Project No. 848228

DISCOvERIE

Development, dIagnostic and prevention of gender-related Somatic and mental COmorbitiEs in iRritable bowel syndrome In Europe

Workpackage 9

Deliverable D9.1

To integrate the data provided by ESM app and HumanITcare platform with data from WP2-6 and to feed the repository

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List of Abbreviations

API: Application Programming Interface
DPA: data processing agreement
DTA: data transfer agreement
e-Health: electronic health
FIQ: Fibromyalgia Impact QuestionnaireGAD-7: Generalized Anxiety Disorder scale
GDPR: General Data Protection Regulation
IBS: Irritable Bowel Syndrome
IBS-SSS: Irritable Bowel Syndrome - Severity Scoring System
PHQ-9: Patient Health Questionnaire (9 questions)
MFI: Multidimensional Fatigue Inventory
RPM: remote patient monitoring
WP: work package

Glossary

IBS-subtypes are defined by the Rome IV criteria:

- IBS-C: constipation-predominant IBS
- IBS-D: diarrhoea-predominant IBS
- IBS-M: IBS with mixed bowel habits
- IBS-U: IBS-unclassified
- Missing

IBS-groups are based on the definitions as used in WP2:

- IBS-alone: patients with IBS without comorbidities
- IBS-comorbid:
    - Mental: patients with IBS and mental comorbidity (i.e., depression or anxiety)
    - Somatic: patients with IBS and somatic comorbidity (i.e., fibromyalgia or chronic fatigue syndrome)
- IBS-multicomorbid: patients with IBS and both mental and somatic comorbidity

Questionnaires:

- PHQ-9: a depression module, which scores each of the nine DSM-IV criteria for depression and can be used to monitor the severity of depression and to make a tentative diagnosis of depression. The questionnaire has cut points for mild, moderate, moderately severe, and severe depression.
- FIQ: measures the severity of fibromyalgia across three domains, i.e. function, overall impact and symptoms.
- GAD-7: anxiety measure including seven anxiety symptoms, with cut-off levels for mild, moderate, and severe anxiety.
- IBS-SSS: a five-item questionnaire (visual analogue scales) measuring the severity of IBS symptoms, with cut-off levels to define mild, moderate and severe IBS.

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- MFI: a 20-item scale designed to evaluate the severity of fatigue, assessing five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue.

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Deliverable D9.1
[To integrate the data provided by ESM app and HumanITcare platform with data from WP2-6 and to feed the repository]

Introduction

This report for D9.1, *to integrate the data provided by ESM app and HumanITcare platform with data from WP2-6 and to feed the repository*, outlines the work performed thus far to integrate data collected in WP9 with data from other WPs. WP9, the e-Health (electronic health) monitoring work package (WP) of the DISCOvERIE-project, aims to provide a better understanding of the relationship between digestive symptoms and clinical manifestations of mental and non-mental comorbidities in patients with irritable bowel syndrome (IBS). The main output of this WP will be the classification of behavioural patterns underlying clinical manifestations of gastrointestinal dysfunction and comorbid mental and somatic disorders in IBS patients, with special regard to stress and sex/gender issues and nutritional and other lifestyle factors. Two e-Health monitoring platforms, the ESM-application and the HumanITcare-platform, have been implemented in the prospective cohort (WP2) for remote and momentary assessment of self-reported gastrointestinal, mental (e.g. stress, anxiety, and depression) and extraintestinal somatic symptoms (e.g. widespread pain, fatigue), physical activity and environmental factors. Detailed monitoring of these individuals that at the same time are clinically phenotyped (WP2) and will be 'biologically' analysed (WP3-6), allows us to create profiles of each IBS phenotype and to get further insight into related risk factors and underlying mechanisms. Below, we provide an overview of the e-Health applications, details on the work accomplished for each of them, and present a summary of results thus far. Additionally, we outline the plans for further analysis (related to deliverable 9.2).

Main text

WP9 is centered around the implementation of two e-Health applications, the ESM-application (lead by UM) and the HumanITcare-platform (lead by VHIR), to collect digital clinical data in combination with lifestyle factors/environmental triggers from patients in the DISCOvERIE study, which will then be analyzed to obtain the clinical phenotype of patients and potential symptom triggers.

E-Health applications overview

ESM-application

At Maastricht University, an electronic smartphone-based patient-reported outcome measure (PROM) based on the Experience Sampling Methodology (ESM) has been developed, specifically for use in populations with IBS. The ESM is a momentary assessment method collecting repeated measurements randomly during the day in the natural situation and environment of the subjects, thereby limiting recall and ecological bias. These repeated in-the-moment assessments result in an extensive and longitudinal individual pattern of symptoms and can provide insight into the complex interplay between symptom formation and potential daily life triggers over a one-week period. A previously developed smartphone application (Vork et al., (2017). *Neurogastroenterol Motil.*) has been adjusted to use the ESM in the DISCOvERIE-project. This ESM-based PROM application is further called the Qdot-application. An Ldot application (designed specifically for use in settings where safe storage of personal data is needed, conform GDPR), has been built to facilitate the study logistics in line with the DISCOvERIE-project.

Patients will complete the Experience Sampling Method for seven consecutive days during their regular daily life via the Qdot-application on their own smartphone. The Qdot-application will send out an auditory signal ('beep') 10 times a day at random moments between 07:00AM and 10:00PM. For 10 minutes following the signal participants can complete a questionnaire, *i.e.,* the developed PROM. After these 10 minutes the questionnaire will not be available until the next beep and is considered missing data. Therefore, subjects are instructed to complete as many questionnaires as possible each day, as soon as possible following each beep. The questions will be identical between the different moments during the day. The questionnaires consist of 30 questions about symptoms, defecation, psychological factors, environments and nutrition and drug use (see Figure 1.).

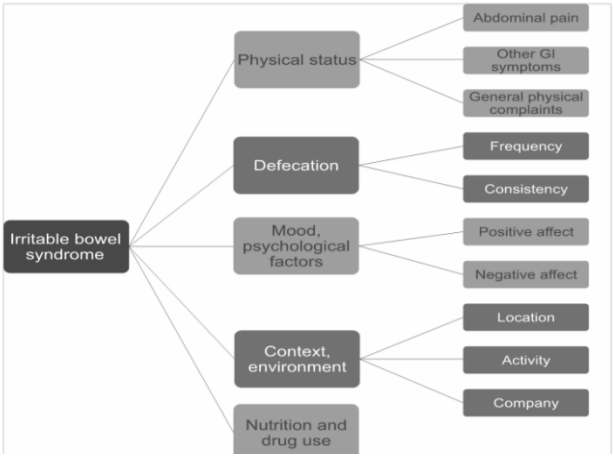

Figure 1. Data collected via the ESM-based PROM application (Qdot-application).

