Work package number [9]	WP7	Lead beneficiary [10]	2 - CIMH
Work package title	Implementation Strategies, Processes, Outcomes and Costs		
Start month	1	End month	48

Objectives

1. To tailor, optimize and evaluate detailed implementation strategies for the Digital Mobile Mental Health intervention (DMMH) at each site and, in close collaboration with WP5 (stakeholder engagement) identify key contextual factors that influence implementation outcomes using the 'non-adoption, abandonment, scale-up, spread, and sustainability' (NASSS) implementation science framework (task 7.1).
2. To investigate a) Reach (i.e., service user participation), b) Effectiveness (defined as the interaction of efficacy × implementation in real-world settings) of implementing the DMMH in routine clinical care settings in a pragmatic cluster-randomized controlled trial (cRCT), iii) Adoption of the DMMH in routine clinical care settings, iv) Implementation of the DMMH (defined as delivery of the DMMH as intended by clinicians) and v) Maintenance (defined as the extent to which the DMMH becomes part of routine care at 3- and 6-month follow-up) (RE-AIM), which, consistent with the RE-AIM framework88, will provide the basis for assessing the public health impact of implementation and scale-up of the DMMH (task 7.2; see also separate document "Template for essential information to be provided for proposals including clinical trials (Clinical study No. 1)").
3. To evaluate the process of implementing the DMMH in routine clinical care pathways using a realist evaluation framework in combination with the NASSS framework to identify in vivo configurations of contexts, and mechanisms of change, and how these are associated with outcomes of implementation and
intervention. These will be iteratively examined in the introduction and implementation of the DMMH within existing pathways to care and treatment frameworks, which will attend to 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 (task 7.3).
4. 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 standard care (task 7.4).

Description of work and role of partners

WP7 - Implementation Strategies, Processes, Outcomes and Costs [Months: 1-48]
CIMH, KU Leuven, UEDIN, UK BA, UPJS, UKHD
Task 7.1. Optimizing the DMMH implementation strategies (CIMH, UEDIN, UKHD, KU Leuven, UK BA, UPJS)
Jointly with WP5 (stakeholder engagement) and other work packages (i.e., WP2-4, WP6), we will first specify and optimize our strategies for implementation of the DMMH into practice. The chosen implementation strategies will include:
a) the DMMH information technology system (see 1.3.6), which adheres to prevailing standards and regulations, particularly regarding data protection;
b) an intervention manual (consistent with the Template for Intervention Description and Replication Checklist), training and support package for clinicians and services to facilitate the use of the DMMH with service users;
c) a well-balanced package of tailored information, counselling, and reminders for service users to motivate and enable them to use the DMMH.

These strategies will purposefully vary somewhat between the different clinical sites to address local requirements. A detailed, factual description of the DMMH intervention and implementation strategies 'as planned' will be tailored to, and optimized based on, the requirements of each site. Building on the work carried out in WP5 (stakeholder engagement), we will generate an a priori assessment of anticipated barriers and facilitators that influence implementation, using the 'non-adoption, abandonment, scale-up, spread, and sustainability' (NASSS) implementation science framework. This has been specifically proposed for the implementation of novel technologies and will be used to optimize, in close collaboration with WP5, the DMMH implementation strategies with regard to the 7 domains of this framework: the condition or illness (i.e., a mental disorder), the technology, the value proposition, the adopter system (comprising professional staff, service users, and informal caregivers), the organization(s), the wider (institutional and societal) context, and the interaction and mutual adaptation between all these domains over time. Findings from the qualitative framework analysis method, which has been designed to inform policy will directly inform tailoring of our implementation strategies to local requirements. These will be further adopted and finalized based on findings from

other work packages (i.e., WP2-4, WP6) prior to the start of the cRCT. In the planned field research (in task 7.2 and 7.3), the NASSS framework will be applied in the context of a realist evaluation approach148, which forms part of task 7.3, for analysis of implementation processes in vivo. This implies that we will explore user experiences to identify contextual factors and mechanisms of change that actually influence implementation and intervention outcomes.

