Work package number [9]	WP4	Lead beneficiary [10]	2 - CIMH
Work package title	Modeling		
Start month	1	End month	48

Objectives

• Implementation of robust low level statistics for DMMH.
• Identify predictive behavioural contingencies for mental health at the single subject level.
• Identify optimal leveraging points from analysis of predictors for improving mental health.
• Establish a cross-site validated analysis tool which harvests the potential of big (time series) data for forecasting individual health trajectories.

Description of work and role of partners

WP4 - Modeling [Months: 1-48]
CIMH, KU Leuven
The DMMH intervention app assesses multivariate and multimodal time series data providing a rich source of information on the overall behaviour and mental state of an individual across the entire sampling period. WP4 is dedicated to analyse the multimodal (ESM and sensor data) time series data extracting relevant patterns as well as crucial predictive features.

WP4 is organized in terms of two main approaches: task 4.1 will focus on delivering and implementing simple robust low level statistics of the data collected within the consortium in interaction with WP7, based on prior knowledge and existing empirical data. Task 4.2 & 4.3 will then apply modern state-of-the-art deep time series models, based on recurrent neural networks, for multi-modal and multi-scale data integration, identification of novel predictors from higher-level nonlinear feature combinations, and subject-level prediction of individual health trajectories.

Task 4.1. Basic data characteristics, robust statistics, and visualization (M1-M12) (CIMH, KU Leuven)
To obtain the basic statistics for visualization in WP2 and implemented in WP7, as well as to provide a solid
baseline to which to compare the more advanced methods below, WP4 will first focus on simple, quick to compute, statistically robust (low standard error), and easy to interpret statistics that describe distributional properties of the data and covariation between different feature dimensions. These involve mean levels and variability of symptoms/ contextual factors over time, as indicators of symptom/context level and volatility, and their mutual comparison to detect key personalized strengths and weaknesses. Next, they involve simple statistical time series tools for tracking symptoms and contextual factors, and their correlations, over time, such as auto-regressive moving-average (ARMA) models or measures of mutual predictability (Granger causality), allowing to obtain basic insight into how symptoms/ context variables co-occur or predict one another over time. Finally, to capture clinically significant moments of change, or tipping points, within the behavioural trajectories as they are unfolding across larger periods of time, WP4 will use statistical change point detection techniques as developed in Leuven (e.g., 138) and Mannheim (e.g., 139) to detect reliable phase changes in mean levels as a function of, for instance, instalment of treatment or a particular change in treatment over time. Methods for the correction of family-wise error rate, such as the Holm-Bonferroni procedure, regularization techniques in model estimation, and measures of out-of-sample prediction error, will be adopted to minimize the risk of false positives to inform clinical decision making. Outcomes from 'lower–level' statistics and machine learning predictors will be summarized and delivered to the visualization platform in a clinically meaningful and accessible way.

Task 4.2. Machine learning for multimodal data integration (M13-48) (CIMH)
Machine learning models developed in the present context need to efficiently exploit the multivariate and multimodal time series structure, and at the same time be able to adapt to the individual user, to make single subject inferences (e.g., 140, 141). Here, WP4 will infer deep time series models (DTSMs) based on recurrent neural networks (RNNs) from the individual app-based time series, as these are particularly suited to learn dynamical models of single subject behaviour, can adapt over time, and can, once trained on the (multimodal) measurements, be simulated to forecast and examine effects of environmental factors and interventions 25-27, 142. The DTSMs will be used to identify interpretable behavioural contingencies underlying changes in the subjects' trajectories. By
analysing trained model parameters, WP4 will be able to infer which behavioural variables, or multimodal variable combinations, and external factors are most strongly connected with each other. WP4 will further receive input from WP5 regarding missing data in the form of indicator, categorical, or count variables which may contain

information about the mental health status or individual patterns of interaction with the mobile device, and can be explicitly included as response variables in the subject models.

Task 4.3. Development of efficient cross-site big data integration framework for multi-modal time series (M13-M30) (CIMH)
Behaviour is very subjective and not each individual may sample the same environmental contexts and contingencies. Often we may not even observe many of the factors affecting state changes at the single subject level, as ESM ratings may not be dense enough or important environmental information is lacking. These factors make solid predictions at the subject level challenging. WP4 will address these issues by developing efficient data integration schemes which make use of the entire data sets collected across the different sites of the consortium. The idea is that by pre-training DTSMs on similar data from different individuals, the models already learn predictive (low level) features common to all subjects and therefore provide a good starting point for inference at the single subject level. If this feature could be learned at the group level, less training data will be required at the single subject level. By big data integration, individualized models could even recognize dependencies which were never encountered by the specific individual but likely play a role in her/his behaviour. A DTSM pre-trained on
many subjects could infer contingencies at the subject-level by 'filling in' gaps in the individual behavioural history through knowledge gained at the group level. After pre-training DTSM on larger cohorts, personalized subject level models are then obtained by 'fine-tuning' the pre-trained models on the individual subjects' behaviour. Technically, inference (training) of DTSMs will be performed in a hierarchical Bayesian framework143,144.

This big data approach will be cross-validated across the different implementation sites in the consortium. In fact, this consortium spread across multiple countries, including many different personal histories, provides a unique opportunity for validating and advancing DTSM approaches that are expected to be robust with respect to
particularities of specific proband subpopulations, recording procedures, cultural, economical, or lifestyle factors. By analysing the inferred models at both the single subject and group levels, we expect to gain further insight into the factors which contribute to user compliance overall, and in that sense hamper or promote implementation.