HumanITcare-platform

HumanITcare is a remote patient monitoring (RPM) platform developed by 'FollowHealth SL' and can remotely collect daily data from patients. With an API-based solution, the platform is highly adaptable since any data source can be integrated, including medical devices, wearables & other platforms. The aim of this solution is to streamline the remote follow-up of chronically ill patients so that medical professionals can make better clinical decisions and be alerted when there is a potential point for attention in a patient. It is also used to collect data for clinical research as it can be downloaded for later analysis.
In this case, the HumanITcare platform has been adapted to collect data from IBS patients during 4 weeks at baseline and during 4 weeks after 2 years of the follow-up. The customization of the platform included data collection from:

- A wearable device (Fitbit), which collects heart rate, activity and sleep data
- Patients' reported (validated) questionnaires (PHQ-9, MFI, GAD-7, IBS-SSS, FIQ), which collect data from symptoms, quality of life, and comorbid disorders amongst others. Use of questionnaires was aligned with WP2.

A complete overview of data collected can be found in the tables below:

Table 1. Continuous data collected through the HumanITcare platform.

FITBIT DATA (during 1 month at basal monitoring & 1 month at post monitoring)		
	Indicator	**Description**
Sleep Data (every sleep period)	**date_of_sleep**	The date on which the sleep took place.
	is_main_sleep	Wether the sleep is the main sleep or not (nap).
	start_time	The start time in which the sleep took place.
	end_time	The end time in which the sleep took place.
	duration	The total duration of the sleep.
	time_in_bed	Time spent in bed in minutes.
	minutes_after_wakeup	Minutes elapsed since the monitored woke up.
	minutes_asleep	Minutes spent asleep.
	minutes_awake	Minutes spent awake.
	minutes_to_fall_asleep	The amount of minutes that it took the monitored to fall asleep.
	score	Score for sleep.
Heart Rate Intraday Data (every minute)	**start_time**	The start time in which the beats per minute were counted.
	end_time	The end time in which the beats per minute were counted.
	value	The value for the heart rate (every minute).
	unit	The unit in which the heart rate is given.
Calories Intraday Data (every minute)	**start_time**	The start time in which the calories were burned.
	end_time	The end time in which the calories were burned.
	level	The level of activity in the given time.
	mets	The mets value in the given time.

	value	The number of calories burned (every minute).
	unit	The unit in which the calories are given.

Table 2. Questionnaire data collected through the HumanITcare platform.

Questionnaire	Data
PHQ-9	Questionnaire's answers of 4 points in time: · Basal (15 days after inclusion) · Basal (30 days after inclusion) · Post (15 days after reinclusion) · Post (30 days after reinclusion)
GAD-7	Questionnaire's answers of 4 points in time: · Basal (15 days after inclusion) · Basal (30 days after inclusion) · Post (15 days after reinclusion) · Post (30 days after reinclusion)
MFI	Questionnaire's answers of 4 points in time: · Basal (15 days after inclusion) · Basal (30 days after inclusion) · Post (15 days after reinclusion) · Post (30 days after reinclusion)
FIQ	Questionnaire's answers of 4 points in time: · Basal (15 days after inclusion) · Basal (30 days after inclusion) · Post (15 days after reinclusion) · Post (30 days after reinclusion)
IBS-SSS	Questionnaire's answers of 4 points in time: · Basal (15 days after inclusion) · Basal (30 days after inclusion) · Post (15 days after reinclusion) · Post (30 days after reinclusion)

Completion at baseline is at time of inclusion. Data completion 'post' is after 2 years of follow up as part of the longitudinal cohort of WP2.

Completion of the e-Health tools:
The HumanITcare platform is completed during four weeks at baseline as well as at follow-up (t=2 years), while the Qdot-application is only completed at baseline, on 7 consecutive days during one of the four weeks they were using the HumanITcare platform (see also figure 2).
The recruitment of patients for WP9 is directly linked to the inclusion of patients for WP2, *i.e.,* only patients included for the cross sectional and/or longitudinal cohort are invited to participate for the ESM-application and the humanITcare platform. Thereby, the personalized digital phenotypes to be obtained from the e-Health platforms can be combined with baseline data collected as part of WP2 (*i.e.,* patients demographics, clinical data, questionnaires) and WP3-6 (*i.e.,* biological samples) for integrated analysis.

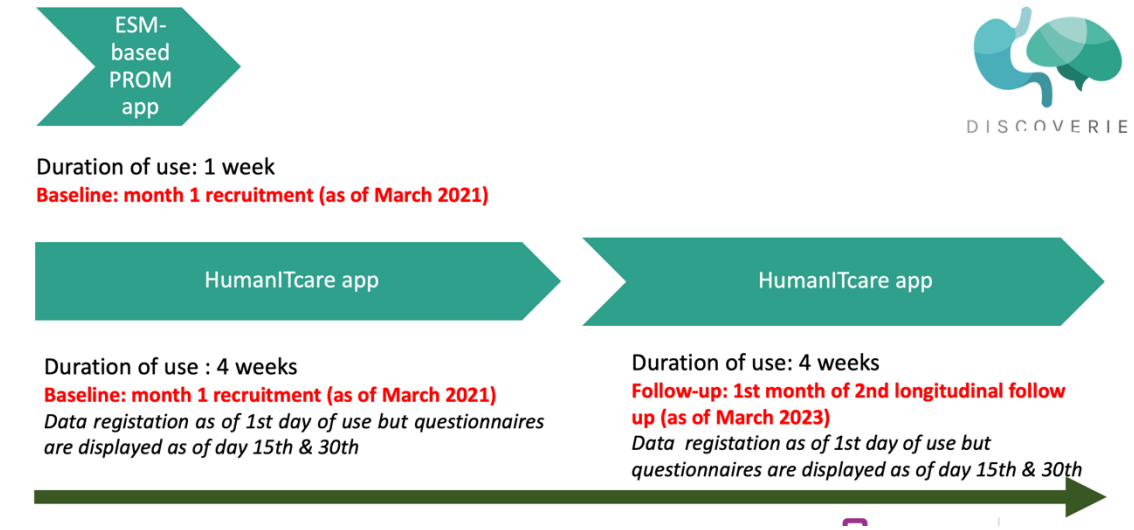

Figure 2. Time overview of completion of the e-Health tools.

