multi-act

Deliverable D1.8

Report on the integration of Patient Reported Outcomes and perspectives into the Collective Research Impact Framework (CRIF).

"This deliverable makes the link between WP1 and WP3. The Patient Report Dimension of research impact is integrated in the CRIF as core and transversal fifth dimension of the Master Scorecard.".

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No 787570

PROJECT ACRONYM:	A Collective Research Impact Framework and multi-variate models to foster the true engagement of actors and stakeholders in Health Research and Innovation
CONTRACT NUMBER:	787570
DISSEMINATION LEVEL:	Public
NATURE OF DOCUMENT:	Report

TITLE OF DOCUMENT:	Report on the integration of Patient Reported Outcomes and perspectives into the Collective Research Impact Framework (CRIF).
REFERENCE NUMBER:	D1.8
WORKPACKAGE CONTRIBUTING TO THE DOCUMENT:	WP1
VERSION:	V0.6
EXPECTED DELIVERY DATE:	31/07/2020
DATE:	02/08/2020
AUTHORS (name and organization):	Deborah Bertorello, Giampaolo Brichetto, Paola Zaratin (FISM)
Review and contributors	Valentina Tageo - Fondazione Italiana Sclerosi Multipla Onlus (FISM) Natalia matuszak, Marcin Kautsch, Patryk Sierpowski - Dane-I-Analizy.pl Sp z o.o. (DIA) Francesca Spagnoli, Andrea Gavazzi, Luca Molinari - Ernst & Young Financial Business Advisors (EY) Françoise Van Hemelryck - European Brain Council (EBC) Sabri Ben Rommane - European Health Management Association (EHMA) Florence van Steenbrugghe - Fondation Pour L'aide A La Recherche Sur La Sclérose En Plaques (ARSEP) George Tsakirakis, Sofia Tsekeridou - INTRASOFT International (INTRA) Juliette Senn, Nicolas Garcia Torea, Carlos Larrinaga - Universidad De Burgos (UBU)

	Ericka Costa, Michele Andreaus - Università Degli Studi Di Trento (UNITN) Anna Kork, Eija Vinnari - Tampereen Yliopisto (TUNI)
Acknowledgements	**Patient Engagement Group:** Timothy Coetzee, National Multiple Sclerosis Society; Lars Klüver, Danish Board of Technology Foundation - Engage2020; Paola Kruger, European patient Academy (EUPATI); Paola Mosconi, Mario Negri Institute Italy; Federica Balzani, Associazione Italiana Sclerosi Multipla Onlus (AISM)

Short description of the Deliverable (as in the DoA):
This document details the link between WP1 "Enabling Science with and of patient input" and WP3 "Impact Assessment Model (IAM) development & assessment to the case of research initiatives" and report the activities to integrate the Patient Report Dimension in the Collective Research Impact Framework (CRIF) as core and transversal fifth dimension of the Master Scorecard.

REVISION HISTORY

REVISION	DATE	COMMENTS	AUTHOR (NAME AND ORGANISATION)
V0.1	25/06/2020	First draft	Deborah Bertorello (FISM)
V0.2	02/07/2020	Review and implementation by Task T1.5 Leader and Coordinator	Deborah Bertorello, Giampaolo Brichetto, Paola Zaratin (FISM)
V0.3	13/07/2020	Consortium review	Deborah Bertorello, Giampaolo Brichetto, Paola Zaratin - Italian Multiple Sclerosis Foundation (FISM) Dane-I-Analizy.pl Sp z o.o. (DIA) Ernst & Young Financial Business Advisors (EY) European Brain Council (EBC) European Health Management Association (EHMA) Fondation Pour L'aide A La Recherche Sur La Sclérose En Plaques (ARSEP) Intrasoft International (INTRA) Universidad De Burgos (UBU) for the Academic Team: Università Degli Studi Di Trento (UNITN) Tampereen Yliopisto (TUNI)
V0.4	29/07/2020	Review by Patient Engagement Group,	**PEG:** Timothy Coetzee - National Multiple Sclerosis Society

		and Consortium reviewers; WP1 Leader and Coordinator finalization (FISM)	Lars Klüver - Danish Board of Technology Foundation - Engage2020 , Paola Kruger - European Patient Academy EUPATI Paola Mosconi - Mario Negri Institute, Federica Balzani - Associazione Italiana Sclerosi Multipla Onlus (AISM). **Consortium reviewers**: Ericka Costa - UNITN, Andrea Gavazzi - EY Deborah Bertorello, Giampaolo Brichetto, Paola Zaratin - Italian Multiple Sclerosis Foundation (FISM)
V0.5	31/07/2020	WP1 Leader and Coordinator finalization (FISM)	Deborah Bertorello, Giampaolo Brichetto, Paola Zaratin - Italian Multiple Sclerosis Foundation (FISM)
V0.6	02/08/2020	Editing and submission	Valentina Tageo - Italian Multiple Sclerosis Foundation (FISM)

FILENAME: MULTI-ACT_D1.8_FISM_20200802_v0.6

STATEMENT OF ORIGINALITY:

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

TABLE OF CONTENT

EXECUTIVE SUMMARY 7
1 INTRODUCTION 10
1.1 Purpose of this document 10
1.2 Structure of document 11
1.3 Abbreviations 11
1.4 Glossary 13
2 BACKGROUND 16
2.1 Enabling Science with and of Patient Input 16
2.1.1 Measuring outcome that matter most to patients - Science of Patient Input 18
2.2 Patient Reported Outcomes (PROs): report of functional aspects 19
2.3 The Patient Reported Dimension (PRD) 19
3 METHODOLOGY 21
3.1 Building on existing PROs initiatives 22
3.1.1 The Patient Reported Outcomes Initiative for MS (PROMS) 23
3.1.2 iConquerMS developed by Accelerated Cure Project for MS 24
4 INTEGRATION OF PRD INTO THE CRIF 26
4.1 PRD's aspects and indicators 26
4.2 Relation to the other dimensions of the Master scorecard D3.6 26
4.3 PRD Taxonomy and Digital Toolbox 28
4.4 Indicators' groups 29
4.4.1 Functional aspects: PRO Indicators 30
4.4.2 Description of PROs Indicators 31
4.4.3 Taxonomy of PROs Indicators 32
4.4.4 Psycho-social aspects: indicators for Return on Engagement (RoE) 33
4.4.5 Description of RoE Indicators 33
4.4.6 Taxonomy of RoE Indicators 34
5 OPPORTUNITIES FOR EXPLOITATION OF PRD 36
5.1 Machine Learning algorithm applied to PROs 36
5.2 PRO data collection in the Digital Toolbox 37

5.2.1 Data protection and processing measures 39
6 CONCLUSION 40
APPENDIX 1 – Patient Reported Dimension Master Scorecard 41
APPENDIX 2 – PROMs 42
A2.1 ABILHAND - Manual Ability Measure 42
A2.2 Anxiety and Depression Scale (HADS) 43
A2.3 Life Satisfaction Index (LSI) 44
A2.4 Modified Fatigue Impact Scale (MFIS) 45
A2.5 NeuroQoL – Example of search online 46
A2.6 Twelve Item MS Walking Scale (MSWS-12) 47
A2.7 OAB-q Over Active Bladder Function (QAB-q) 48

EXECUTIVE SUMMARY

MULTI-ACT is developing a strategic Collective Research Impact Framework (CRIF) in the area of brain diseases by using Multiple Sclerosis (MS) as a case study. The MULTI-ACT framework aims to allow for effective cooperation of all relevant stakeholders in multi-stakeholder health research initiatives (MSRIs) and includes tools and guidelines for the governance, the stakeholder engagement, and the impact assessment of such initiatives, and foresees patients as key stakeholder in the Health Research & Innovation (R&I) process.

The mission-related dimension is one explicit driver for co-accountability approach developed by MULTI-ACT project. Starting from the agenda of multi-stakeholder MS research initiatives, this model is extensible and applicable in defining the scope of health research as well as in providing new metrics for the evaluation of its results. Conventional metrics related to the excellence dimension are integrated with new measures related to the economic and financial dimension (efficiency) and to the social dimension that relates to achieving mission success (efficacy; one explicit driver of the MULTI-ACT co-accountability approach). The Patient-Reported Dimension (PRD) is applied in a transversal modality throughout the four dimensions of MULTI-ACT model as a tool for enabling the Science of Patient Input.

The CRIF merges three MULTI-ACT outcomes: Governance Model[1], the Patient Engagement[2] guidelines and the Co-accountability Model[3]. The Master Scorecard (MSC) is an adaptive tool for the application of the CRIF and its five dimensions. The MSC consists of a detailed list of indicators evaluating aspects of measurement linked to the different dimensions that can be tailored into different contexts and missions.

This document details the link between "WP1 Enabling Science WITH and OF patient input" and "WP3 Co-accountability Model development & assessment to the case of research initiatives", and reports the activities performed to integrate the PRD in the CRIF as core and transversal fifth dimension of the Model, including additional indicators in the MSC and in the Digital Toolbox.

PROs are investigated as metrics that "enable Science of Patient Input" by measuring the impact of R&I on outcomes that matter most to patients. Measuring impact of health research on PRD will maintain patients engaged as key stakeholder.

The PRD includes indicators that are reported by patients, family and caregivers. The indicators can be a collection of answers to questionnaires (e.g. PRO) and active and/or passive data collection without the intervention of the clinicians (e.g. eHealth via App/ICT devices like wearables or electronic bracelets).

The activities devoted to develop the PRD build mainly on two current initiatives of FISM in the PROs domain, the Patient Reported Outcomes Initiative for MS (PROMS) and the PROMOPRO-MS database.

