IMMERSE

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List of abbreviations

CA - Competent Authority

IB - Investigators Brochure

ICF - Informed Consent Form

IFU - Information For Use

RCT - randomized controlled trial

WP - Work Package

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1. Summary

The first study subject approvals package can be delivered as expected: i) The RCT was planned and the study protocol (clinical investigation plan, CIP) written, reviewed and approved by members of WP7. ii) Based on the CIP, we registered the trial in the ISRCTN trial register with the following registration number: ISRCTN15109760. iii) The CIP and further study documents have been submitted to local ethics committees (EC) and competent authorities (CA) in all participating sites. A summary of the status of the first-wave submissions at all study sites is included in this report. At the time of writing this report, we already received approvals in all participating countries.

The deliverable report is the result of an intense collaboration between WPs and clinical investigation sites. We regard the contributions of WP6, as well as WP2, 3, 4, and 5 as well as all PIs of WP7 in the past 18 months. Without this close collaboration it would not have been possible to meet the targets of the deliverable in all countries.

2. Deliverable report

D 7.2 First study subject approval package

2.1 Introduction

In the following sections, we report on the first study subject approvals package which includes i) the final version of the study protocol approved by the first regulatory agency or ethics committee, ii) registration of the randomized controlled (RCT) trial in a trial registry, and iii) approvals required for the first participant enrolment. The process used to develop this deliverable is explained and the collaborations with other Work Packages (WPs) are elaborated.

In section 2.2, we report on the process of finalizing the Clinical Investigation Plan. Based on the Clinical Investigation Plan, the IMMERSE RCT has been prospectively registered at a trial registry (see section 2.3). In section 2.4, we report on the status of ethical and regulatory approvals at all investigating centers.

2.2 Clinical Investigation Plan

The Clinical Investigation Plan (CIP) of the cluster-randomized controlled trial includes a description of the study protocol and all procedures. The design of the trial, the selection criteria, the outcome assessments and their frequency and a description of the intervention and the implementation strategies are described in the CIP. A first draft of the CIP was developed and internally reviewed by all WP7 members in December 2021 (Month 9). In the following months, open questions were resolved in meetings and discussions within WP7 and in close collaboration with other work packages. Input by WP2 on risk evaluation and results from usability tests has been integrated to the CIP. The CIP has been reviewed by the monitoring company in February 2021. A substantial challenge for the deliverable was the integration of the RCT in the clinical routines of the eight centers participating in the project. This integration was achieved through several remote meetings between the sponsor of the

trial (CIMH) as well as the research team members and the principal investigators of each investigating center, in order to receive comments and inputs on the objectives, the methodology and the implementation strategies. All WP7 members contributed to adapt the final version of the CIP to reflect the individual participant population, characteristics of participating clinicians, and to fulfill local as well as national requirements. The CIP has also been reviewed and discussed by the Data Monitoring and Ethics Committee (DMEC).

The final version has been signed by the chief investigator, the coordinating investigator and the trial statistician. It has been submitted to the local ethics committees and competent authorities (see section 2.4). The CIP is a confidential document. Thus, the CIP is not included in the public version of this deliverable. However, we are currently aiming to publish the study protocol in a peer reviewed journal.

The synopsis of the CIP has been translated to the national languages. Please see Appendix A for the English synopsis.

2.3 Registration of the trial in a clinical trial register

The study has been prospectively registered at the ISRCTN trial register, a primary clinical trial registry recognized by WHO and ICMJE, on August 3rd 2022. The registration number is ISRCTN15109760 (Reininghaus, 2022).

2.4 Regulatory approvals required for the trial

The trial we are about to conduct is an Other Clinical Investigation (article 82) according to Medical Device Regulation (EU MDR 2017/745). Competent authorities and ethics committees have to review the documentation on the clinical investigation and the device involved in the clinical investigation before providing approval. The MDR requests several documents to be submitted. These include the CIP (see section 2.2), the Clinical Investigation Plan, the Information For Use, the Investigators Brochure, and the study information and consent form. In the following we report on the development of each document.

Besides the Clinical Investigation Plan (see section 2.2), we drafted the Clinical Evaluation Plan (CEP). The Clinical Evaluation Plan entails the description of the device, clinical benefits, outcome parameters, a section on clinical safety, methods for analysis, and acceptability of benefit-risk ratio.