1. Overview of the work performed thus far.

The main work carried out by WP9 was primarily focused on adjusting the application for the DISCOvERIE project. In the first reporting period, we customized the app, translated content into multiple languages, and ensured alignment with study requirements. Patient recruitment commenced during this period. In the second reporting period, we intensified patient recruitment and collected all required study data. Below the specific work for each of the e-Health application is described.

ESM-application

In total, six centers have used the ESM-application (UM, KUL, UGOT, VHIR, UNIBO and UMF). This ESM-application was already available in Dutch (for UM and KUL) and Swedish (for UGOT) and English language. For the DISCOvERIE-project, the English version was translated into Spanish, Italian and Romanian. The participating partners translated the PROM, with help of UM providing the necessary templates and instructions to do this in a validated manner (*i.e.,* by dual translation by native speaking experts) in IBS), and offering assistance if necessary. When the application was translated, the three participating centers conducted cognitive interviews with patients to check whether the PROM had been translated in a comprehensible way (*i.e*., linguistic validation). This had already been done for the Dutch and Swedish translations as part of a previous project.
Subsequently, several test rounds were conducted with the ESM application by UM as well as by all participating centres, to implement the final modifications in all languages. An Ldot application (designed specifically for use in settings where safe storage of personal data is needed, conform GDPR), has been built to facilitate the study logistics in line with the DISCOvERIE-project. Access credentials were created for all partners and provided to all the professionals and researchers of the centers that are going to participate in the study and are responsible for the inclusion of patients. In addition to all this, the application has been optimized for use by both Android phones and iPhones. UM also provided input when more information on ESM and its security measures (such as for a DPIA) was requested by ethics committees from participating centers.

The Qdot application was ready for use when the participating centres started their inclusions. A total of six centers used the ESM-application (UM, KUL, UGOT, VHIR, UNIBO and UMF). The UM ESM team monitored the data collection progress of each participant from the participating centers to ensure that all required data were collected. In addition to this, practical tips were provided to all centers in order to support efficient and adequate data collection and to enhance compliance of participants. During the monthly follow-up meetings with the participating centers of WP2-4-9, UM provided updates on the recruitment status and offered assistance where needed. In addition, individual support was provided to participating centers and study participants via email, phone calls or digital meetings in case of problems or questions. Overall, there were no major technical problems with the ESM application during data collection period. In case of minor technical problems, the problem was immediately investigated and solved as soon as possible, with direct communication with the participating center concerned.

Data collection was complete by the beginning of March 2023. For the data transfer between Maastricht University and the ESM participating centers, all data transfer agreements (DTA) were finalized during the second reporting period. In addition, an amendment to the DTA is added regarding data processing agreements (DPA).

HumanITcare-platform

In total, eight centers have used the ESM-application (UM, KUL, UGOT, VHIR, UNIBO, SU, SKU and UMF). The first step so the HumanITcare platform could be used in the project was to translate it and made it available in the App Store / Play Store of the participating countries. The app was already available in English, Spanish and Catalan (VHIR), and needed to be translated into Swedish (for UGOT), Dutch (for UM, SKU and KUL), Italian (for UNIBO), Romanian (for UMF) and Hungarian (for SU). The translations were validated with each center (as for the ESM-application) to ensure a comprehensive and proper translation. Then, a plan for each center was created in the HumanITcare platform and configured to collect the expected data, including the custom digital clinical questionnaires (PHQ-9, MFI, GAD-7, IBS-SSS, FIQ) in the corresponding language – which were available as part of WP2. Once all was prepared, access credentials were created and provided to all the professionals and researchers of the centers responsible for the inclusion of patients. In addition, 15 Fitbit devices were sent to each of the participating centers (VHIR, UGOT, SKU, GUF, KUL, UNIBO, UM, SU, UMF) for use it to collect automatically participants' data. After use, these were returned by the participants, and cleaned for re-use to be able to recruit more participants.
Finally, the HumanITcare team handed over user manuals to each center, both for professionals (web) and for participants (app); and several training sessions were conducted to show how to use the platform in a real use case and solve doubts.
Meetings with participant centers were also held to prepare all documentation needed for their ethics committee approval, considering the data collection through HumanITcare and Fitbit and following the EU regulations.

With the ethics committee's approval in place, participating centers started recruiting patients and registering them into the HumanITcare platform. The HumanITcare team monitored the data collection progress of each participant and provided data status reports to ensure that all required data were collected. In addition to this, practical tips were provided to all centers in order to support efficient and adequate data collection and to enhance compliance of participants. During the monthly follow-up meetings with the participating centers of WP2-4-9, HumanITcare provided updates on the recruitment status and offered assistance where needed. In addition, individual support was provided to participating centers and study participants via email, phone calls or digital meetings in case of problems or questions. Overall, there were some technical problems with the HumanITcare application during participants monitoring, but solutions were provided on short notice and data collection continued as expected.

Data collection of the baseline period was completed by the end of March 2023. Currently, the follow-up period is ongoing to collect data from participants after 2 years. For the data collection, a Data Processing Agreement (DPA) is being signed between FollowHealth SL and each participating centers.

Monitoring and optimizing inclusion

In addition to the specific work described above for each e-Health application, the ESM team and the humanITcare team worked together with all recruiting centers, while acknowledging the boundaries of ethics guidelines, to enhance complete data collection for each participating patient to ensure maximal overlap for joint analysis. Participating patients were stimulated to use the 1-week Qdot-application within the 4-week period of the HumanITcare platform to ensure maximal overlap for joint analysis of WP9. In addition, as WP9 is part of the WP2 prospective cohort, joint analysis with WP2 phenotyping data

and WP3-6 biological samples data will be conducted. The use of Qdot-application and HumanITcare was integrated in the castor CRF (WP2).