Task 7. 2. Implementation outcomes evaluation (CIMH, UEDIN, UKHD, KU Leuven, UK BA, UPJS)
In field research at each of the clinical sites, we will examine reach, effectiveness, adoption, implementation and maintenance of the DMMH approach and the strategies for its implementation in routine practice following the Reach-Effectiveness-Adoption-Implementation-Maintenance (RE-AIM) framework88[3] in a multi-centre, parallel-group cluster randomized controlled trial (cRCT). A detailed description of the design and methodology of this clinical trial is provided in the "Template for essential information to be provided for proposals including clinical trials (Clinical study No. 1)" as required.

Design: In the cRCT, 24 clinical units (as the cluster and unit of randomization) within mental health services at eight sites in four European countries will be randomly allocated to one of two conditions: (a) the experimental condition, in which participants receive the intervention in addition to treatment as usual (TAU) or (b) the control condition, in which service users are provided with TAU. Justification of design: This design reflects the optimum design for investigating all aspects of the RE-AIM framework, with a particular focus on deriving estimates of effectiveness of DMMH implementation with low risk of bias, while at the same time allowing for an in-depth process evaluation (task 7.3) as well as optimal generalizability of study findings, given the naturalistic field setting. Further, an unbalanced randomization allocation ratio of 2:1 will be used to allow for more detailed investigation of implementation aspects and protect against attrition.

Study population: We will recruit a total of 432 service users (intervention and control condition combined; allowing for a 17% attrition rate) and around 100 clinicians from 24 clusters across all sites in an estimated recruitment period of 6 months. While this sample size may seem relatively small compared with other areas of medicine, it is sufficient to test our primary hypothesis and, hence, balances sample size requirements with feasibility of achieving recruitment targets, given there is strong evidence that recruitment of people with mental health problems for clinical trials depends on their mental health state and hence is particularly time intense and resource heavy.

Intervention: The tailored implementation strategies and the DMMH intervention will be provided in clinical units allocated to the experimental condition of the study (in addition to TAU). Individual service users will have access to the DMMH intervention offered by the clinician in charge of their treatment (i.e., psychiatrists, psychologists, specialist mental health nurses, or other key workers) during their admission to one of the clinical units randomized to the experimental condition for 6 months of the intervention period. In the control condition, service users are provided with TAU.

Outcome measures: The evaluation will focus on range of outcomes relating to Reach, Effectiveness, Adoption, Implementation, and Maintenance of the DMMH, covering service user experience, implementation success, and health outcomes (including service user safety).

Task 7.3. Implementation process evaluation (CIMH, UEDIN, UKHD, KU Leuven, UK BA, UPJS)
Closely connected with the outcomes evaluation (task 2), we will conduct a detailed process evaluation to provide in-depth insight into the implementation and maintenance of DMMH and associated processes and to establish what works, for whom, in what circumstances, in what respects, to what extent, and why. The quantitative data collected as part of task 7.2 using the RE-AIM framework will describe the specific outcome patterns and investigate quantitative metrics of implementation/intervention fidelity and healthcare practice (see above). However, this will not in itself explain underlying processes that generate these patterns. We will utilise a mixedmethod approach that combines the strengths of quantitative and user-based experiences to produce a coherent and plausible explanation. We will attend to individual person-, system- and context-based factors that influence the effective use, implementation, and maintenance of DMMH within existing pathways to care and treatment frameworks across different mental health settings.

Study design: This process evaluation will use a mixed-methods approach and take a realist evaluation approach, which will be combined with the RE-AIM and NASSS frameworks used in task 7.1 and 7.2. This implies that configurations of contextual factors, mechanisms of implementation, and outcomes of the implementation and intervention are explored across all levels of agents within the intervention and its implementation (i.e., individual participants, clinicians, managers and system administrators, and socio-economic and contextual factors that may impact their intentionality, behaviour and decision making at different stages of the intervention).