[1] MULTI-ACT Deliverable D5.4: "MULTI-ACT Governance Model for collaborative initiatives", Jun 2019, https://www.multiact.eu/project-deliverables/

[2] MULTI-ACT Patient Engagement Guidelines, short version v0.1 May 30th 2020, https://www.multiact.eu/project-deliverables/

[3] MULTI-ACT Deliverable D3.6: "MULTI-ACT Master Scorecard", Nov 2019, https://www.multiact.eu/project-deliverables/

The PROMOPRO-MS database and related research activities are also strictly connected and developed in partnership with the US PCORI[4] funded initiative of Accelerated Cure for MS, namely iConquerMS[5].

This document contextualises the PRD by providing information on the current use of PROs in R&I, details the methodology and the actions performed to integrate the PRD into the CRIF – including an overview on the connection with existing initiatives on Patient Reported Outcomes (PROs). It presents the aspects and indicators included under the PRD, their relation with the Master Scorecard (D3.6), their integration into the Digital Toolbox and related taxonomy, and concludes by presenting opportunities for exploitation and the potential for applying machine[6] learning algorithms to PROs data collection functionality in the Digital Toolbox.

In particular, the MULTI-ACT Digital Toolbox 2.0, building on the PROMOPRO-MS database, will provide the interface to collect data related to PRO indicators and facilitate the use of the indicators, laying the groundwork for the development and implementation of the data collection algorithm in the exploitation phase of MULTI-ACT. The algorithm could build on the relevant FISM initiatives and database on PROs and related results[7].

The PRD is of outmost importance to evaluate the impact of R&I on outcomes that matter most to patients and maintain patients and stakeholders engaged along the R&I continuum. The PRO data collection provides opportunity to exploit the outcomes of MULTI-ACT and it's of utmost importance for the research & healthcare community, for research outcomes evaluation (e.g. use of PROs in clinical trials or observational studies), R&I impact assessment, but also in healthcare for monitoring of disease progression and evolution.

The next steps will be directed to implement the PRD into the Digital Toolbox 2.0 (available by October 2020) and to seek for exploitation opportunities, such as data collection function and machine learning algorithms and/or development of ad hoc PROs on Return on Patient Engagement, building on the MULTI-ACT Patient Engagement Guidelines. A dedicated exploitation plan will be developed and included in D8.5.

The PRD include aspects and indicators of "Science of Patient input" (i.e. RoE related to the psycho-social aspects; PROs related to functional aspects).

In particular, MULTI-ACT focuses on the PROs (functional reported aspects) as it foresees the development of PROs as key indicators of impact, instrumental to enable a multi-stakeholder approach and effective patient engagement, and the current deliverable aim to meet this strategic intent. The fact that PROs are scientifically validated measures reported by the patients (final beneficiary of the health research) capture the interest of all the stakeholders.

[4] Patient-Centered Outcomes Research Institute (www.pcori.org)
[5] https://www.iconquerms.org/for-researchers
[6] Machine learning is an application of artificial intelligence (AI) that provides systems the ability to automatically learn and improve from experience without being explicitly programmed. Machine learning focuses on the development of computer programs that can access data and use it learn for themselves.
[7] Brichetto G, Monti Bragadin M, Fiorini S, et al. The hidden information in patient-reported outcomes and clinician-assessed outcomes: multiple sclerosis as a proof of concept of a machine learning approach. Neurol Sci. 2020;41(2):459-462. doi:10.1007/s10072-019-04093-x

However, also the psychosocial reported aspects (RoE) are important, and as reported in the landscape analysis, there is the need to develop effective metrics. To this regard, a development plan for RoE indicators is also included in this document.

1 INTRODUCTION

MULTI-ACT is developing a strategic **Collective Research Impact Framework (CRIF)** in the area **of brain diseases** by using **Multiple Sclerosis** (MS) as the first case study. The project foresees patients as key stakeholders in the Health Research & Innovation (R&I) process. The MULTI-ACT framework aims to allow for effective cooperation of all relevant stakeholders in multi-stakeholder health research initiatives and includes tools and guidelines for the governance, the stakeholder engagement, and the impact assessment of such initiatives.

This document reports the task "T1.5 Integration of Patient Reported Outcomes (PROs) and perspectives in the CRIF", deliverable D1.8 of the Work Package n.1 "Enabling Science with/of Patient Input".

In T1.5, PROs are investigated as metrics that "Enable Science OF Patient Input" by measuring the impact of R&I on outcomes that matter most to patients. Measuring impact of health research on Patient Reported Dimension will maintain patients engaged as key stakeholder.

In "WP3 Co-accountability Model development & assessment to the case of research initiatives", the MULTI-ACT Co-accountability Model and its Master Scorecard have been developed to measure the effects/changes/results that the initiative brings about and to properly respond to the changing stakeholders needs. The Master Scorecard consists of five dimensions of accountability. The mission-related dimension is one explicit driver for the co-accountability approach developed by MULTI-ACT project. In this model, conventional metrics related to the **excellence** dimension are integrated with the **economic and financial** dimension (efficiency), and to the **social** dimension. The **Patient-Reported Dimension** is applied in a transversal modality throughout the 4 dimensions of the co-accountability model (i.e. mission/efficiency, excellence, efficacy, and social).

D1.8 details the metrics related to the Patient Reported Dimension and the methodology to include them in the Co-accountability Model, its Master Scorecard and Digital Toolbox.

Following the MULTI-ACT Patient Engagement Guidelines[8] (WP1, D1.6), indicators to evaluate the effectiveness of patient engagement on outcomes that matter to patients have been developed under the activities of T1.5 and included in D1.8 and the MULTI-ACT Digital Toolbox as a sub-set of the Patient Reported Dimension.

1.1 Purpose of this document

This document presents and details the link between "WP1 Enabling Science WITH and OF patient input" and "WP3 Co-accountability Model development & assessment to the case of research initiatives", and reports the activities performed to integrate the Patient Report Dimension in the Collective Research Impact Framework (CRIF) as core and transversal fifth dimension of the MULTI-

[8] MULTI-ACT Patient Engagement Guidelines, short version v0.1 May 30th 2020, https://www.multiact.eu/project-deliverables/

ACT Co-accountability Model [9], and its indicators under the related Master Scorecard and function of the Digital Toolbox.

1.2 Structure of document

Section 1 introduces the D1.8 document.

Section 2 provides background information for D1.8. It contextualises the Patient Reported Dimension (PRD) by providing information on WP1, on the current use of PROs in R&I and on the concept for the PRD.

Section 3 details the methodology and the actions performed to integrate the PRD into the CRIF. This section also provides overview on the connection with existing initiatives on Patient Reported Outcomes (PROs).

Section 4 presents the aspects, indicators groups and indicators included under the PRD, including the relation with the Master Scorecard (D3.6), the taxonomy and their integration into the Digital Toolbox.

Section 5 presents the opportunities for exploitation of PRD, and the potential for PRO data collection and for applying machine learning algorithm to PROs data collection, and develop the related functionalities in the Digital Toolbox.

Section 6 summarizes the conclusions and the next steps.

Appendixes:

- Appendix 1. Patient Reported Dimension Master Scorecard
- Appendix 2. PROMs scales

1.3 Abbreviations

Acronyms	
AI	Artificial Intelligence
App	Application
CAO	Clinician Assessed Outcomes
CRIF	Collective Research Impact Framework
EAB	External Advisory Board
EDSS	Expanded Disability Status Scale
GA	Grant Agreement
HADS	Hospital Anxiety & Depression Scale
ICT	Information and Communications Technology
LSI	Life Satisfaction Index
LSS	Life Satisfaction Score

[9] The MULTI-ACT Collective Research Impact Framework (CRIF) is the overall MULTI-ACT Framework that includes the Governance Model, the Patient Engagement and the Co-accountability Model. The Master Scorecard (MSC) is an adaptive tool for the application of the Co-accountability Model and its five dimensions. The MSC consists of a detailed list of indicators evaluating aspects of measurement linked to the different dimensions that can be tailored into different contexts and missions.

M-FIS	Modified Fatigue Impact Scale
ML	Machine Learning
MS	Multiple Sclerosis
MSWS-12	Twelve Item Multiple Sclerosis Walking Scale
MSC	Master Scorecard
NeuroQoL	Quality of Life in Neurological Disorders
PEG	Patient Engagement Group (see D1.2 for PEG rationale and composition)
PF	Patient Forum
PROMs	Patient Reported Outcome Measures
PROs	Patient Reported Outcomes
PwMS	People with Multiple Sclerosis
R&I	Research and Innovation
RFPOs	Research Funding & Performing Organisations
ROE	Return on Engagement (in WP1 it refers to the value of Patient Engagement[10])
ROI	Return on Investment
RRI	Responsible Research & Innovation
WP	Work Package
OAB-Q	Over Active Bladder Questionnaire
Work Packages	
WP1	Enabling the science with and of patient inputs
WP2	Development of the information sharing application (MULTI-ACT Toolbox 2.0)
WP3	Integrated Accountability Model (IAM) development & assessment to the case of research initiatives
WP4	Implementation of the MULTI-ACT framework
WP5	Health collaborative initiatives structures and policies
WP6	Collective Research Politics: governance and guidelines
WP7	Transferability and test of the methodology beyond MS
WP8	Dissemination and exploitation
WP9	Project Coordination, Management and Quality Assurance
WP1 Deliverables[11]	
D1.1	Scoping methodology of existing procedures and initiatives for patient engagement across R&I
D1.2	Patient engagement focus group (PEG) establishment
D1.3	Preliminary landscape analysis of patient engagement initiatives and gaps identification
D1.4	Consolidated mapping of existing patient engagement initiatives and analysis of gaps and barriers to patient engagement in current health R&I processes
D1.5	Preliminary version of the MULTI-ACT Patient Engagement in Health R&I guidelines

[10] https://imi-paradigm.eu/determining-the-value-of-patient-engagement/
[11] After EC approval, the MULTI-ACT public deliverables are published at https://www.multiact.eu/project-deliverables/

D1.6	Final version of the MULTI-ACT Patient Engagement in Health R&I guidelines
D1.7	White paper for innovative routes for patient engagement
D1.8	Report on the integration of Patient reported outcomes and perspective into the CRIF

1.4 Glossary

Please refer to D9.1 for classification and glossary.