Several meetings were arranged to supervise and assist the centers in patient enrollment and to keep each other updated on the joint analysis status. A detailed follow-up by ESM and HumanITcare teams, supported by both the monthly project meetings and bilateral contact, was performed to mitigate technical issues and to ensure patient participation and compliance during the monitoring period. Communication was effective between all partners despite COVID-19 related delays. At the online monthly follow-up meetings, as well as bilateral meetings, there was extensive dialogue between the leaders and researchers of WP2, 4, and 9 and partners from recruiting centers. The discussions involved sharing information, monitoring progress, and potential problems. Additionally, UM and VHIR facilitated communication with all work packages in the DISCOvERIE project by providing project updates and consultations via email and participating in Consortium Meetings such as the General Assembly and Steering Committee meeting, as well as video calls with specific work packages. Lastly, several online video meetings were held specifically for WP9 with the leader, co-leader, HumanITcare partner, and ESM partner to discuss progress and plans for WP9.

The main issue for both e-Health platforms was meeting a minimum requirement of 33% of questionnaires for ESM and a minimum of 7 days of Fitbit data collected for HumanITcare to be completed for inclusion in the analyses. Initial completion rates for both the ESM and HumanITcare questionnaires were low. To improve completion rates, the ESM and HumanITcare teams provided guidance through practical tips based on experience, manuals, and one-on-one meetings with participating centers. Also, HumanITcare app was updated during the project to provide a better user experience and increase participant compliance. Completion rates improved significantly during the second reporting period.

Patient inclusion was based on the inclusion of patients for WP2. In general, recruitment started later than expected and was delayed for reasons related to the COVID-19 pandemic. COVID-19 also affected the speed of recruitment. In particular, recruitment started between months 15 and 17 (March/May 2021) in most institutions. Therefore, an amendment was requested (and approved) to extend the duration of the WP9 tasks (extension of the WP duration from M1-40 to M1-42).

2. Summary of results

Data sets of the eHealth applications have been combined with baseline data from WP2 (e.g. demographics, clinical phenotypes etc.). Additionally, we have examined the extent of overlap with data collected in other work packages (WPs). First the individual results for this will be presented, followed by the results for participants who have completed both ESM and HumanITcare data collection.

ESM-application

A total of 271 patients were enrolled in the ESM part of the project. However, due to low (predefined) compliance, some of the patients (n=59) cannot be included in the data analysis. In total, 212 patients completed at least 33% of the total of 70 questionnaires. and can be included in the data analysis, exceeding the target of 180 patients. As shown in the figure 3., not all centers reached the pre-set target of 30 participants for various reasons, including e.g., low compliance of their participants, and less commitment to e-Health monitoring. However, other centers were able to compensate for these numbers, thereby exceeding the overall target of 180 patients for the ESM part of the project.

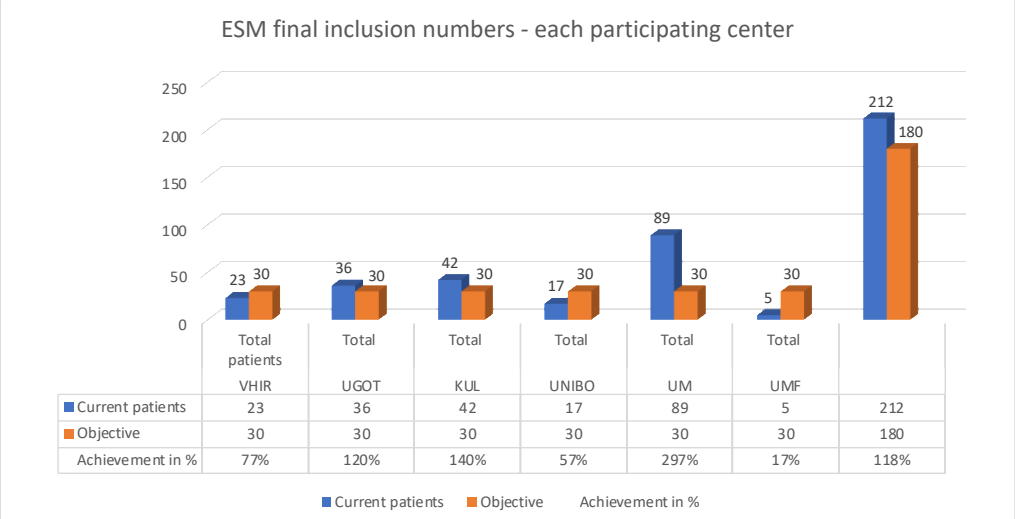

Figure 3. Final inclusion numbers of ESM participants, shown for each participating center.

Patients eligible for analysis had a mean age of 42.4 (±14.8) years and were predominantly female (79.7%). The majority had IBS-D, followed by IBS-M and IBS-C. Further details are given in table 3. Figure 4. shows the distribution of ESM participants across the three defined IBS-groups (IBS-alone, IBS-comorbid, or IBS-multicomorbid), with a predefined objective of 60 patients per group. Overall, the distribution was comparable to WP2, including the lower number of patients in the IBS-multicomorbid group.

Table 3. Results of descriptive analysis for patients who performed ESM (n=212).

	Patients who performed ESM (n=212)
Age (mean, SD)	42.4 (±14.8)
Gender (female, %)	169 (79.7%)
IBS-subtype	
- IBS-C	52 (24.5%)
- IBS-D	82 (38.7%)
- IBS-M	60 (28.3%)
- IBS-U	11 (5.2%)
- Missing	7 (3.3%)
IBS-group	
- IBS-alone	102 (48.1%)
- IBS-comorbid	
○ Mental	51 (24.1%)
○ Somatic	15 (7.1%)
- IBS-multicomorbid	44 (20.8%)
Blood collected	209 (98.6%)
Faeces collected	206 (97.2%)
Urine collected	195 (92.0%)
Biopsies collected	31 (14.6%)
MIST performed (WP4)	59 (27.8%) *
MAST performed (WP4)	98 (46.2%) *

**Data collection for WP4 ongoing, final numbers unknown at this point*

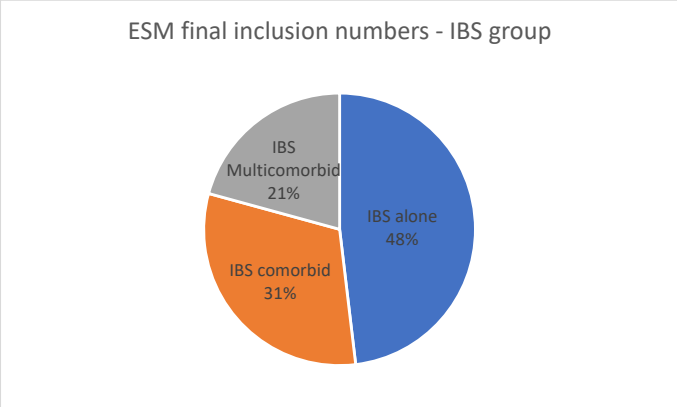

Figure 4. Distribution of ESM participants in the pre-defined IBS-groups.