Study population: Service users, health professionals, managers and system administrators in the clinical units allocated to the experimental condition will be approached for this process evaluation, and a purposeful sample of 40 service users, 40 clinicians and 40 managers/system administrators will be selected (i.e., 10 per country per group, with the aim to include participants from various backgrounds).

Measures: Using interviews and (subsequently) questionnaires with service users, clinicians and managers/system administrators, the contextual factors and change processes in the uptake of DMMH and the implementation strategies will be explored. The interviews will be semi-structured and focused on the broad domains specified by the NASSS framework. Subsequent questionnaires will be informed by the results of these interviews, and use validated measures as far as available as well as newly developed questions. The measurements will be tailored to the specific topic and focus on the processes of implementation of DMMH in healthcare settings. The measurements aim to document these processes in each of the sites as well as to explore the role of a range of contextual determinants (as specified in the NASSS framework) of implementation and intervention outcomes. We will also explore unexpected consequences (positive or negative) on service users and healthcare professionals, such as impacts on clinical teams and organizations. Taken together, this will allow us to identify key aspects of successful and effective implementation of the DMMH in routine clinical pathways and treatment settings from a participatory perspective.

Data analysis: The data analysis will adopt a realist evaluation approach, thus explores for configurations of context, mechanisms and outcomes148. For categorizing the types of factors that influence implementation of DMMH, the NASSS framework will be used. Realist evaluation uses a theory-driven approach to evaluate healthcare programmes and the integration of mHealth methods in existing service and health care settings. This approach will evaluate programme implementation by building on perceptions about the complex and dynamic interactions observed between the context (specific settings where the programme is implemented), mechanisms (participants' decisions and actions), and outcomes (intended and unintended effects) involved in the programme. We will seek to fully understand how participants, embedded within context, triggered mechanisms of the programme to produce specific outcomes using the Framework Analysis method for moving between theory and data. The emphasis of realist evaluation is to explain how a programme works, whilst identifying features that can be used to improve a programme and its implementation potential.

Task 7.4. Economic evaluation (UKHD)
The economic evaluation serves the dual objective of providing information on the costs and cost structure of delivering the DMMH intervention under different health care systems characterizing different implementation models and of establishing its value for money. As such, it will include both a detailed cost analysis and a costutility analysis conducted based on data collected as part of the cRCT (task 7.2).

Cost analysis: The cost analysis aims at capturing economic costs adopting a societal prospective. Accounting for economic costs entails establishing the value of all resources consumed by the intervention. In line with this, we will assess direct and indirect costs incurred both within and beyond the healthcare system, specifically: (a) costs incurred to develop and set up the digital solution; (b) costs related to health service use and associated social care and informal care to the patients enrolled in the trial; and (c) their related production losses150. Ad hoc surveys for implementers will be used to capture resource consumption associated with the development and implementation of the DMMH solution (as part of task 7.2 and 7.3). Resource consumption associated with the provision of health services, social care, informal care, and production losses will be captured using the Client Service Receipt Inventory (CSRI)151, a resource-consumption tool validated across European settings, as part of the cRCT (task 2).

Unit costs will be derived from secondary documents, including financial statements of the software development company, healthcare provider, health insurance, and social service financial records, and country-specific wage information. Our analysis will differentiate start-up from implementation costs as well as fixed from variable costs and will trace costs across activities (e.g. App set-up, training, service provision, etc.) and across cost-categories (e.g. personnel, equipment, etc.). Conducting the work in four different countries provides the unique opportunity to carry out a comparative analysis, identifying costs and their drivers across different health system settings and related implementation models.