App (Application): a computer program that is designed for a particular purpose and that performs a particular task or set of tasks.

Abilhand: Name of the questionnaire to measure manual ability perceived by the patients. It assesses bimanual ability as an interview-based test focused on the perceived difficulty. The measure has been validated in Multiple Sclerosis, as well as chronic stroke, rheumatoid arthritis, systemic sclerosis, neuromuscular disorders and hand surgery adult patients. More information at www.rehab-scales.org. See Appendix 2.

eHealth: Healthcare practice supported by electronic processes and communication. Usage of the term varies as it covers just not the "Internet medicine", but also "virtually everything related to computers and medicine". In particular, eHealth related to medicine and neurodegenerative diseases is focused on the possibility to acquire discrete data on self-reported measures (electronic patient reported outcomes), electronic performance measure and electronic clinician assessed outcomes.

Indicator: A quantitative or qualitative factor or variable that provides a simple and reliable means to measure achievement, to reflect the changes connected to an intervention, or to help assess the performance of a development actor (OECD, 2010[12]).

Machine Learning: Machine learning is an application of artificial intelligence (AI) that provides systems the ability to automatically learn and improve from experience without being explicitly programmed. Machine learning focuses on the development of computer programs that can access data and use it learn for themselves. Machine learning algorithms build a mathematical model based on sample data, known as "training data", in order to make predictions or decisions without being explicitly programmed to do so.

Master Scorecard (MSC): MSC is an adaptive tool for assessing the research impact across five CRIF dimensions. The scorecard consists of a detailed list of indicators evaluating aspects of measurement linked to the different dimensions that can be tailored into different contexts and missions. By facilitating assessing research impact, selection of appropriate indicators and monitoring progress, the Master Scorecard demonstrates how the organisation is producing impact in line with its mission.

Patient(s): In order to clarify terminology for potential roles of patients' interaction presented in this and other MULTI-ACT documents, we use the term "patients" which covers the following definitions:

- **"People with the disease":** persons with lived experience of the disease;

[12] Glossary of Evaluation and Results Based Management (RBM) Terms. Retrieved from https://www.oecd.org/dac/evaluation/dcdndep/31950400.pdf.

- **"People affected by the disease":** persons or groups that are affected by the disease, including family members and caregivers.

Patients' organizations: consumer advocacy organizations involved with the population of interest. "Patients' organisations are defined as not-for profit organisations which are patient focused, and whereby people with a disease and/or their carers (the latter when patients are unable to represent themselves) represent a majority of members in governing bodies"[13]. Within the context of MULTI-ACT Patients' organizations play an important role in patient engagement as boundary body between priorities/outcomes that are individual patients' perspective (a, b) to priorities/outcomes that work at population level. Patient Organization's Representatives are persons who are mandated to represent and express the collective views of a patient organization on a specific issue or disease area.

Patient Reported Outcomes (PROs): "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (FDA, 2009), "any outcome evaluated directly by the patient him/herself and based on patient's perception of a disease and its treatment(s)" (European Medicines Agency, 2014). PROs are measured with standardized, validated questionnaires and tools, the Patient Reported Outcomes Measures (PROMs). In the context of D1.8, the terms PROMs and PROs are used in the text as synonyms and interchangeably.

Patient Reported Outcomes Measures (PROMs): standardized, validated questionnaires (which are also called instruments) completed by patients to measure their perception of their functional well-being and health status (National Health Service, 2009). PROMs are questionnaires measuring the patients' views of their health status. PROMs are used to assess a patient's health status at a particular point in time. PROMs tools can be completed either during an illness or while treating a health condition. In some cases, using pre- and post-event PROMs can help measure the impact of an intervention. PROMs are tools used to measure patient-reported outcomes (PROs). In the context of D1.8, the terms PROMs and PROs are used in the text as synonyms and interchangeably.

Promoter(s): promoters are the actors that decide to implement MULTI-ACT Governance Model within their existing or new organizations. After the implementation of the Model, they will be part of the governance bodies (i.e. Leadership Board) (see D5.4[14]).

Research & Innovation Path (R&I Path): sequence of processes and activities in R&I where patients can be engaged in order to maximize the impact of R&I. Governance Program Level and Project Development Levels are distinguished[15] :

- **Program Level:** Breaking down the boundaries, Setting research priorities, Steering institutions, Design and planning, Executing research, Evaluating research, Translation to community.
- **Project Level:** Design & plan, Conduct & operate, Evaluation, Translation to community.

[13] https://www.eu-patient.eu/About-EPF/what-is-a-patient-organisation/
[14] MULTI-ACT Deliverable D5.4: "MULTI-ACT Governance Model for collaborative initiatives", Jun 2019, https://www.multiact.eu/project-deliverables/
[15] For more information on the 7 steps R&I path please read the "MULTI-ACT Patient Engagement Guidelines, short version v0.1 May 30th 2020", https://www.multiact.eu/project-deliverables/

Return on Engagement (RoE): the benefit and impact resulting from performing patient engagement in R&I. Evaluating whether engagement adds value for different stakeholder groups can be an effective tool to further support patient engagement and requires the development metrics to measure the "return on engagement". It should always be evaluated together by both the engaging and engaged parties in line with the co-accountability approach of MULTI-ACT.

Return on Investment (ROI): a measure of the efficiency of an investment as a percentage of return relative to the investment's cost.

Science WITH patient input: intellectual and practical activity that occurs when patients meaningfully and actively collaborate in the governance, priority setting, and conduction of research, as well as in summarizing, distributing, sharing, and applying the results. In the context of MULTI-ACT, the **Science *with* patient input** aims to **maximize** the impact of R&I toward a transformational mission by engaging patients. The Science *with* patient input will then be executed in the MULTI-ACT Governance model by applying the MULTI-ACT Patient Engagement Strategy included in the present guidelines.

Science OF patient input: intellectual and practical activity that occurs when data of people with a disease are collected and used (active and passive contribution) to evaluate impact of R&I. In the context of MULTI-ACT, data about patients' experiences[16] outside the clinic (Science of patient input) are critical to **evaluate** the impact of mission-oriented health research on outcomes that matter most to patients[17]. A great deal of momentum surrounds the application of new technologies, such as mobile devices and other digital platforms, to both deliver care and generate real-world data on patients' experiences.

Stakeholder: "any individual or group that is affected by, who can influence or may have an interest in the outcomes of an organization's actions" (Freeman, 1984)[18,19].

Transformational mission: a mission as transformational or transformative means 'changing forms'. Transformational health research is a term that became increasingly common within the science and health policy community in the 2000s for research that shifts or breaks existing scientific paradigms.

---

[16] Schneeman K., Barton V., Huneycutt B. (2019), Advancing Models of Patient Engagement: Patient Organizations as Research and Data Partners, The Milken Institute, available at https://milkeninstitute.org/reports/advancing-models-patient-engagement-patient-organizations-research-and-data-partners.

[17] The Master Scorecard provides a selection of (qualitative and quantitative) indicators of research impact enable the translation of MULTI-ACT mission and agenda into action, integrating a set of top indicators on efficacy, efficiency, excellence, social impact and patient reported impact, co-selected within a multi-stakeholder perspective.

[18] Freeman E. R. (1984). Strategic management: a stakeholder approach (Latest edi). Boston, MA.

[19] **MULTI-ACT stakeholders' categories: Patients:** people with the disease (persons with lived experience of the disease); and people affected by the disease (persons or groups that are affected by the disease, including family members and caregivers). **Patient organizations:** patient associations, advocacy organizations. **Society:** individual citizens, civil society organizations and networks. **Payers and purchasers:** public or private entities responsible for underwriting the costs of health care. **Care providers:** health and social care organizations and professionals (doctors, nurses, etc.). **Policy makers:** EU institutions; national, regional and local policy makers. **Regulators:** regulatory agencies (e.g. agencies for the scientific evaluation and safety monitoring of medicines, i.e. the European Medicine Agency EMA); Health Technology Assessment (HTA) bodies. **Industry:** companies developing and selling health products (drugs, devices, applications, etc.) and services. **Research and education organizations:** Research Organizations; Universities; Education Providers; Foundations; Other research projects.

2 BACKGROUND

This section provides background information for the Patient Reported Dimension (PRD) shedding light on the concept of enabling Science with and of Patient Input (which were the core topics of MULTI-ACT WP1), on current uses of PROs in R&I, and by contextualizing the PRD.

2.1 Enabling Science with and of Patient Input

The notion of Responsible Research Innovation (RRI)[20] argues that excellence, validity and relevance are connected by engaging patients and society in the research continuum as key stakeholders with decision making role. RRI calls to action for multi-stakeholder governance and effective patient engagement.

The first RRI's call to action for effective patient engagement is the **need for a multi-stakeholder governance**. Conventional accountability models of Research and Innovation are usually not able to represent claims of the involved stakeholders, including patients. New accountability models are needed to enable Return On Engagement (ROE) and Return On Investment (ROI) by each stakeholder with the common goal of developing effective treatments and care for patients.

The second RRI's call to action is to enable patient as a key stakeholder by "**designing with the end in mind"**. Enabling patient engagement as a key stakeholder means:

- Understand patients and society needs and expectations for engagement (including underrepresented patients).
- Develop a sustainable process to optimize "science with patient input" in key decision-making points across research continuum.
- Develop agreed "science of patient input" metrics to increase evidence demonstrating the impact of patient engagement on multi-stakeholder research agenda (return on meaningful engagement).
- Ensure maximum synergies with other initiatives focusing on the development of **"science with and of patient input"** in research continuum.