The completion rate of the ESM questionnaires was found to be promising, with a mean number of beep questionnaires completed per patient of 44.12 (±10.9). The ESM protocol involved a total of 70 beeps, indicating that, on average, participants responded to approximately two-thirds of the total beep questionnaires sent.

The successful integration of data from various WPs for this deliverable has revealed a significant overlap between ESM data and the data collected in WP2-6, as presented in Table 3. Specifically, nearly all ESM participants had blood samples (99%), faeces samples (97%), and urine samples (92%) collected as part of other WPs. As biopsies were collected in a smaller number of patients by a few centres, the overlap between ESM data collected and biopsies collected was lower. Furthermore, while data collection for WP4 is still ongoing, there is a notable portion of ESM participants who also underwent

MIST and/or MAST procedures, indicating promising overlap in this area as well. The substantial overlap between ESM data and data collected in other WPs underscores the efficacy of our data collection efforts and highlights the potential for seamless integration of analyses in the DISCOvERIE project.

HumanITcare-application

A total of 379 patients were enrolled in the HumanITcare part of the project (discarded and abandoned participants have already been excluded from this total number). However, due to low compliance, some of the patients (n=28) cannot be included in the data analysis. In total, 351 patients can be included in the data analysis, exceeding the target of 300 patients. As shown in the figure 5., not all centers reached their target of participants for various reasons, including e.g., low compliance of their participants, and less commitment to e-Health monitoring. However, other centers were able to compensate for these numbers.

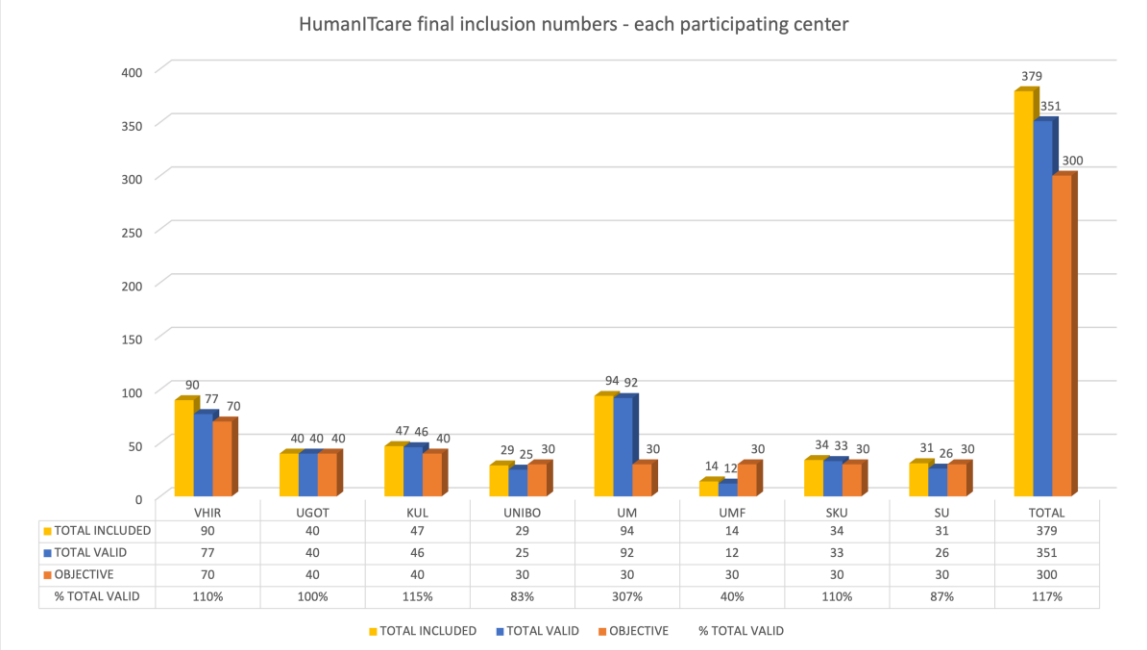

Figure 5. Final inclusion numbers of HumanITcare participants, shown for each participating center.

Patients had a mean age of 41.4 (±13.4) years and were predominantly female (73.8%). More demographics can be found in table 4. Figure 6. shows the distribution of HumanITcare participants across the defined IBS-groups (IBS-alone, IBS-comorbid, IBS-multicomorbid, Disease control mental + somatic, Disease control mental, Disease control somatic, and healthy control).

Table 4. Results of descriptive analysis for patients who performed HumanITcare (n=351).

	Patients who performed HumanITcare (n=351)
Age (mean, SD)	41.4 (±13.4)
Gender (female, %)	259 (73.8%)
IBS-subtype - IBS-C - IBS-D	 90 (25.6%) 116 (33.0%)

- IBS-M - IBS-U - Missing	86 (24.5%) 49 (14.0%) 10 (2.8%)*
IBS-group - IBS-alone - IBS-comorbid o Mental o Somatic - IBS-multicomorbid - Healthy control - Disease control mental + somatic - Disease control mental - Disease control somatic - Missing	 106 (30.2%) 59 (16.8%) 18 (5.1%) 55 (15.7%) 12 (3.4%) 21 (6.0%) 15 (4.3%) 22 (6.3%) 43 (12.3%)
Blood collected	347 (98.9%)
Faeces collected	345 (98.3%)
Urine collected	288 (82.1%)
Biopsies collected	72 (20.5%)
MIST performed (WP4)	--- **
MAST performed (WP4)	--- **

**Data missing at this point will be completed for the final analysis.*
***Data collection for WP4 ongoing, final numbers unknown at this point.*