Cost-utility analysis: In line with the effectiveness evaluation, to assess the value for money of the intervention, we will consider treatment as usual as comparator to the DMMH solution. In line with existing literature152, we aim at conducting a cost-utility analysis (CUA), measuring outcomes in terms of Quality-Adjusted Life Years (QALYs). Our choice is aligned with the scope of the intervention, which targets individuals with a diverse range of mental disorders, and which therefore calls for an outcome measure, such as QALYS, which can capture health gains across a variety of conditions. Moreover, relying on QALYs as outcome measure also allows us to account for unintended potential adverse health effects. We will capture the utility associated with a given health state using the EQ-5D153-5L tool administered

at baseline, post-intervention, 3- and 6-month follow up of the cRCT (task 2). The survey assesses health along five dimensions (morbidity, self-care, usual activities, pain/discomfort, and anxiety/depression), each evaluated along a five-level scale, resulting in a total of 3125 possible states. Utility weights to be attached to the values emerging from the survey will be derived from the literature. Costs and benefits of the DMMH intervention compared to treatment as usual will be brought together analytically to derive the intervention incremental cost-utility ratio (ICUR), i.e. a measure of the incremental cost incurred by the DMMH intervention in relation to the incremental benefit (measured as QALY saved) produced by it. We will conduct both a pooled and country-specific analysis. Findings will be assessed against national and international costutility and affordability thresholds. We will conduct a sensitivity analysis to test the robustness of the findings to cost and consequence assumptions built within the models and hence establish the extent to which the economic value of the DMMH intervention is robust via à vis variations in its costs and consequences.

Extended cost-utility analysis: In addition to standard cost-utility analysis, we will aim to conduct an extended cost-utility analysis, building on existing literature on extended cost-effectiveness154 to adjust emerging methodologies to our outcome measure. We will derive distributional impacts from merging information derived from our QALY survey with information on socio-economic status embedded within the array of instruments administered as part of the effectiveness analysis. This extended economic evaluation will enable policy makers to take into account efficiency and equity criteria at once, enabling a better assessment of existing trade-offs when considering to scale-up the DMMH intervention.

In planning, we have purposefully chosen to reflect the heterogeneity of service user populations encountered in clinical practice in mental health services at CIMH, PCN, NHS Tayside, NHS Lothian, KU Leuven University Hospital. This is in line with calls for pragmatic randomized controlled trials that aim to optimize external validity. This is required to ensure proof-of-principle and a proper evaluation of implementation and scalability of the DMMH approach, which will be key to delivering evidence on implementation strategies that are generalizable to different healthcare systems and contexts. We will address the heterogeneity of service users suffering from mental disorders based on our previous and ongoing work on transdiagnostic phenotypes of psychopathology including as part of the international HiTOP consortium. This will allow us to directly model and derive quantitative, dimensional measures of the heterogeneity of psychopathology in our service user populations.

As detailed above, the large variety in service user populations will be quantified based on our previous and ongoing work on transdiagnostic phenotypes of psychopathology including as part of the international HiTOP consortium. This will allow us to quantify heterogeneity and investigate impacts across these populations.

Building on the work carried out in WP5, WP7 will generate an a priori assessment of anticipated barriers and facilitators that influence implementation, using the ‘non-adoption, abandonment, scale-up, spread, and sustainability’ (NASSS) implementation science framework. This will be used to optimize implementation strategies and overcome barriers for successful implementation of the DMMH. Findings from the qualitative framework analysis method, which has been designed to inform policy will directly inform tailoring of our implementation strategies to local requirements and provide the basis for scaling up. In addition, we will conduct a detailed process evaluation (alongside the cRCT) to provide in-depth insight into contextual factors (including barriers) for implementation and maintenance of DMMH using the realist evaluation framework. This will provide a solid empirical basis for successful implementation and scaling up the DMMH.