Furthermore, the Information for Use (IFU) has been developed in collaboration with WP2. This document entails the description of the MoMent app and dashboard and will be handed out to service users and clinicians in the intervention condition.

In addition, principal investigators and study staff at each investigation center will be provided with the Investigators Brochure (IB). This document has been drafted in collaboration with WP2. We invited all researchers in WP7 and all Principal Investigators as well as the monitoring company for review. The final version of the IB has been signed by the principal investigators.

The study information and consent forms for service users, clinicians and team leads have been drafted in collaboration with WP6. The template of the study information and informed consent forms has then been translated to all languages of the Consortium and adapted to meet local requirements. At the Scottish site, for example, the study information and consent form has been reviewed by a service user board which provided feedback on the readability of the text. For German participants aged 14 to 18 years a separate study information and consent form has been developed based on the general version in response to a query by the local ethics committee.

In some sites, recruitment flyers and the collection of questionnaires and interviews (see D 7.1) has also been submitted to ethics committees for review.

2.4.1 Overview of the submission process

The EUDAMED IT system has been established and developed by the European Commission in order to facilitate coordination of information regarding medical devices on the EU market. The EUDAMED system entails several modules. By the time of submission the module on clinical investigations was not in place yet. So, we could not use the system to submit the documents on the clinical investigation to one leading competent authority. Thus, we had to submit the trial in the different countries in parallel. Please see table 1 for an overview of the status in each country.

In line with the MDR (EU 2017/745) as well as to German national regulations (MPDG), an evaluation of the competent ethics committee, and a notification to the competent authority (BfARM) is required in order to perform an Other Clinical Investigation. We used the German Medical Devices Information and Database System (DMIDS) to submit all documents to one leading ethics committee, the ethics committee II of the Medical Faculty Mannheim, Heidelberg University. This ethics committee first evaluated the clinical investigation. A second ethics committee, the ethics committee of the Medical Association of the state Baden-Württemberg, evaluated the suitability of the second German investigation center (PZN Wiesloch). See table 1 for more details. We obtained approval for the clinical investigation to be conducted at the CIMH on 26.10.22.

In Belgium, the clinical investigation has been submitted via the Common European Submission Portal (CESP) to the competent authority (FAMHP) and to local ethics committees. According to national law a joint decision was initiated. We received an EUDAMED number (CIV-22-08-040547) by the FAMHP. This number has been added to the study information and consent forms. See table 1 for more details of the submission. We obtained approval by the competent authority and the ethics committee on 21.10.22.

In Scotland, we submitted to the West of Scotland Research Ethics Service. According to national law, no approval of the competent authority is required for Other Clinical Investigations. Approval was obtained on 24.10.22.

In Slovakia, we submitted to two ethics committees (see table 1). We received approval for the investigating center Bratislava on 29.8.22. We are still waiting for the approval for the investigating center Kosice.

Table 1. Status of the submission process per country

Country	Investigating centers	Status
Germany	CIMH, Mannheim PCN, Wiesloch	Submitted by CIMH via DMIDS on 15.8.22. The investigation has been discussed at the EC meeting on August 30th. Minor requests have been addressed on October 5th. The study has been approved to be conducted at the CMIH. For the second German investigation site requests have been addressed on 26.10.22. Waiting for approval.
Belgium	KUL, Leuven St. Kamillus, Bierbeek	Submitted on 22.08.22. A first review of submitted material took place 25.08.22 after which additional information was requested. Additional information was provided on the 4th of September. Minor comments were received 23th of September, these were addressed and resubmitted on 3th of October 2022. The competent authority and the ethics committee approved the clinical investigation on 21.10.22.
Scotland	Lothian Lothian CAMHS	Submitted by UNEDIN 22.07.22, study was discussed at local EC meeting on September 2nd 2022. Revisions were addressed on October 9th 2022. Approval was obtained on 24.10.22 (REC 4, West of Scotland Research Ethics Service, REC reference: 22-WS-0125, IRAS project ID: 318332)
Slovakia	University Clinic Bratislava, Bratislava	Submitted 29.8.2022, study was discussed at local EC meeting on August 31st and was approved at the same date.
	Kosice	Study was discussed at the local EC meeting on 17.08.2022. The local EC requested complete documentation, including all the questionnaires translated into the Slovak language. The process was completed on 19.10.2022. Submitted 21.10.22. Currently waiting for approval; expected approval within two weeks.