W.r.t. data analysis in WP4, heterogeneity between patients is accounted for by providing personalized subject specific feedback in terms of simple statistics and visualization. In the proposed advanced machine learning framework, heterogeneity is also accounted for by fine-tuning and personalizing models on single patient behavior after accounting for common components of variance by integrating over data sets.

WP4 will particularly address differences in impacts across psychiatric disorders by analyzing performance measures indicative of compliance (e.g., missing data and frequency of use), and differences in behavioral trajectories (e.g., differences in dynamics and behavioral contingencies)

Participation per Partner

Partner number and short name	WP4 effort
1 - KU Leuven	1.00
2 - CIMH	48.00
Total	49.00

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D4.1	Set of basic statistics for direct implementation and visualization	2 - CIMH	Report	Public	9
D4.2	Algorithms and software environment for DTSM-	2 - CIMH	Other	Public	36

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
	based multi-modal big data integration				
D4.3	Software for identification, visualization, and feedback of behavioural contingencies	2 - CIMH	Other	Public	48

Description of deliverables

• D4.1: Set of basic statistics for direct implementation and visualization
• D4.2: Algorithms and software environment for DTSM-based multi-modal big data integration
• D4.3: Software for identification, visualization, and feedback of behavioural contingencies

D4.1 : Set of basic statistics for direct implementation and visualization [9]

To obtain the basic statistics for visualization in WP2 and implemented in WP7, as well as to provide a solid baseline to which to compare the more advanced methods below, WP4 will first focus on simple, quick to compute, statistically robust (low standard error), and easy to interpret statistics that describe distributional properties of the data and covariation between different feature dimensions. These involve mean levels and variability of symptoms/ contextual factors over time, as indicators of symptom/context level and volatility, and their mutual comparison to detect key personalized strengths and weaknesses. Next, they involve simple statistical time series tools for tracking symptoms and contextual factors, and their correlations, over time, such as auto-regressive moving-average (ARMA) models or measures of mutual predictability (Granger causality), allowing to obtain basic insight into how symptoms/ context variables co-occur or predict one another over time. Finally, to capture clinically significant moments of change, or tipping points, within the behavioural trajectories as they are unfolding across larger periods of time, WP4 will use statistical change point detection techniques as developed in Leuven (e.g., 138) and Mannheim (e.g., 139) to detect reliable phase changes in mean levels as a function of, for instance, instalment of treatment or a particular change in treatment over time. Methods for the correction of family-wise error rate, such as the Holm-Bonferroni procedure, regularization techniques in model estimation, and measures of out-of-sample prediction error, will be adopted to minimize the risk of false positives to inform clinical decision making. Outcomes from 'lower–level' statistics and machine learning predictors will be summarized and delivered to the visualization platform in a clinically meaningful and accessible way.

D4.2 : Algorithms and software environment for DTSM-based multi-modal big data integration [36]

Machine learning models developed in the present context need to efficiently exploit the multivariate and multimodal time series structure, and at the same time be able to adapt to the individual user, to make single subject inferences (e.g., 140, 141). Here, WP4 will infer deep time series models (DTSMs) based on recurrent neural networks (RNNs) from the individual app-based time series, as these are particularly suited to learn dynamical models of single subject behaviour, can adapt over time, and can, once trained on the (multimodal) measurements, be simulated to forecast and examine effects of environmental factors and interventions 25-27, 142. The DTSMs will be used to identify interpretable behavioural contingencies underlying changes in the subjects' trajectories. By analysing trained model parameters, WP4 will be able to infer which behavioural variables, or multimodal variable combinations, and external factors are most strongly connected with each other. WP4 will further receive input from WP5 regarding missing data in the form of indicator, categorical, or count variables which may contain information about the mental health status or individual patterns of interaction with the mobile device, and can be explicitly included as response variables in the subject models.

D4.3 : Software for identification, visualization, and feedback of behavioural contingencies [48]

Behaviour is very subjective and not each individual may sample the same environmental contexts and contingencies. Often we may not even observe many of the factors affecting state changes at the single subject level, as ESM ratings may not be dense enough or important environmental information is lacking. These factors make solid predictions at the subject level challenging. WP4 will address these issues by developing efficient data integration schemes which make use of the entire data sets collected across the different sites of the consortium. The idea is that by pre-training

DTSMs on similar data from different individuals, the models already learn predictive (low level) features common to all subjects and therefore provide a good starting point for inference at the single subject level. If this feature could be learned at the group level, less training data will be required at the single subject level. By big data integration, individualized models could even recognize dependencies which were never encountered by the specific individual but likely play a role in her/his behaviour. A DTSM pre-trained on many subjects could infer contingencies at the subject-level by ‘filling in’ gaps in the individual behavioural history through knowledge gained at the group level. After pre-training DTSM on larger cohorts, personalized subject level models are then obtained by ‘fine-tuning’ the pre-trained models on the individual subjects’ behaviour. Technically, inference (training) of DTSMs will be performed in a hierarchical Bayesian framework143,144.

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS12	Identification of interpretable behavioural traits and contingencies in personalized DTSM models	2 - CIMH	24	
MS16	Development of multi-site big data approach for ESM and DTSM models	2 - CIMH	30	
MS21	Cross-site validation of big data approach	2 - CIMH	40	