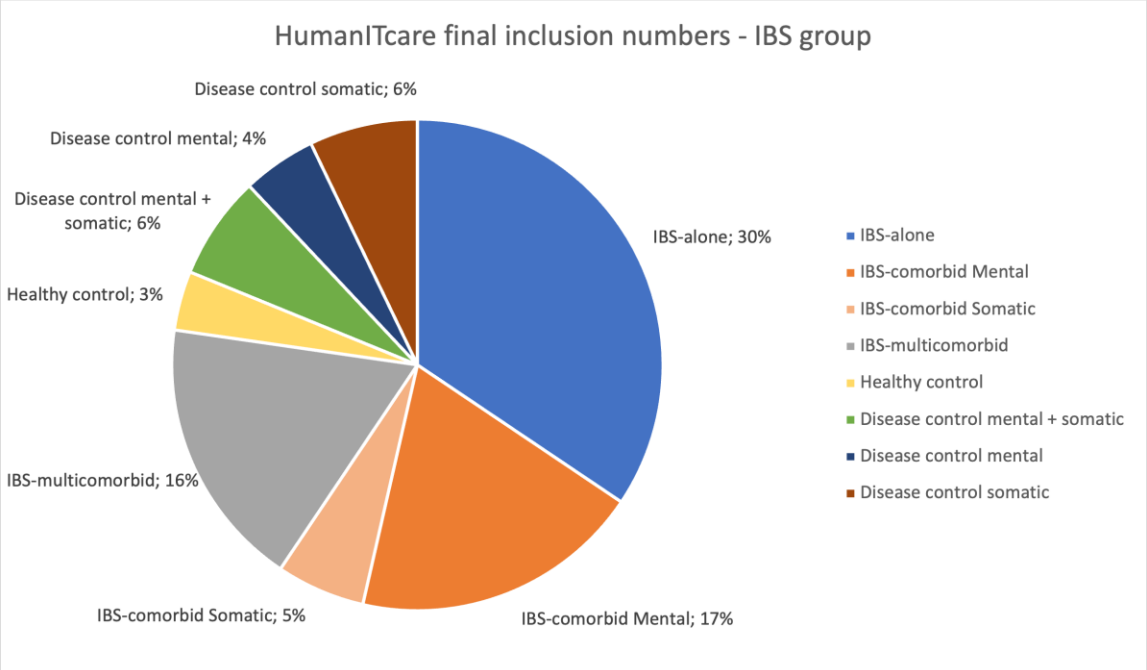

Figure 6. Distribution of HumanITcare participants in the pre-defined IBS-groups.

The successful integration of data from various WPs for this deliverable has also revealed a significant overlap between ESM data and the data collected in WP2-6, as presented in Table 4. Specifically, nearly all HumanITcare participants had blood samples (98.9%), faeces samples (98.3%), and urine samples (82.1%) collected as part of other WPs. As biopsies were collected in a smaller number of patients by a few centres, the overlap was lower. The substantial overlap between HumanITcare data and data collected in other

WPs underscores the efficacy of our data collection efforts and highlights the potential for seamless integration of analyses in the DISCOvERIE project.

Table 5 shows the results of descriptive analysis on data collected via HumanITcare. Participants displayed a high level of compliance. Wearable usage was remarkably consistent, with participants wearing their wearables nearly every day during the 30-day measurement period, resulting in mean days with heart rate, calories, and sleep data collection ranging between 25 and 30 days (the maximum period counted is 35 days to have a little margin).
Regarding the questionnaires on the HumanITcare-platform, completion rates were lower, with participants completing between 50.1% and 57.3% of the 15-day questionnaires between day 10 and day 20, and between 42.7% and 46.7% of the 30-day questionnaires between day 25 and day 35.
Overall, these results emphasize the sufficient data were collected for analyses and showcase the participants' active engagement in data collection through this e-Health application.

Table 5. Results of descriptive analysis on data collected for patients who performed HumanITcare (n=351).

	Patients who performed HumanITcare (n = 351)
Number of days with heartrate measurement (mean, SD)	30.1 (±6.8)
Number of days with calories measurement (mean, SD)	28.6 (±5.9)
Number of days with sleep measurement (mean, SD)	25.2 (±8.7)
IBS-SSS questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30(±5 days, day 25-35)	 195 (55.6%) 161 (45.9%)
PHQ-9 questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30(±5 days, day 25-35)	 201 (57.3%) 163 (46.4%)
GAD-7 questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30 (±5 days, day 25-35)	 199 (56.7%) 163 (46.4%)
MFI questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30 (±5 days, day 25-35)	 199 (56.7%) 164 (46.7%)
FIQ questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30 (±5 days, day 25-35)	 176 (50.1%) 150 (42.7%)

Combined data from ESM and HumanITcare applications

A total of 173 patients successfully completed both e-Health applications while having a 7-day overlap period with ESM and HumanITcare data. Patients had a mean age of 42.8 (±14.9) years and were predominantly female (78.6%). The distribution of these patients across participating centres and other demographics can be found in Table 5. Figure 6. shows the distribution of ESM-HumanITcare participants across the three defined IBS-

groups (IBS-alone, IBS-comorbid, or IBS-multicomorbid). Overall, the distribution was comparable to WP2, including the lower number of patients in the IBS-multicomorbid group.

Table 6. Results of descriptive analysis for patients who performed ESM and HumanITcare (n=173).

	Patients who performed ESM and HumanITcare (n = 173)*
Age (mean, SD)	42.8 (±14.9)
Gender (female, %)	136 (78.6%)
IBS-subtype	
- IBS-C	43 (24.9%)
- IBS-D	70 (40.5%)
- IBS-M	46 (26.6%)
- IBS-U	9 (5.2%)
- Missing	5 (2.9%)
Inclusion centre	
- KUL	28 (16.2%)
- UGOT	22 (12.7%)
- UM	86 (49.7%)
- UMF	1 (0.6%)
- UNIBO	15 (8.7%)
- VHIR	21 (12.1%)
IBS-group	
- IBS-alone	90 (46.2%)
- IBS-comorbid	
o Mental	41 (23.7%)
o Somatic	13 (7.5%)
- IBS-multicomorbid	39 (22.5%)
Blood collected	171 (98.8%)
Faeces collected	171 (98.8%)
Urine collected	161 (93.1%)
Biopsies collected	27 (15.6%)
MIST performed (WP4)	49 (28.3%) **
MAST performed (WP4)	72 (41.6%) **

**Patients who have an overlap period of 7 days with ESM and HumanITcare*
***Data collection for WP4 ongoing, final numbers unknown at this point*