Participation per Partner

Partner number and short name	WP7 effort
1 - KU Leuven	38.00
2 - CIMH	76.40
3 - UEDIN	46.40
4 - UK BA	21.40
5 - UPJS	23.80
7 - UKHD	28.80
Total	234.80

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D7.1	Consolidated descriptions of interventions and implementation strategies for each of the participating sites	2 - CIMH	Report	Public	18
D7.2	H - Requirement No. 12	2 - CIMH	Report	Public	18
D7.3	H - Requirement No. 11	2 - CIMH	Report	Public	28
D7.4	Completion of 'Report on status of posting results'	2 - CIMH	Report	Public	48
D7.5	Report on the implementation process evaluation	2 - CIMH	Report	Public	48
D7.6	Report on the economic evaluation	2 - CIMH	Report	Public	48

Description of deliverables

• D7.1: Consolidated descriptions of interventions and implementation strategies for each of the participating sites

Implementation outcomes evaluation (see separate document “Template for essential information to be provided for proposals including clinical trials”):

• D7.2 Completion of ‘First study subject approvals package’
• D7.3 Completion of 'Midterm recruitment report'
• D7.4 Completion of 'Report on status of posting results'
• D7.5: Report on the implementation process evaluation
• D7.6: Report on the economic evaluation

D7.1 : Consolidated descriptions of interventions and implementation strategies for each of the participating sites [18]

Jointly with WP5 (stakeholder engagement) and other work packages (i.e., WP2-4, WP6), we will first specify and optimize our strategies for implementation of the DMMH into practice. The chosen implementation strategies will include: a) the DMMH information technology system, which adheres to prevailing standards and regulations, particularly regarding data protection; b) an intervention manual (consistent with the Template for Intervention Description and Replication Checklist), training and support package for clinicians and services to facilitate the use of the DMMH with service users; c) a well-balanced package of tailored information, counselling, and reminders for service users to motivate and enable them to use the DMMH. These strategies will purposefully vary somewhat between the different clinical sites to address local requirements. A detailed, factual description of the DMMH intervention and implementation strategies ‘as planned’ will be tailored to, and optimized based on, the requirements of each site. Building on the work carried out in WP5 (stakeholder engagement), we will generate an a priori assessment of anticipated barriers and facilitators that influence implementation, using the ‘non-adoption, abandonment, scale-up, spread, and sustainability’ (NASSS) implementation science framework84. This has been specifically proposed for the implementation of novel technologies and will be used to optimize, in close collaboration with WP5, the DMMH implementation strategies with regard to the 7 domains of this framework: the condition or illness (i.e., a mental disorder), the technology, the value proposition, the adopter system (comprising professional staff, service users, and informal caregivers), the organization(s), the wider (institutional and societal) context, and the interaction and mutual adaptation between all these domains over time. Findings from the qualitative framework analysis method, which has been designed to inform policy will directly inform tailoring of our implementation strategies to local requirements. These will be further adopted and finalized based on findings from other work packages (i.e., WP2-4, WP6) prior to the start of the cRCT.

D7.2 : H - Requirement No. 12 [18]

For each clinical study, the following documents/information must be submitted as a deliverable (in one package) prior to enrolment of first study subject: (i) Final version of study protocol as submitted to regulators/ethics committee(s), (ii) Registration number of clinical study in a WHO- or ICMJE-approved registry (with the possibility to post results), (iii) Approvals (ethics committees and national competent authority if applicable) required for invitation/enrolment of first subject in at least one clinical centre.

D7.3 : H - Requirement No. 11 [28]

'Midterm recruitment report' - Deliverable to be scheduled for the time point when 50% of the study population is expected to have been recruited. The report shall include an overview of recruited subjects by study site, potential recruiting problems and, if applicable, a detailed description of implemented and planned measures to compensate delays in the study subject recruitment.

D7.4 : Completion of 'Report on status of posting results' [48]

Completion of report on status of posting results from analyses on a) Reach (i.e., service user participation), b) Effectiveness (defined as the interaction of efficacy × implementation in real-world settings) of implementing the DMMH in routine clinical care settings in a pragmatic cluster-randomized controlled trial (cRCT), iii) Adoption of the DMMH in routine clinical care settings, iv) Implementation of the Digital Mobile Mental Health (DMMH) intervention (defined as delivery of the as intended by clinicians) and v) Maintenance (defined as the extent to which the DMMH becomes part of routine care at 3- and 6-month follow-up) (RE-AIM), which, consistent with the RE-AIM framework, will provide the basis for assessing the public health impact of implementation and scale-up of the DMMH.