3. Conclusion

The first study subject approvals package can be delivered as expected. By the time of writing the report we received approval by ethics committees and regulatory agencies not only in one but in all participating countries. Thus, all submitted documents that are necessary for the conduct of the study have been approved and are in place.

The deliverable report is the result of an intense collaboration between WPs and clinical investigation sites. We regard the contributions of WP6, as well as WP2, 3, 4, and 5 as well as all PIs of WP7 in the past 18 months. Without this close collaboration it would not have been possible to meet the targets of the deliverable in all countries.

4. References

Reininghaus, U. (2022). Implementing digital mobile mental health in routine care. ISRCTN. https://doi.org/10.1186/ISRCTN15109760

5. Annex

Annex A: Synopsis of the Clinical Investigation Plan

Title	**Strategies, processes, contextual factors, outcomes, and costs of implementing Digital Mobile Mental Health in routine care in four European countries: a parallel-group cluster randomized controlled trial**
Investigational Device	The Digital Mobile Mental Health (DMMH) intervention consists of **(1)** the **MoMent App**, a digital application for mobile devices based on Experience Sampling Methodology (ESM), to systematically monitor service users' self-reported momentary mental state, mood, symptoms, activities, context, therapy goals, key problem areas, and momentary quality of life in daily life; and **(2)** the **MoMent Management Console** that allows clinicians to **(a)** tailor the idiosyncratic treatment goals and questionnaires that are presented by the MoMent App (together with the individual service user), and **(b)** generate reports that provide meaningful information from the self-report data using the integrated **MoMent dashboard**, an interface to visualize and distil the collected data into tailored feedback to the service users and their clinicians.

Population	Service users (n=432) and clinicians (n=100) comprise the study population in this 'other clinical investigation', a multi-centre, parallel-group cluster randomized controlled trial (cRCT), who will be recruited from 3 clinical units (clusters) in each of the 8 clinical sites (i.e., n=54 service users per site; n=18 service users per unit) and, thus, a total of 24 units (clusters), which will be selected pre-randomization. In addition, 40 service users, 40 clinicians and 40 managers/IT-system administrators allocated to the experimental condition (i.e., 10 per country and group) will be approached for the process evaluation.
Duration	The investigation will be conducted in the period from **September 2022** to **September 2024** at eight clinical sites within mental health services in Belgium, Germany, Scotland, and Slovakia.
Objectives	**1.** To investigate **i) R**each (i.e., service user participation), **ii) E**ffectiveness (defined as the interaction of efficacy × implementation in real-world settings) of implementing the DMMH in routine clinical care settings in a pragmatic cRCT, operationalized as greater service user engagement (with their core treatment) in the experimental than control condition at 2-month post-baseline as primary outcome, **iii) A**doption of the DMMH in routine clinical care settings, **iv) I**mplementation of the DMMH (defined as delivery of the DMMH as intended) and **v) M**aintenance (defined as the extent to which the DMMH becomes sustainable part of routine care at 6-month and 12-month post-baseline) in service users and clinicians. **2.** To understand how service users leverage the DMMH intervention to support their health and wellbeing, and evaluate the process of implementing the DMMH intervention into routine clinical care, we will use a realist evaluation framework in combination with the 'non-adoption, abandonment, scale-up, spread, and sustainability' (NASSS) framework to identify individual person-, system- and context-based factors that influence or determine the most responsive and effective use and implementation of DMMH within and across different mental health care settings. **3**. To investigate the economic costs of implementing the DMMH intervention, identifying cost drivers under different delivery models of care, and to determine the cost-utility and the extended cost-utility of the intervention vis à vis treatment as usual.
Primary endpoint	The **primary endpoint** will be patient-reported service engagement assessed with the Service Attachment Questionnaire (SAQ) at 2-month post-baseline, a measure of service users' experience of, and engagement with, their treatment and service (to establish **Effectiveness**).