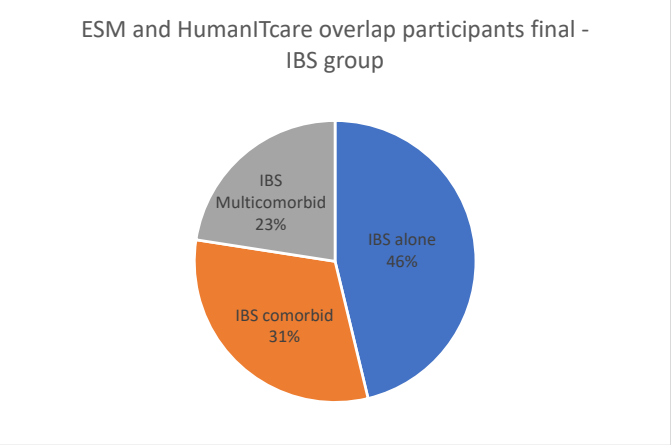

Figure 7. Distribution of ESM-HumanITcare participants in the pre-defined IBS-groups.

The successful integration of data for patients who have completed both ESM and HumanITcare has revealed a significant overlap between WP9 data, and the data collected in WP2-6, as presented in Table 3. Specifically, nearly all ESM participants had their blood samples (99%), faeces samples (99%), and urine samples (93%) collected as part of other WPs. As biopsies were collected in a smaller number of patients by a few centres, the overlap between WP9 data collected and biopsies collected was lower. Furthermore, even though data collection for WP4 is still ongoing, there is already a notable portion of ESM participants who underwent MIST and/or MAST procedures, indicating promising overlap in WP4 as well. This substantial overlap between WP9 data and data collected in other WPs highlights the successes of our integrated data collection efforts and emphasizes the potential for seamless integration of analyses in the DISCOvERIE project.

Table 7 shows the results of descriptive analysis on data collected via both e-Health applications for patients who have completed both ESM and HumanITcare in an overlap period of 7 days. Participants displayed a high level of compliance, completing an average of 45.1 (±10.7) ESM beep questionnaires throughout the study period. Additionally, wearable usage was remarkably consistent, with participants wearing their wearables nearly every day during the 30-day measurement period, resulting in mean days with heart rate, calories, and sleep data collection ranging between 26 and 29 days. These findings indicate a commendable level of compliance with both the ESM-application and wearing the wearable, ensuring substantial data collection for analyses.
Regarding the questionnaires on the HumanITcare-platform, completion rates were moderate, with participants completing between 61% and 71% of the 15-day questionnaires between day 10 and day 20, and between 57% and 62% of the 30-day questionnaires between day 25 and day 35.
Overall, these results emphasize the sufficient data were collected for analyses and showcase the participants' active engagement in data collection through the e-Health applications. The combination of comprehensive ESM beep questionnaires and data collected via the HumanITcare platform provides a robust basis for integrated analysis within WP9 and facilitates seamless integration with other work packages.

Table 7. Results of descriptive analysis on data collected via both e-Health applications for patients who performed ESM and HumanITcare (n=173).

	Patients who performed ESM and HumanITcare (n = 173)
ESM beep questionnaires completed (mean, SD)	45.1 (±10.7)
Number of days with heartrate measurement (mean, SD)	27.7 (±5.6)
Number of days with calories measurement (mean, SD)	28.6 (±4.5)
Number of days with sleep measurement (mean, SD)	26.3 (±6.6)
IBS-SSS questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30(±5 days, day 25-35)	 118 (68.2%) 107 (61.9%)
PHQ-9 questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30(±5 days, day 25-35)	 121 (69.9%) 105 (60.7%)
GAD-7 questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30 (±5 days, day 25-35)	 122 (70.5%) 108 (62.4%)
MFI questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30 (±5 days, day 25-35)	 119 (68.8%) 104 (60.1%)
FIQ questionnaires completed - Day 15 (±5 days, day 10-20) - Day 30 (±5 days, day 25-35)	 105 (60.7%) 98 (56.7%)

3. Data analysis

As a critical component of our deliverable to integrate data from the ESM app and HumanITcare platform with data from WP2-6 into a comprehensive repository, we successfully completed data collection for both the ESM data and baseline HumanITcare data in March 2023.

Before concluding data collection, both teams collaborated extensively on developing separate and joint data analysis plans. This ensures a cohesive approach to data analysis across both e-Health applications.

Subsequently, data from both e-Health applications were extracted from their respective platforms and combined to form a final data file for each application. Furthermore, to create a comprehensive overview data file for WP9, we merged and combined general data from both e-Health applications. Additionally, we gathered relevant general information from other work packages (WPs) and incorporated it into the WP9 overview data file.

Moving forward, the further data analysis plan for each application can be found below.

ESM data analysis plan

The ESM data will be analyzed for the defined objectives separately and through integrated analyses with both ESM and HumanITcare data and data collected through other WPs. Below is the step-by-step data action plan:

1. Data extraction and data cleaning (finalized).

2. Detailed overview of other data needed for ESM analysis (WP2, HumanITcare, WP3-6; finalized).

3. Inventory of ESM data needed by other WPs and preparation of a template/syntax for data extraction and transfer for partners who request it (ongoing).

4. A detailed analysis plan for the ESM data has been generated, in short:
- With the ESM-prom (Qdot-application) data, detailed symptom patterns over a one-week period will be generated for individual patients. These will then be combined with WP2 data for comparison between patients with and without comorbid conditions, and further analyzed to identify potential triggers and the impact of further host characteristics (as obtained by the detailed phenotyping as part of WP2). An example for potential analysis is shown in Figure 4.
- Data of the Qdot-application will also be combined with data from the HumanITcare platform (ad T9.2) regarding *e.g.*, physical activity, heart rate variability and sleep, to include their impact on symptom occurrence and symptom patterns.
- Finally, based on the potential triggers analyzed, such as stress or diet-microbiome related, results of the MIST and MAST (WP4) and analyses in bio samples (WP3, 5, 6) will be compared between subgroups of patients with different profiles, to further substantiate a pathophysiological role of potential triggers and to identify potential predictive markers. The latter may aid identifying ‘the right treatment for the right patient’.

