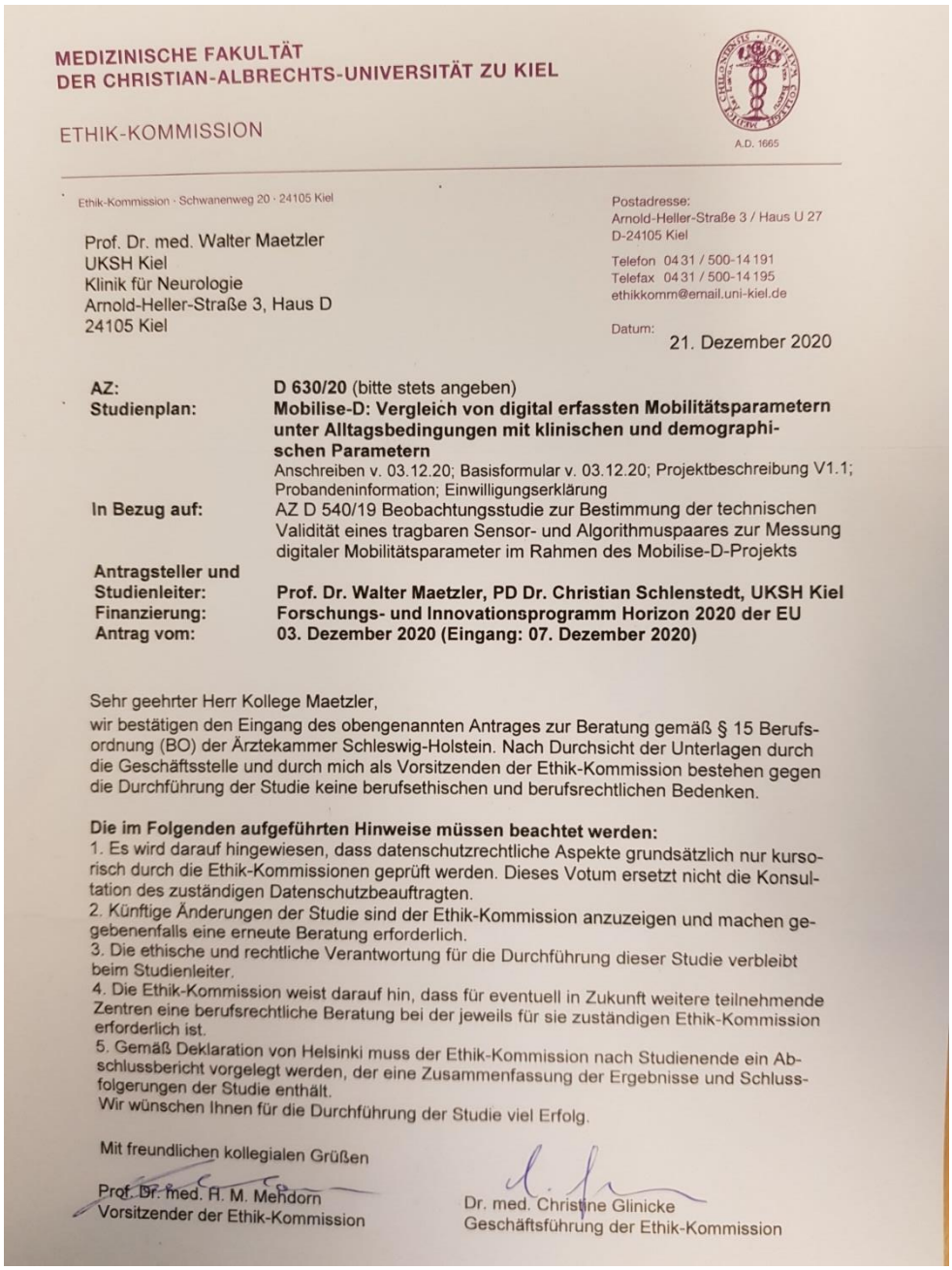
5 Conclusions

With ethical applications being approved, submitted or close to submission, the project is set for study start in April 2021. As the main application led by UNEW has been provisionally approved, no major issues are expected to be raised by the other LECs. Necessary amendments need be and will be submitted early in 2021 to allow for timely study start. This will be overseen by the WP4 lead in close collaboration with site leads.