Secondary endpoints	The following **secondary endpoints** will be assessed based on patient-, clinician- and researcher-rated measures (to establish **Effectiveness**) at 2-month, 6-month, and 12-month post-baseline: ● clinician- and researcher-rated service engagement measured with the Service Engagement Scale (SES) (Tait *et al.*, 2002) (at 2-month, 6-month, and 12-month post-baseline) as well as patient-reported service engagement, measured with the Service Attachment Questionnaire (SAQ) (Goodwin *et al.*, 2003) at 6- and 12-month post-baseline as a secondary outcome. ● personal recovery measured with the patient-rated Questionnaire about the Process of Recovery (QPR) (Neil *et al.*, 2009) ● self-management measured with the patient-rated Mental Health Self-management Questionnaire (MHSEQ) (Coulombe *et al.*, 2015) ● shared decision making measured with the patient- and clinician-rated 9-item Shared Decision-Making Questionnaire (SDM-Q-9) (Kriston *et al.*, 2010) modified to be used with the clinician administering the DMMH ● personalized therapy goal attainment measured with Goal Attainment Scaling (GAS) (Turner-Stokes, 2009) ● social functioning measured with a section of the patient-rated Social Functioning Scale (SFS) (Birchwood *et al.*, 1990), and with ESM (Harvey *et al.*, 2011) ● loneliness and isolation measured with the UCLA Loneliness Scale(Russell, 1996) ● mental ill-health measured with the researcher-rated Clinical Global Impression (CGI) scales (Guy, 1976), patient-rated General Health Questionnaire (GHQ-12) (Gnambs and Staufenbiel, 2018), and with ESM (Myin-Germeys *et al.*, 2018) ● quality of life measured with the patient-rated Manchester Short Assessment of Quality of Life (MANSA)) (Priebe *et al.*, 1999) and with ESM (Myin-Germeys *et al.*, 2018) ● quality-adjusted life years (QALYs) measured with the EQ-5D-5L (Herdman *et al.*, 2011) and the use of health services (incl. variation in the delivery of Treatment As Usual (TAU)), social care, informal care, and production losses will be measured with the Client Service Receipt Inventory (CSRI) (Chisholm *et al.*, 2000) as a basis for the **economic evaluation** ● reflective functioning measured with the Reflective Functioning Scale (RF) (Fonagy *et al.*, 2016)

- emotion regulation measured with the brief version of the Difficulties in Emotion Regulation Scale (DERS-16)(Bjureberg *et al.*, 2016)

Further, the following secondary outcomes will be assessed to establish Reach, Adoption, Implementation, and Maintenance:

- **Reach** assessed with individual-level measures of service user participation (i.e., the number of service users consented by clinicians to offer the DMMH, the number of service users participating in, and dropping out from, the DMMH during the intervention period will be recorded)
- **Adoption** assessed based on the proportion of clinicians and service users having used key components of the DMMH intervention and implementation strategies (using a checklist)
- **Implementation** will be assessed based on collecting data on the following aspects: 1) implementation fidelity (extent to which the planned implementation strategies have been used as intended by clinicians; 2) intervention fidelity (use of DMMH, i.e., frequency and timing of completing the MoMent app (service users), frequency and duration of accessing and modifying specific components of the MoMent dashboard (service users and clinicians), progression toward individual treatment goals (service users), and other App usage data); 3) health care practice (frequency of clinical decisions made by clinicians based on the DMMH, frequency of shared clinical decisions (by service users and clinicians) based on the DMMH, frequency of changes in care in response to the DMMH, burden for clinicians to use the DMMH assessed using a self-report measure in service users and clinicians)
- **Maintenance** assessed as intended and actual continuation of using the DMMH (based on App and dashboard usage data) at 6-month (t_2) post-baseline during which service users and clinicians continue to have access to the DMMH and implementation strategies and 12-month (t_3) post-baseline during which service users and clinicians still have access to the DMMH but implementation strategies for service users and clinicians requiring active support by the research team will be discontinued. An exploration of maintenance, or sustainability, will also form part of the process evaluation.
- **Other study parameters** will include basic socio-demographic and clinical characteristics (incl. clinical/working diagnosis), family history of mental disorder, comorbidity, duration of illness, alcohol/substance use (TAPS (McNeely *et al.*, 2016)), self-injurious thoughts and behaviors (SITBI; (Fox *et al.*, 2020, Nock *et al.*, 2007)), paranoid thoughts (Revised Green Paranoid Thought Scale; R-GPTS (Freeman *et al.*, 2021)), childhood trauma (CTQ; (Bernstein *et al.*, 2003)), threatening experiences

(List of Threatening Experiences; LTE (Brugha and Cragg, 1990)), and experiential avoidance (Brief Experiential Avoidance Questionnaire; BEAQ (Gamez *et al.*, 2014)). In the process evaluation, data on NASSS will be collected using qualitative interviews. The working alliance inventory (WAI-P, WAI-T; (Munder *et al.*, 2010)) will be used to assess the relationship between practitioner and patient. Additionally, the Media and Technology Usage and Attitudes Scale (MTUAS; (Rosen *et al.*, 2013)) will be employed to assess affinity for technology. **Safety** will be assessed across three levels of risk: 1) symptom exacerbation, undesired effects of treatment and severe adverse events in compliance with good clinical practice and the medical device regulation (clinical safety), 2) distress, interference, burden, and any other effects (incl. adverse events) directly related to the DMMH (mHealth safety), 3) unusual activity patterns (system/privacy protection).