The MULTI-ACT project aims to help meeting the RRI call to action (i.e. for multi-stakeholder R&I governance, patient and society engagement in R&I, and the need to "design with the end in mind") with four main inter-connected outcomes:

- **A (new) governance model allowing effective cooperation** of (all) relevant stakeholders in multi-stakeholder research initiatives and transformative governance.[21]
- **(Innovative) guidelines** for (effective) patient engagement across the health research and innovation path.[22]

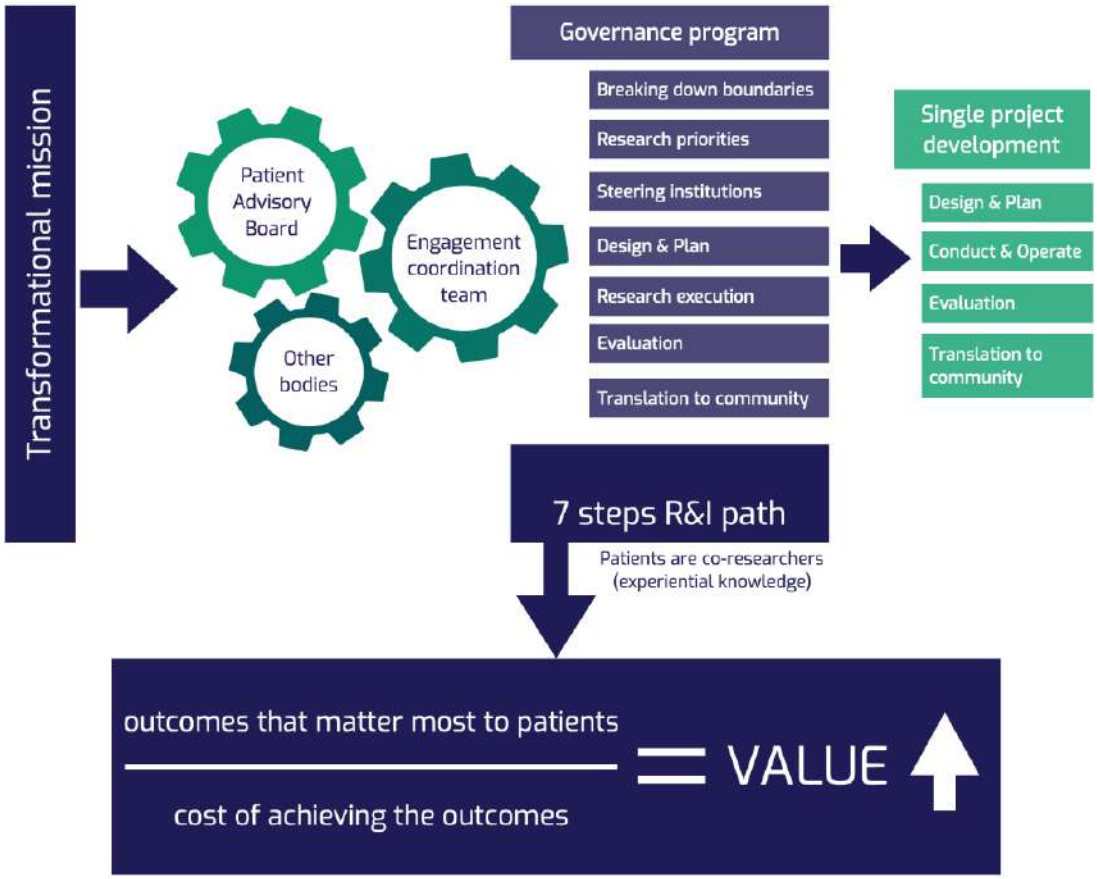
[20] https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation
[21] Deliverable D5.4: "MULTI-ACT Governance Model for collaborative initiatives", Jun 2019, https://www.multiact.eu/project-deliverables/
[22] Deliverable D1.6: "MULTI-ACT Patient Engagement Guidelines", May 2020, https://www.multiact.eu/project-deliverables/

- **A (new) tool for the assessment of the research impact** across different dimensions (including scientific excellence, mission goals achievement, social, economic and patient-reported impacts).[23]
- A **Digital Toolkit that** integrates the MULTI-ACT model and tools and that is designed to support the application by Multi-stakeholder Research Initiative of the CRIF (i.e. Governance Model, Patient Engagement, Impact Assessment Model and MSC).[24]

MULTI-ACT is focused on Brain Diseases and uses MS as the first case study with the ultimate goal to extend the MULTI-ACT framework and tools to initiatives in other Brain Disease Research Agendas.

The MULTI-ACT project foresees patients (as well as their families and caregivers) as key stakeholders in the Health Research and Innovation process. Hence, the project aims to contribute to the development of **"science with and of patient input"**.

Figure 1 MULTI-ACT Value of patient engagement



The value and effectiveness of MULTI-ACT relies on impacting outcomes that matter to patients while being sustainable in achieving this goal. Patient Engagement strategies directed to engage patients

[23] Deliverable D3.6: "MULTI-ACT Master Scorecard", Nov 2019, https://www.multiact.eu/project-deliverables/
[24] WP2 MULTI-ACT Digital Toolbox (D2.1, D2.6)

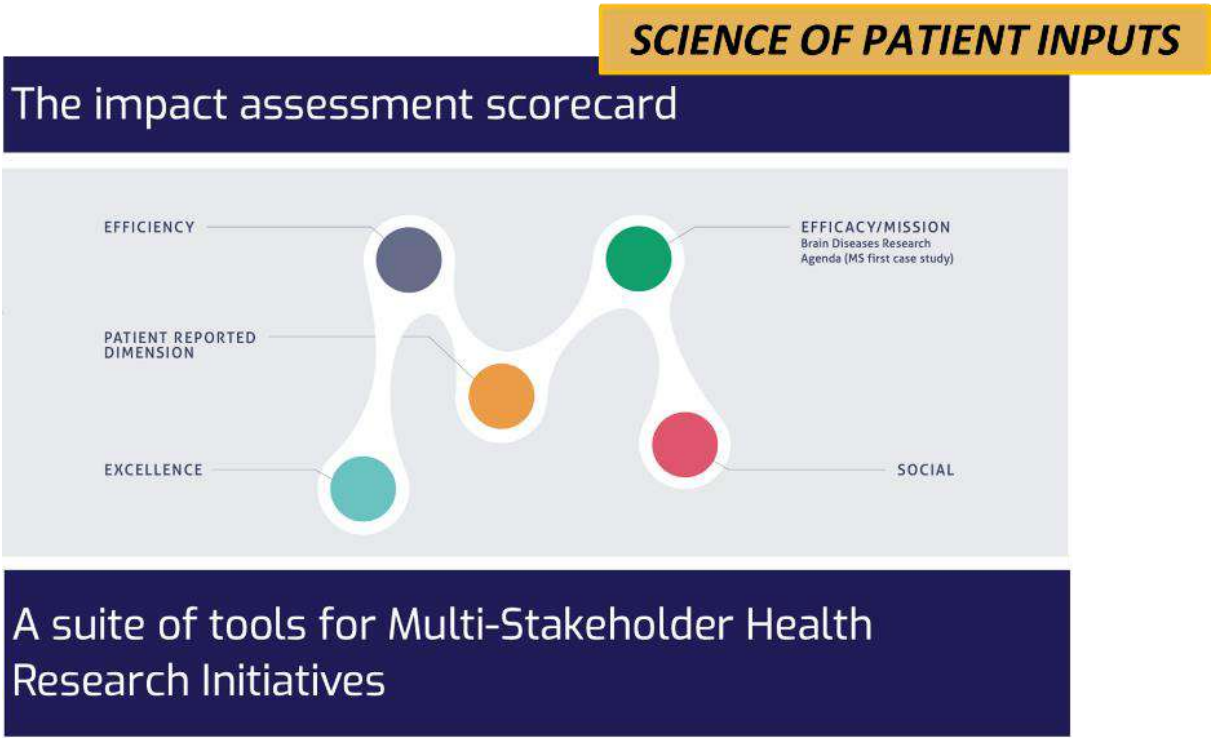
through the 7-steps R&I path, both in the governance of R&I (*with*[25]) and in its impact assessment (*of*[26]), are instrumental to meet transformational mission's health R&I.

To enable **Science WITH patient inputs** and make patients as a key stakeholder in the Multi-stakeholders Research Initiatives, MULTI-ACT proposes a governance model allowing effective cooperation of all relevant stakeholders, while to enable **Science of Patient Input**, MULTI-ACT integrated the patient-reported dimension in a transversal way throughout the four dimensions of the MULTI-ACT co-accountability model and Master Scorecard.

2.1.1 Measuring outcome that matter most to patients - Science of Patient Input

MULTI-ACT stems from the acknowledgement that stakeholder engagement in health research and innovation is an important pathway to achieving impact. It will create and implement a new model allowing for the effective cooperation of all relevant stakeholders.

Figure 2 MULTI-ACT Co-accountability Model



The mission-related dimension is one explicit driver for the co-accountability approach developed by MULTI-ACT project.

Starting from the agenda of multi-stakeholder MS Initiatives, this model will be applicable in defining the scope of health research, as well as new metrics for the evaluation of its results. Conventional metrics related to the excellence dimension are integrated with new measures related to the economic

[25] **Science WITH patient inputs** occurs when patients meaningfully and actively collaborate in the governance, priority setting, and conducting of research, sharing, and applying the results

[26] **Science OF patient inputs** occurs when data of people with a disease are used (active and passive contribution) to evaluate the impact of R&I.

and financial dimension (efficiency) and to the social dimension that relates to achieving mission success (efficacy; one explicit driver of the MULTI-ACT co-accountability approach).

The patient-reported dimension is applied in a transversal way throughout the four dimensions of the MULTI-ACT model as a tool for enabling the science of Patient Input.