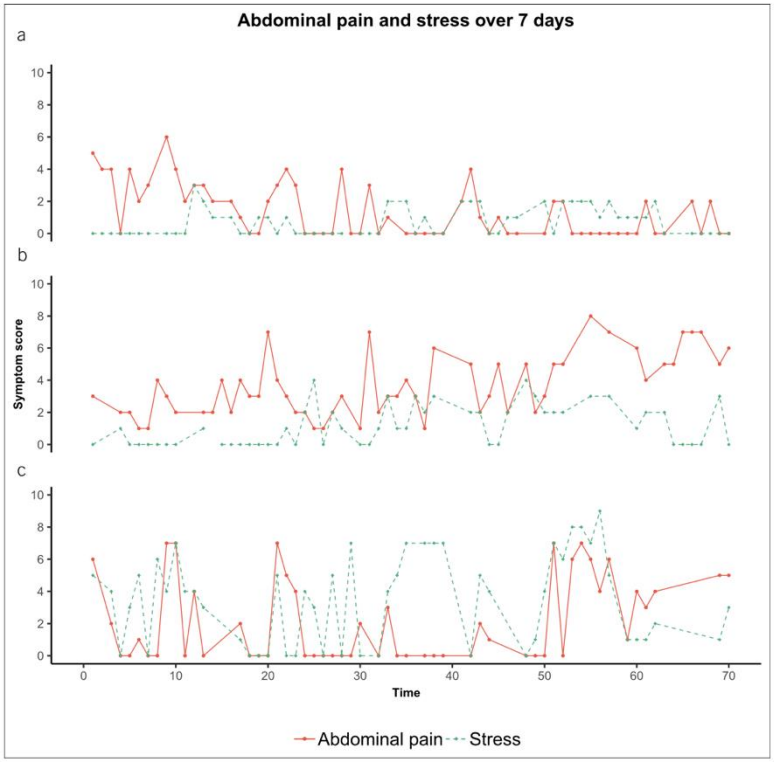

Figure 8. ***Example of ESM data analysis on identifying potential triggers. Copy from Vork et al. (2020), Clinical and translational gastroenterology.***

Symptom severity scores for abdominal pain and stress, on 70 random time points over 7 days, separately for 3 subjects with IBS. The heterogeneity between subjects with IBS is shown by the different patterns of stress and abdominal pain; also indicated by the difference in corresponding regression coefficients for (a) 20.23, (b) 0.07, and (c) 0.28.

HumanITcare data analysis plan

The HumanITcare data will be analyzed for the defined objectives separately and through integrated analyses with both ESM and HumanITcare data and data collected through other WPs.
The detailed analysis of the HumanITcare data will be performed after the follow-up period finishes, which is currently ongoing. So results presented in this report belong to a prior analysis regarding demographic data and data cleaning.

Below is the step-by-step data action plan:

1. Data extraction and data cleaning (in progress).
2. Detailed overview of other data needed for analysis (WP2, WP3-6).
3. Inventory of HumanITcare data needed by other WPs and preparation of a template/syntax for data extraction and transfer for partners who request it.
4. A detailed analysis plan for the HumanITcare data has been generated, in short:

Fitbit data will focus on sleep quality, heart rate variability and physical activity (using calories spent) to compare data between groups.

Continuous data will be presented as the mean and SD or as the median (with IQR) depending on the normality of the distribution and will be compared between groups using the Student *t* test or the Wilcoxon rank-sum test.
Categorical data will be presented as the number (%) and were compared using the chi-square or Fisher exact test.
The change in the average daily Fitbit variables (as calories spent or heart rate) will be calculated by subtracting the mean at first 4-weeks from the mean at second 4-weeks (second year of follow-up).
A mixed model for repeated measures will be used to compare the changes between the different IBS-subtypes and IBS-groups for the custom digital clinical questionnaires (PHQ-9, MFI, GAD-7, IBS-SSS, FIQ). The changes of each questionnaire will be first analyzed in each group (IBS-subtype and IBS-groups) by comparing the parameters at baseline (first month of assessment) with those at follow up (second year). The comparisons will be performed using the paired *t* test or Wilcoxon signed rank test. Next, the changes in the parameters will be compared between the different IBS-subtypes and groups using the Student *t* test. We will correlate the results of these questionnaires with the Fitbit variables and ESM results. Moreover, these results will be correlated with other biological variables of WP2 and WP3-6.
The baseline data will also be used to evaluate changes over a short period of time (i.e. 4 weeks) in relation to changes in IBS symptoms and comorbid symptoms scores (after 15 and 30 days, see also table 6). Additionally, Fitbit data will be analysed in conjunction with the ESM data and the derived symptom profiles (see also ESM).

Conclusion

In conclusion, this report marks a significant milestone for the WP9 e-Health monitoring work package within the DISCOvERIE-project, as it highlights the successful integration of data collected from the ESM app and the HumanITcare platform with data from WP2-6. For the ESM application, a total of 212 patients were available with sufficient data for further analyses, as opposed to the target of 180 patients. For the HumanITcare, a total of 351 patients was included (target was 300 patients). Additionally, 173 patients successfully completed both e-Health applications, with a 7-day overlap period of ESM and HumanITcare data. Overall, the distribution follows the baseline data of WP2, and thereby a representative sample of patients did complete the eHealth applications. Descriptive analyses yielded promising results, showing high compliance among ESM participants, and consistent wearable usage. The successful integration of data from both e-Health applications and other work packages into one comprehensive overview file lays a strong foundation for analysing the interplay between gastrointestinal, mental, and somatic symptoms in IBS patients using ESM and HumanITcare data separately, followed by integrated WP9 analysis. Moreover, the significant overlap between WP9 data and data collected in other WPs shows the success of our integrated data collection efforts and underscores the potential for seamless integrated analyses with other WPs, enabling a comprehensive and multi-dimensional approach to address the research objectives of the DISCOvERIE project.

The aim of WP9 is to gain a comprehensive understanding of the relationship between digestive symptoms and clinical manifestations of mental and non-mental comorbidities in patients with IBS. By implementing the ESM application and the HumanITcare platform at baseline in the prospective cohort of WP2, we successfully collected digital clinical data, lifestyle factors, and environmental triggers from patients in the DISCOvERIE study. An analysis plan has been made and further analyses, including follow-up visits, will be performed and detailed in the *deliverable D9.2 "To set-up a report of the digital phenotype of patients with IBS and comorbid conditions, and predictive models in order to move from eHealth to intelligent health (iHealth)".*

Appendix – Questionnaires

PHQ-9

MFI

GAD-7

IBS-SSS

FIQ