Appendix A – *Overview: submission status at all sites*

Date filled in	**Site**	**Submitted**	**Submission Date**	**Current status**	**Changes requested**	**Approval date**
		y/n	(or envisaged date)		**if yes - please add document**	
16.12.2020	Stuttgart	y	01.12.2020	pending		
17.12.2020	Kiel	y	02.12.2020	approved		21.12.2020
16.12.2020	Trondheim	y	08.12.2020	pending		
18.12.2020	Leuven (COPD)	y	09.12.2020	Phase 1 (CTC file number) pending		
18.12.2020	Leuven II (PD)	y	09.12.2020	Phase 1 (CTC file number) pending		
16.12.2020	Newcastle	y	12.11.2020	provisional approval	yes	
17.12.2020	Northumbria	y	12.11.2020	see UNEW		
17.12.2020	Athens	n	15.01.2020			
	Tel Aviv	n				
16.12.2020	Erlangen	y	07.12.2020	under review		
18.12.2020	Zürich	n	15.01.2020			
16.12.2020	London	y	12.11.2020	see UNEW		
	Barcelona	n				
18.12.2020	Großhansdorf	n	30.01.2020			
	Milano	n				
16.12.2020	Sheffield	y	12.11.2020	see UNEW		
	Montpellier	n				

Appendix B Study Approval Kiel



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Datum: 21. Dezember 2020

AZ:	**D 630/20** (bitte stets angeben)
Studienplan:	**Mobilise-D: Vergleich von digital erfassten Mobilitätsparametern unter Alltagsbedingungen mit klinischen und demographischen Parametern** Anschreiben v. 03.12.20; Basisformular v. 03.12.20; Projektbeschreibung V1.1; Probandeninformation; Einwilligungserklärung
In Bezug auf:	AZ D 540/19 Beobachtungsstudie zur Bestimmung der technischen Validität eines tragbaren Sensor- und Algorithmuspaares zur Messung digitaler Mobilitätsparameter im Rahmen des Mobilise-D-Projekts
Antragsteller und Studienleiter:	**Prof. Dr. Walter Maetzler, PD Dr. Christian Schlenstedt, UKSH Kiel**
Finanzierung:	**Forschungs- und Innovationsprogramm Horizon 2020 der EU**
Antrag vom:	**03. Dezember 2020 (Eingang: 07. Dezember 2020)**

Sehr geehrter Herr Kollege Maetzler,
wir bestätigen den Eingang des obengenannten Antrages zur Beratung gemäß § 15 Berufsordnung (BO) der Ärztekammer Schleswig-Holstein. Nach Durchsicht der Unterlagen durch die Geschäftsstelle und durch mich als Vorsitzenden der Ethik-Kommission bestehen gegen die Durchführung der Studie keine berufsethischen und berufsrechtlichen Bedenken.

Die im Folgenden aufgeführten Hinweise müssen beachtet werden:
1. Es wird darauf hingewiesen, dass datenschutzrechtliche Aspekte grundsätzlich nur kursorisch durch die Ethik-Kommissionen geprüft werden. Dieses Votum ersetzt nicht die Konsultation des zuständigen Datenschutzbeauftragten.
2. Künftige Änderungen der Studie sind der Ethik-Kommission anzuzeigen und machen gegebenenfalls eine erneute Beratung erforderlich.
3. Die ethische und rechtliche Verantwortung für die Durchführung dieser Studie verbleibt beim Studienleiter.
4. Die Ethik-Kommission weist darauf hin, dass für eventuell in Zukunft weitere teilnehmende Zentren eine berufsrechtliche Beratung bei der jeweils für sie zuständigen Ethik-Kommission erforderlich ist.
5. Gemäß Deklaration von Helsinki muss der Ethik-Kommission nach Studienende ein Abschlussbericht vorgelegt werden, der eine Zusammenfassung der Ergebnisse und Schlussfolgerungen der Studie enthält.

Wir wünschen Ihnen für die Durchführung der Studie viel Erfolg.

Mit freundlichen kollegialen Grüßen

Prof. Dr. med. H. M. Mehdorn
Vorsitzender der Ethik-Kommission

Dr. med. Christine Glinicke
Geschäftsführung der Ethik-Kommission