Science OF patient inputs occurs when data of people with a disease are used (active and passive contribution) to evaluate the impact of R&I.

Measuring impact of health research on Patient Reported Dimension will maintain patients engaged as key stakeholder.

2.2 Patient Reported Outcomes (PROs): report of functional aspects

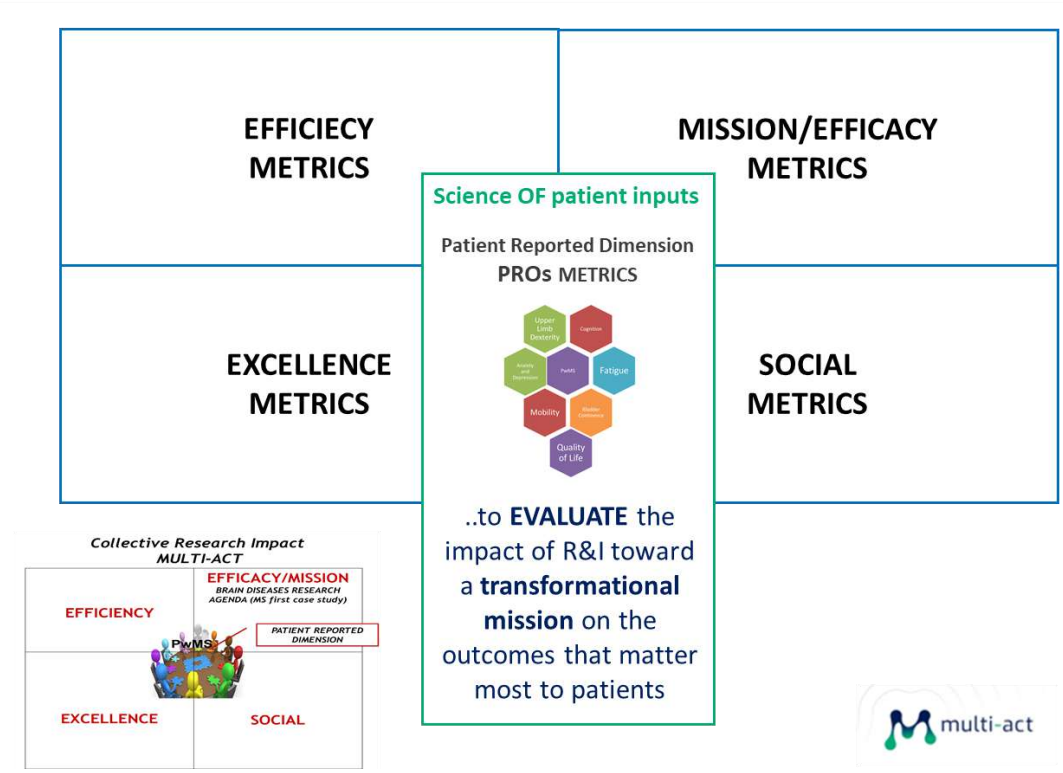
Patient Reported Outcomes (PROs) are a core example of patient engagement. However, there is still much room for improvement towards a truly participatory approach in the design of the measures themselves, which are right now settled mainly in a top-down approach by clinicians. Most PRO measures are categorized as either generic or targeted. However so far, PROs have been mainly used in post-marketing, observational studies. PROMs are increasingly used as secondary or tertiary outcomes in multiple sclerosis clinical trials on disease-modifying therapies and symptomatic treatments, whereas in rehabilitation trials are used as primary or co-primary outcomes. It is well known that there are several limitations to the use of PROMs in clinical trials and clinical activities. In particular, there is a lack of a set of standard measures and some available measures are of uncertain validity and were created without using modern test development methodology. In order to overcome these limitations, the ideal process would be to find a proper medium between PROs that work at population level in R&I and PROs that can be individualized for use in clinical practice. In this context, the Electronic health technologies (e-Health) could help meeting this challenge and could play an increased role in filling the gaps between PROs use in R&I versus clinical practice.

2.3 The Patient Reported Dimension (PRD)

Following Section 2.1.1, the Patient Reported Dimension (PRD) is the fifth dimension of the MULTI-Master Scorecard/Co-accountability Model[27], applied in a transversal modality throughout the four dimensions: Mission-Efficacy (explicit driver), Excellence, Economic, Social. The PRD, and its indicators, is as tool for enabling the Science of Patient Input since it includes indicators that are reported by patients, family and caregivers. The indicators can simply be a collection of answers to questionnaires (e.g. PRO) and active and/or passive data collection without the intervention of the clinicians (e.g. eHealth via App/ICT devices like wearables or electronic bracelets).

[27] The MULTI-ACT Collective Research Impact Framework (CRIF) is the overall MULTI-ACT Framework that includes the Governance Model, the Patient Engagement and the Co-accountability Model. The Master Scorecard (MSC) is an adaptive tool for the application of the Co-accountability Model and its five dimensions. The MSC consists of a detailed list of indicators evaluating aspects of measurement linked to the different dimensions that can be tailored into different contexts and missions.

Figure 3 Integration of Patient Reported Dimension into the CRIF



3 METHODOLOGY

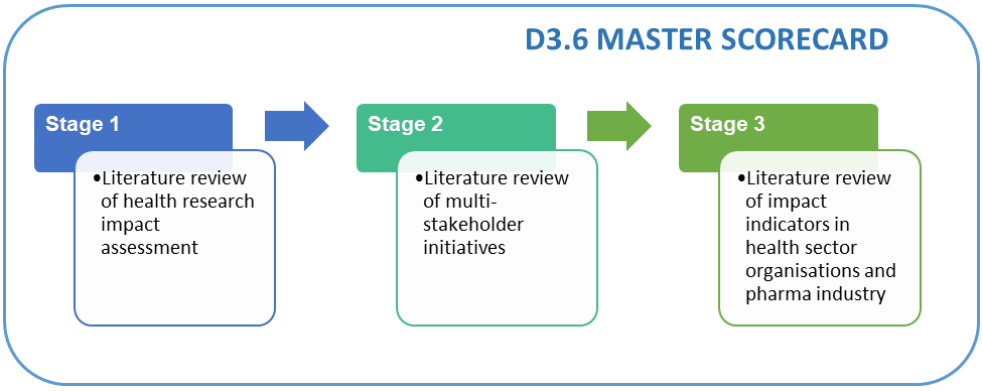
The integration of the PRD into the Co-accountability Model entailed a series of activities:

- ✓ Identification of relevant Aspects for the PRD.
- ✓ Selection of PRO measures to be proposed as indicators for each Aspect.
- ✓ Design of the Taxonomy for the indicators of the PRD.
- ✓ Integration of the PRO indicators in the MSC (first release available in D3.6) and Digital Toolbox.
- ✓ Analysis of Aspects/Indicators of the D3.6 MSC that have been included under PRD because they met the inclusion criteria (i.e. they are reported by the patients without intervention of the clinician). In particular, the indicator "Life Satisfaction Score" resulted from the literature review in WP3 and included in D3.6 MSC was finally moved to PRD as it is reported by patients via questionnaires with no intervention of the clinician.
- ✓ Development of PRD indicators able to assess the effectiveness of Patient Engagement from the patient perspective building on the indicators included in the MULTI-ACT Patient Engagement Guidelines (D1.6).
- ✓ Development of aspects for the indicator that evaluate the Return on Patient Engagement (RoE) included in D1.6, and assignment of the correspondent dimension.

The methodology used to identify the PRD aspects and indicators built on:

1. previous activities described in D3.6 MSC (see *Figure 4 Development of WP3 Indicator Database*: the **WP3 Literature review** of *i) health research impact assessment, ii) multi-stakeholder initiatives, and iii) impact indicators in health sector organisations and pharma industry)*, and the final **structure of the Co-accountability Model and MSC**: e.g. concept for the aspect/dimensions, the format on how to describe indicators, the template for the excel database, and also some indicators that emerged from the WP3 literature review and met the inclusion criteria for the PRD[28].

Figure 4 Development of WP3 Indicator Database



[28] The "Life Satisfaction Score" indicator was moved to PRD as it is reported by the patient without intervention of the clinicians and met the inclusion criteria of the PRD.

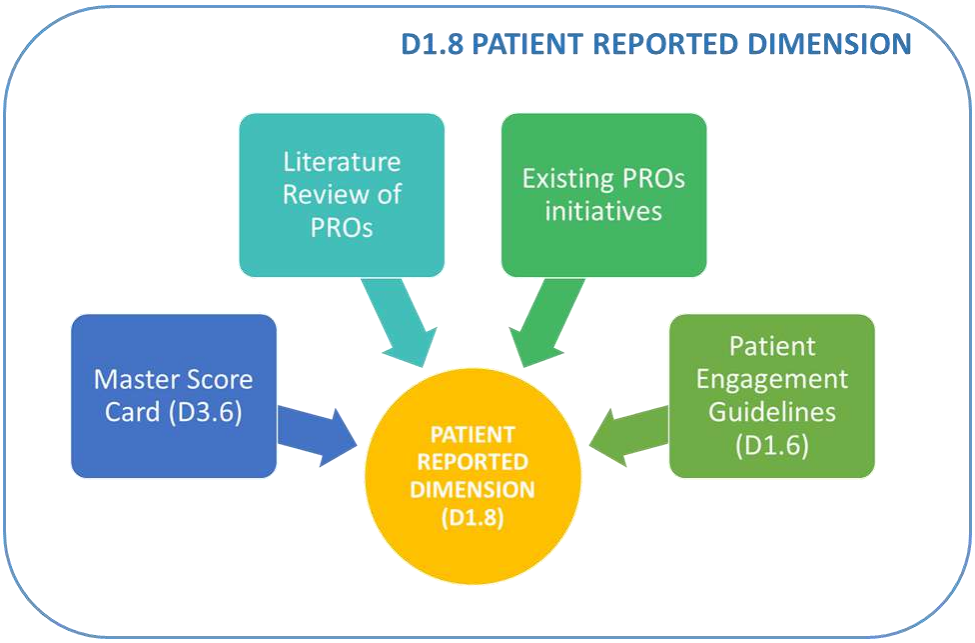
2. the **Literature Review**[29] on current evidence of PRO usage for R&I assessment and PRO relevant existing initiatives (T1.5);

3. the **Patient Engagement Guidelines**[30] (D1.6).