Design	A multi-centre, parallel-group cluster randomized controlled trial (**cRCT**) will be conducted as an 'other clinical investigation', in which **24 clinical units** (as the cluster and unit of randomization) at **eight sites** in four European countries are randomly allocated using an unbalanced 2:1 ratio to one of two conditions: (a) the **experimental condition**, in which participants receive, over a 6-month period, the DMMH intervention and implementation strategies in addition to treatment as usual (TAU) or (b) the **control condition**, in which service users are provided with TAU. **Outcome data** in service users and clinicians will be collected at **four time points**: at baseline (t_0), 2-month post-baseline (t_1)), 6-month post-baseline (t_2), and 12-month post-baseline (t_3).
Inclusion Criteria	***Inclusion criteria for service users****:* aged 14 years and older, help-seeking for mental health problems and deemed sufficiently unwell to be accepted for specialist mental health treatment, in contact with local inpatient, outpatient or community mental health services at the participating clinical sites, ability to provide informed consent. ***Inclusion criteria for clinicians*****:** providing care and being the clinician in charge of treatment for included service users in one of the 24 clinical units at the participating clinical sites. ***Inclusion criteria for health care system administrators and managers*****:** members of health care system administrators and managers in the participating clinical sites.
Exclusion criteria	***Exclusion criteria for service users****:* evidence that psychiatric symptoms are precipitated by an organic cause (incl. a diagnosis of ICD-10 F00-F09); significant risk to themselves or others; clinical diagnosis of intellectual disability (ICD-10 F70-79) or disorders of psychological development (ICD-10 F80-89) that are sufficiently severe to impair a person's ability to provide informed consent; medical or psychological contra-indication (as judged by the clinician in charge), self-reported inability or unwillingness to use a smartphone to collect ESM data, not fluent and not literate in German (Germany), Dutch (Belgium), Slovak (Slovakia) or English (Scotland), short life expectancy/terminal illness.

Procedure	Randomisation of clinical units to the experimental and control condition will be carried out using a validated and concealed procedure carried out by an independent researcher and not the outcome assessors, who will be blind to allocation status for screening and assessments at all time points. Clinicians in the experimental condition will be informed about allocation status and will be offered implementation strategies required prior to delivering the DMMH to service users (e.g., intervention manual, training package). Initial screening and permission for the research team to contact service users will be via clinicians at clinical sites. Following detailed informed consent procedures, eligibility will be established in service users, who provided informed consent. Outcome data in service users and clinicians will be collected at four time points: i) at baseline (t_0) (i.e., prior to the start of the 6-month intervention period in the experimental condition); ii) at the end of an initial 2-month period for focused delivery of the DMMH and implementation strategies ('2-month post-baseline' (t_1)), in which service users and clinicians will receive the relevant implementation strategies (i.e., tailored information, counselling, and reminders for service users; support package for clinicians) and will be required to use the DMMH intervention for at least four weeks within this 2-month period, which forms part of the 6-month intervention period; iii) at the end of the 6-month intervention period during which service users and clinicians continue to have access to the DMMH intervention and implementation strategies ('6-month post-baseline' (t_2), equivalent to assessment at 'post-intervention'); and iv) 6 months after the end of the intervention period during which service users and clinicians still have access to the DMMH intervention but implementation strategies for service users and clinicians requiring active support by the research team will be discontinued ('12-month post-baseline' (t_3), equivalent to a '6-month follow-up'). After completion of baseline assessment, service users in the experimental condition will be offered relevant implementation strategies (i.e., a package of tailored information, counselling, and reminders) and the DMMH intervention (in an initial 2-month period for focused delivery. The cRCT will be accompanied by a process and economic evaluation of the implementation of the DMMH intervention into the context of routine clinical care settings in four European countries.