D7.5 : Report on the implementation process evaluation [48]

Report on the implementation process evaluation to provide in-depth insight into the implementation and maintenance of DMMH and associated processes and to establish what works, for whom, in what circumstances, in what respects, to what extent, and why. The quantitative data collected as part of task 7.2 using the RE-AIM framework will describe the specific outcome patterns and investigate quantitative metrics of implementation/intervention fidelity and healthcare practice. However, this will not in itself explain underlying processes that generate these patterns. We will utilise a mixed-method approach that combines the strengths of quantitative and user-based experiences to produce a coherent and plausible explanation. We will attend to individual person-, system- and context-based factors that influence the effective use, implementation, and maintenance of DMMH within existing pathways to care and treatment frameworks across different mental health settings.

D7.6 : Report on the economic evaluation [48]

Report on the economic evaluation based on 1) a cost-utility analysis and 2) an extended cost-utility analysis. 1) Cost-utility analysis: In line with the effectiveness evaluation, to assess the value for money of the intervention, we will consider treatment as usual as comparator to the DMMH solution. In line with existing literature, we aim at conducting a cost-utility analysis (CUA), measuring outcomes in terms of Quality-Adjusted Life Years (QALYs). Our choice is aligned with the scope of the intervention, which targets individuals with a diverse range of mental disorders, and which therefore calls for an outcome measure, such as QALYS, which can capture health gains across a variety of conditions. Moreover, relying on QALYs as outcome measure also allows us to account for unintended potential adverse health effects. We will capture the utility associated with a given health state using the EQ-5D-5L tool administered at baseline, post-intervention, 3- and 6-month follow up of the cRCT. The survey assesses health along five dimensions (morbidity, self-care, usual activities, pain/discomfort, and anxiety/depression), each evaluated along a five-level scale, resulting in a total of 3125 possible states. Utility weights to be attached to the values emerging from the survey will be derived from the literature. Costs and benefits of the DMMH intervention compared to treatment as usual will be brought together analytically to derive the intervention incremental cost-utility ratio (ICUR), i.e. a measure of the incremental cost incurred by the DMMH intervention in relation to the incremental benefit (measured as QALY saved) produced by it. We will conduct both a pooled and country-specific analysis. Findings will be assessed against national and international cost-utility and affordability thresholds. We will conduct a sensitivity analysis to test the robustness of the findings to cost and consequence assumptions built within the models and hence establish the extent to which the economic value of the DMMH intervention is robust via à vis variations in its costs and consequences. 2) Extended cost-utility analysis: In addition to standard cost-utility analysis, we will aim to conduct an extended cost-utility analysis, building on existing literature on extended cost-effectiveness to adjust emerging methodologies to our outcome measure. We will derive distributional impacts from merging information derived from our QALY survey with information on socio-economic status embedded within the array of instruments administered as part of the effectiveness analysis. This extended economic evaluation will enable policy makers

to take into account efficiency and equity criteria at once, enabling a better assessment of existing trade-offs when considering to scale-up the DMMH intervention.

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS9	Tailoring and optimization of DMMH intervention and implementation strategies and guidelines for semistructured interviews finalized	2 - CIMH	18	
MS10	Preparation of clinical trial completed	2 - CIMH	18	
MS11	First patient, first assessment	2 - CIMH	19	
MS17	DMMH usage completed by last patient (sample 100% complete)	2 - CIMH	30	
MS18	Data checking: data quality, validity, completeness and integrity, 50% of sample	2 - CIMH	36	
MS20	Recruitment and assessment of 100% of sample completed	2 - CIMH	36	