In particular the MULTI-ACT Patient Engagement Guidelines provide a selection of indicators for assessing the Return on Patient Engagement (RoE) that have been analyzed for their inclusion in the PRD and the MULTI-ACT Master Scorecard/co-accountability model.

The final MSC to be included in the MULTI-ACT Digital Toolbox will merge indicators included in the D3.6 MSC database (dimensions: mission/efficacy, excellence, efficiency, social) and the ones included in the PRD – database of D1.8 providing the full MSC of the CRIF.

Figure 5 Development of Patient Reported Dimension (D1.8)



3.1 Building on existing PROs initiatives

The activities of T1.5 builds mainly on two current initiatives of FISM in the PROs domain, the **Patient Reported Outcomes Initiative for MS (PROMS)** and the **PROMOPRO-MS database**. The PROMOPRO-MS database and related research activities are also strictly connected and developed in partnership with the US PCORI[31] funded initiative of Accelerated Cure for MS, namely iConquerMS[32].

[29] Brichetto G, Zaratin P. Measuring outcomes that matter most to people with multiple sclerosis: the role of patient-reported outcomes. Curr Opin Neurol. 2020;33(3):295-299. doi:10.1097/WCO.0000000000000821

[30] MULTI-ACT Patient Engagement Guidelines, short version v0.1 May 30th 2020, https://www.multiact.eu/project-deliverables/

[31] Patient-Centered Outcomes Research Institute (www.pcori.org)

[32] https://www.iconquerms.org/for-researchers

3.1.1 The Patient Reported Outcomes Initiative for MS (PROMS).

D1.8 directions are aligned with the current international effort on the topic of PROs, in fact the newly born PROMS[33] initiative aims to develop a strategic agenda shared by all relevant stakeholders to help meeting the challenge of developing PRO measures that correspond to the needs of all stakeholders.

The PROMS initiative started in 2019 and funded by European Charcot Foundation and FISM, aims to ensure an informed and quality participation of people with MS in the decision-making processes of research and healthcare regarding their treatments and performances. The initiative focuses on the symptoms and aspects of living with MS that matter most to patients. Efforts to enable the uptake of existing PRO into clinical practice and regulatory agencies decision-making processes will be greatly enhanced and informed by a commonly held strategic PRO research agenda and roadmap, shared by all relevant stakeholders. The PROMS initiative will take a global approach to tackling this challenge. It will advocate for a set of standardised PROs to be used in therapies development and health care and promote research to develop new PROs to meet the needs of all relevant stakeholders. The programme of work will be led and coordinated jointly by the European Charcot Foundation and the MS International Federation. It will build on the experience and expertise of the Italian MS Society, who will act as the lead agency on behalf of the global MSIF movement.

The activities of T1.5 have taken and will take advantage from the collaboration of FISM with the PROMS initiative[34]. The work of PROMS has been indeed influenced by the collaboration with FISM. In fact, PROMS Initiative took insights from the MULTI-ACT Patient Engagement Strategy and Guidelines and adopted the governance body of the Engagement Coordination Team to be in charge of patient engagement activities. Indicators to measure the return on engagement will be used. In the future and exploitation of MULTI-ACT, thanks to the connection between the two initiatives, all results from PROMS could inform and be integrated into the PRD.The PROMOPRO-MS database

FISM in 2013 promoted and funded the initiative: “A new functional PROfile to MOnitor the PROgression of disability in Multiple Sclerosis” (PROMOPRO-MS). This project is mainly focused in identifying a core set of outcomes for monitoring progression of disability in Multiple Sclerosis, allowing more personalized therapeutic and/or rehabilitative interventions in patients with MS.

It is well known that clinical scales currently used for the assessment of people with MS (PwMS) do not provide sensitive measures of disease progression. EDSS and MSFC appear to be inadequate to capture the change of the patients’ clinical condition. PROMOPRO-MS is designed taking into account functional domains that matter most to PwMS prioritized with a clinician driven design. PROMOPRO-MS is based on key scientific questions: identify a set of PCO/PRO related to mobility, fatigue, cognitive performances, emotional status, bladder continence, quality of life (EDSS, FIM™, Abilhand, OAB-Q, M-FIS, SDMT, MoCA Questionnaire, PASAT, HADS, LSI); validating a “functional profile” of MS based on

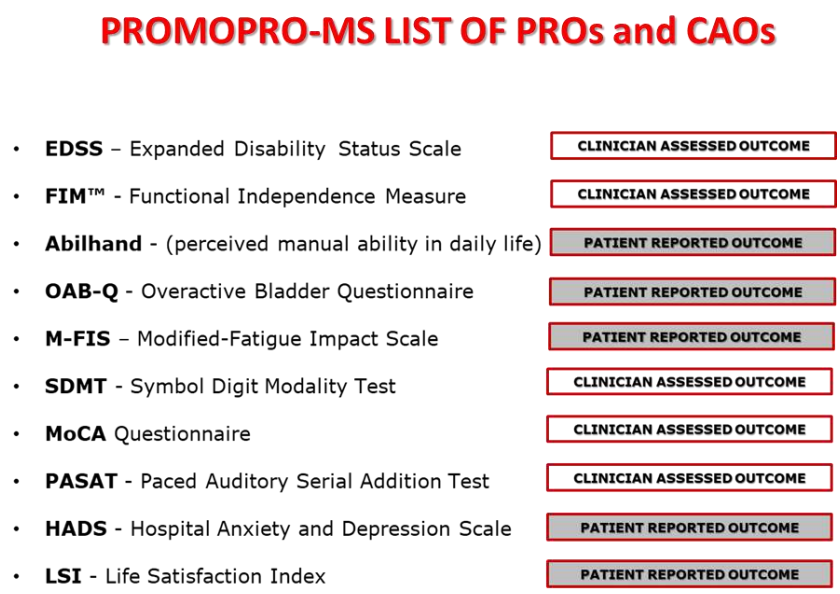
[33] Measuring outcomes that matter most to people with multiple sclerosis. https://www.multiact.eu/publications

[34] The Multiple Sclerosis International Federation (MSIF) and the European Charcot Foundation (ECF) will jointly lead and coordinate the Patient Reported Outcome for Multiple Sclerosis (PROMS) initiative. The Italian MS Society (AISM), through its Foundation (FISM) will act as the MSIF Lead Agency for, and on behalf of the Global MSIF Movement. In this role FISM is also co-chairing the Scientific Steering Committee.

meaningful variables and measures; improving the disease course detection; quantifying disease progression; identifying the best disease predictors.

The PROMOPRO-MS database provided relevant insights for the development of the PRD, such as the most relevant PROs to be included in the PRD to evaluate the impact of R&I on the outcomes that most matter to patients. In fact, the PROs selected for PROMOPRO-MS database and, therefore, for the development of the PRD have been identified through a literature research with the aim of identify the most suitable indicators for the different functional domains involved in prediction of disease evolution.

Figure 6 PROMOPRO-MS: list of PROs and CAOs



3.1.2 iConquerMS developed by Accelerated Cure Project for MS

iConquerMS™[35] is a research network composed of people with MS and people who care about MS contributing with health data, biosamples, knowledge and ideas to enable and accelerate MS research. Data, biosamples and insights contributed by iConquerMS™ participants under informed consent are available to researchers investigating topics important to people with MS. Research topics can include treatments and outcomes, lifestyle and activities, quality of life, employment and finances, health care, biomarkers of MS, and many other topics. iConquerMS™ was created by the non-profit Accelerated Cure Project[36] in collaboration with leading healthcare communications firm Feinstein Kean Healthcare[37] and the Complex Adaptive Systems Initiative[38] at Arizona State University. It is governed by a board and committees populated by experts in various fields, the majority of whom have been diagnosed with MS. iConquerMS™ is supported by the Patient Centered Outcomes Research Initiative

[35] https://www.iconquerms.org/for-researchers
[36] www.acceleratedcure.org
[37] http://fkhealth.com
[38] https://casi.asu.edu

(PCORI) and is part of PCORnet, the National Patient-Centered Clinical Research Network[39], a large, highly representative, national network for conducting clinical outcomes research.

In particular, the connection with FISM and iConquerMS is devoted to understand if the PRO used in both the initiatives are effective and valid to identify disease evolution. This process has developed the concept of META-DATA in PROs that will be used in the PRD.

Figure 7 iConquerMS™ database - Neuro-QoL

Accelerated Cure project for multiple sclerosis

iConquerMS™

Rank Order	Neuro-QoL Domain (5-point Likert scale questions) Scored: 1[worst], 2, 3, 4 , 5[best]	Average Score (N = ~1,400)
1	Fatigue	2.89
2	Satisfaction with Social Roles and Activities	3.09
3	Sleep Disturbance	3.59
4	Positive Affect and Well Being	3.59
5	Ability to Participate in Social Roles and Activities	3.60
6	Anxiety	3.67
7	Cognitive Function	3.71
8	Emotional and Behavioral Dyscontrol	3.92
9	Lower Extremity Functional Mobility	3.93
10	Depression	4.11
11	Stigma	4.17
12	Communication	4.41
13	Upper Extremity Function Fine Motor ADL	4.54

[39] https://pcornet.org/

4 INTEGRATION OF PRD INTO THE CRIF

Task T1.5 deals with the integration of PRD into CRIF. The CRIF is the overall MULTI-ACT Framework that includes the Governance Model, the Patient Engagement and the Co-accountability Model. The Master Scorecard (MSC D3.6) is an adaptive tool for the application of the Co-accountability Model and its five dimensions. The MSC consists of a detailed list of indicators evaluating aspects of measurement linked to the different dimensions that can be tailored into different contexts and missions.

This section presents the aspects and indicators included under the PRD, including the relation with the MSC, the taxonomy and the Digital Toolbox. This section also details the indicators groups (i.e. PRO, RoE), and provides a discussion on the opportunity to exploit the PRD with eHealth indicators.

4.1 PRD's aspects and indicators

The aspects included under the PRD refer to the Functional Domain that matter most to patients, they are n.8, as indicated in the Table 1 Aspects of Patient Reported Dimension.

Table 1 Aspects of Patient Reported Dimension

Patient reported dimension	Description
Patient Satisfaction	Percentage change in how patients' **quality of life** have been improved after the care received (self-reported)
Anxiety and Depression	Percentage change in how patients are satisfied with their level of **anxiety and depression** after the care received (self-reported)
Fatigue	Percentage change in how patients are satisfied with their level of **fatigue** after the care received (self-reported)
Upper-limb dexterity	Percentage change in how patients are satisfied with their level of **upper-limb dexterity** after the care received (self-reported)
Locomotion	Percentage change in how patients are satisfied with their level of **locomotion and lower limb dexterity** after the care received (self-reported)
Cognitive function	Percentage change in how patients are satisfied with their level of **cognitive functions** after the care received (self-reported)
Bladder function	Percentage change in how patients are satisfied with their level of **bladder functions** after the care received (self-reported)
Return on Engagement	Quantitative and qualitative indication on how patients are satisfied with their level of **engagement in R&I** and its final outcomes (self-reported)

4.2 Relation to the other dimensions of the Master scorecard D3.6

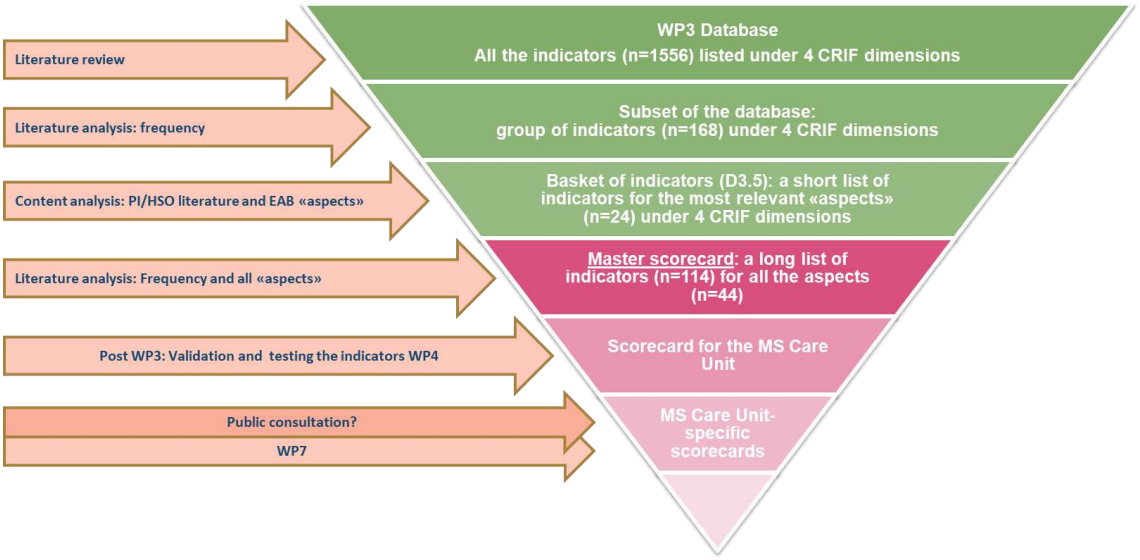
The construction of the Master Scorecard is the main outcome of WP3. The first step was the development of the Database gathering the different indicators for evaluating health research impact and multi-stakeholder initiatives that were identified in the literature reviews. Secondly, the indicators were classified according to the co-accountability dimensions (social, efficiency, mission/efficacy and excellence) and the stage of the research process to which they were related. The Patient-Reported

Dimension is applied in a transversal modality throughout the 4 dimensions of the co-accountability model.

The PRD builds on the structure of the excel format used for the MSC D3.6. In fact, the PRD indicators have been implemented into the Digital Toolbox in the same approach as for the other dimensions.

The D3.6 MSC is merged with the D1.8 PRD to produce the Master Scorecard/Co-accountability model of the CRIF, resulting in 5 dimensions: mission/efficacy, excellence, efficiency, social, and the transversal patient-reported. The *Figure 8 WP3 Work Flow*, show how the WP1 (T1.5) activities are linked to the work flow of WP3.

Figure 8 WP3 Work Flow



The final number of indicators is included in the table below. A description of indicators is available in the excel Appendixes of D3.6 and D1.8, as well as implemented in the Digital Toolbox, that will be publicly available in its second version from November 2020 (i.e. MULTI-ACT Digital Toolbox 2.0).

Table 2 Numbers of CRIF Aspects and Indicators present in the final version of the MSC

Dimension	Aspects	Core indicators	Additional indicators
Patient Reported	8	10	2
Economic	9	9	11
Efficacy	9	9	13
Social	6	7	8
Excellence	20	20	37
Total	**51**	**53**	**69**

4.3 PRD Taxonomy and Digital Toolbox

In order to integrate the PRD into the Digital Toolbox, we defined the taxonomy and integrated the indicators in the D3.6 Master Scorecard database (see APPENDIX 1 – Patient Reported Dimension Master Scorecard).

TAXONOMY

Level 1: CRIF Dimension (i.e. Patient Reported)

Level 2: Aspect (i.e. Functional domains that matter to patients)

Level 3: Indicator Groups (i.e. PROs or eHealth)

Group: Patient Reported Outcomes (PROs)

Level 4: Specific PRO indicator (Core/Additional)

Group: eHealth

Level 4: Specific eHealth indicator (Core/Additional)

The taxonomy has been implemented in the Digital Toolbox (see *Figure 9 Conceptualization of Patient Reported Dimension into the Digital Toolbox*), following the methodology used for all the CRIF Dimensions, which entails defining the higher-level Master Scorecard taxonomy and associating each indicator with their respective taxonomy branch/leaf, as it is shown in *Figure 10 Patient Reported and Other Dimensions into the Digital Toolbox*, and as it has been presented in detail in deliverable D2.5. This allows the integration of all relative information in two separate interlinked entities, allowing any needed changes to be carried out effortlessly, i.e. Re-association of an indicator to a new taxonomy element. The Digital Toolbox is a tool to support the application of the CRIF Framework.

Figure 9 Conceptualization of Patient Reported Dimension into the Digital Toolbox

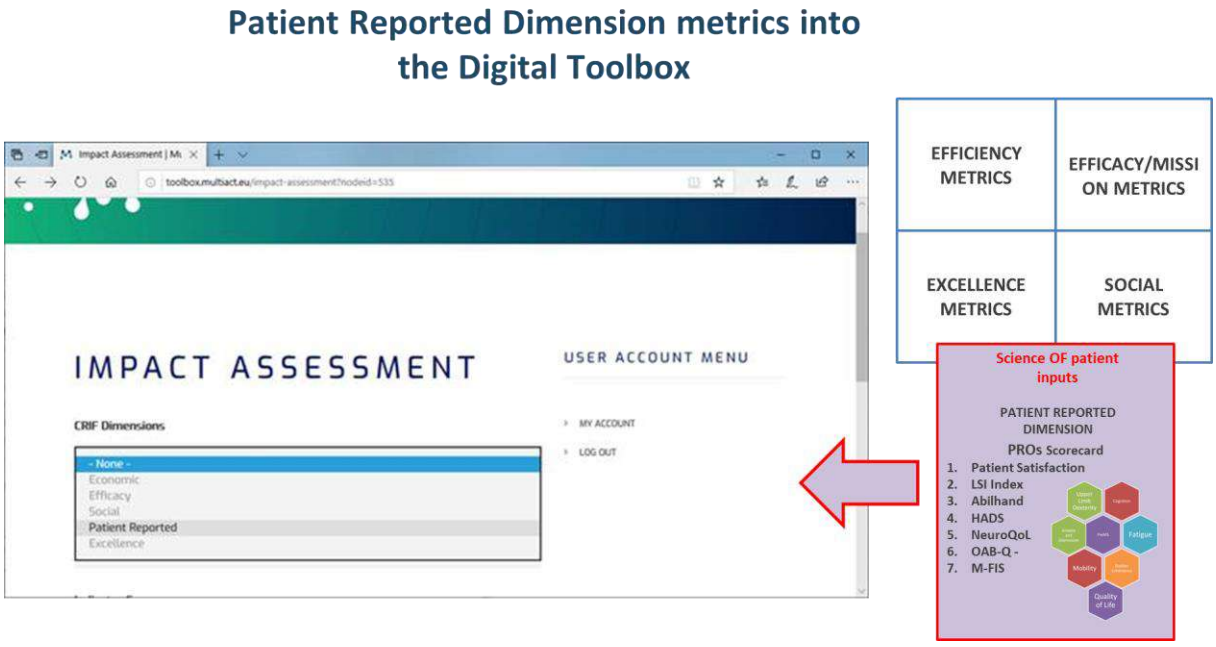
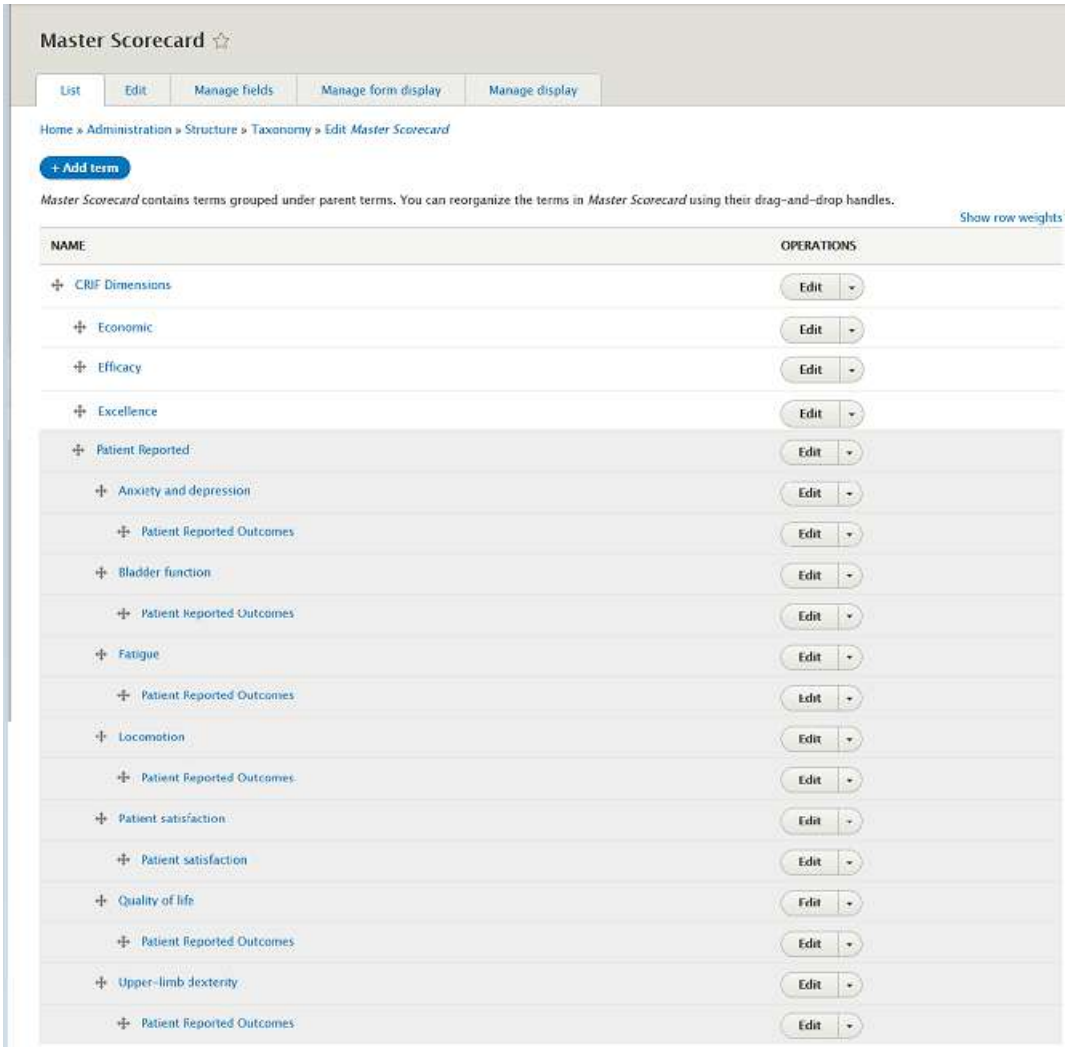


Figure 10 Patient Reported and Other Dimensions into the Digital Toolbox



4.4 Indicators' groups

The PRD includes indicators that are reported by patients, family and caregivers. The indicators can simply be a collection of answers to questionnaires not influenced by clinicians (e.g. PRO) and active and/or passive data collection without the intervention of the clinicians (e.g. eHealth via App/ICT devices like wearables or electronic bracelets). The main aspect of the PRD is that it reports the perspective of the patient (PROs, RoE) or provides continues objective data (eHealth), therefore it's not influenced by the clinician.

The PRD includes aspects and indicators of "Science of Patient input" (i.e. RoE: related to the psychosocial aspects; PROs: related to functional aspects).

In particular, MULTI-ACT focuses on the PROs (functional reported aspects) as it foresees the development of PROs as key indicators of impact, instrumental to enable a multi-stakeholder approach and effective patient engagement, and the current deliverable aim to meet this strategic intent. The fact that PROs are scientifically validated measures reported by the patients (final beneficiary of the health research) capture the interest of all the stakeholders.

The psychosocial aspects (RoE) are important, and as reported in the landscape analysis, there is the need to develop effective indicators. To this regard, a development plan for RoE indicators is also included in this document.

As anticipated in the taxonomy, two main categories of indicators have been identified:

1. Patient Reported Outcomes (PROs)
2. Qualitative indicators to assess the Return on Patient Engagement (RoE)

This paragraph presents the specificity of the two categories and their division in indicators groups.

4.4.1 Functional aspects: PRO Indicators

The PRD includes the so called "Patient Reported Outcomes". Patient-reported outcomes (PROs) are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else[40]" (FDA, 2009), "any outcome evaluated directly by the patient him/herself and based on patient's perception of a disease and its treatment(s)" (European Medicines Agency, 2014).

Figure 11 Functional domains that matter to people with MS (PwMS)

PROs are measured with standardized, validated questionnaires and tools, the Patient Reported Outcomes Measures (PROMs). PROMs are used to assess the patients' views of their health status at a particular point in time. PROMs tools can be completed either during an illness or while treating a health condition. In some cases, using pre- and post-event PROMs can help measure the impact of an intervention.

[40] FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed September 25, 2013.

In the context of D1.8, the terms PROMs and PROs are used in the text as synonyms and interchangeably.

In particular, PROMs have been selected based on the functional domains that matter most to people affected by MS: Quality of Life and Satisfaction, Anxiety and Depression, Fatigue, Upper-limb dexterity, Locomotion, Cognitive function, Bladder function. There is consensus in the clinical and scientific community that not only the long-established Expanded Disability Status Scale (EDSS), but also the Multiple Sclerosis Functional Composite (MSFC) (Fischer JS et al 1999[41]) are inadequate to capture the change of the patients' clinical condition (Cohen JA et al 2012)[42].

4.4.2 Description of PROs Indicators

A brief description of the PROMs is presented in the table below. The full PROMs are presented in APPENDIX 2 – PROMs.

Table 3 Rationale of PROs indicators

Indicator name	Rationale
Life Satisfaction Index	The indicator provides a standardized measure of the percentage change of **patients' satisfaction with their life** and therefore it facilitates comparisons.
Abilhand - Manual ability for adults with upper limb impairment	The indicator provides a standardized measure of the percentage change of patients' satisfaction with their **level of upper-limb dexterity** and therefore it facilitates comparisons.
HADS - Hospital Anxiety and Depression Scale	The indicator provides a standardized measure of the percentage change of patients' satisfaction with their **level of Anxiety and Depressio**n and therefore it facilitates comparisons.
Neuro-QoL - Quality of Life in Neurological Disorders	The indicator provides a standardized measure of the percentage change of patients' satisfaction with their **quality of life** and therefore it facilitates comparisons.
OAB-Q - Overactive Bladder Questionnaire	The indicator provides a standardized measure of patients' satisfaction with their **level of bladder function** and therefore it facilitates comparisons. This indicator is disease-specific (MS).
M-FIS - Modified-Fatigue-Impact-Scale	The indicator provides a standardized measure of patients' satisfaction with their **level of motor, cognitive, psycho-social fatigue** and therefore it facilitates comparisons. This indicator is disease-specific (MS).

[41] Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Mult Scler. 1999;5(4):244-250. doi:10.1177/135245859900500409

[42] Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819-1828. doi:10.1016/S0140-6736(12)61769-3

Twelve Item MS Walking Scale (MSWS-12)	The indicator provides a standardized measure of patients' satisfaction with their **level of locomotion** and therefore it facilitates comparisons. This indicator is disease-specific (MS).

4.4.3 Taxonomy of PROs Indicators

The taxonomy of PRD is presented below:

Level 1 – CRIF Dimension: Patient Reported

Level 2 - Aspect: Patient Satisfaction
- **Indicator Groups**
- **Level 3 - Group: Patient Reported Outcomes (PROs)**
  - Level 4 – Indicator: Neuro-QoL - Quality of Life in Neurological Disorders - Core
  - Level 4 – Indicator: LSI - Life Satisfaction Index - Additional
  - Level 4 – Indicator: Patient satisfaction score[43] - Additional
- **Level 3 - Group: eHealth**
  - Level 4 - Indicator: data on the Quality of Life collected via App/ICT devices (e.g. FISM Mapping-MS[44] device)

Level 2 - Aspect: Anxiety and Depression
- **Indicator Group**
- **Level 3 - Group: Patient Reported Outcomes (PROs)**
  - Level 4 – Indicator: HADS - Hospital Anxiety and Depression Scale - Core
- **Level 3 - Group: eHealth**
  - Level 4 - Indicator: data on Anxiety and Depression collected via App/ICT devices

Level 2 - Aspect: Fatigue
- **Indicator Group**
- **Level 3 - Group: Patient Reported Outcomes (PROs)**
  - Level 4 – Indicator: M-FIS - Modified-Fatigue-Impact-Scale (PRO-MS Specific) - Core
- **Level 3 - Group: eHealth**
  - Level 4 - Indicator: data on the fatigue collected via App/ICT devices

Level 2 - Aspect: Upper-limb dexterity
- **Indicator Group**
- **Level 3 - Group: Patient Reported Outcomes (PROs)**
  - Level 4 – Indicator: Abilhand - Manual ability for adults with upper limb impairment - Core
- **Level 3 - Group: eHealth**
  - Level 4 - Indicator: data on the Upper-limb dexterity collected via App/ICT devices

[43] The indicator Life Satisfaction Score (LSS) was under the Mission/Efficacy Dimension of the Master Score Card (D3.6 – Indicator n.41). It has been moved to PRD as it is reported directly by the patients without intervention of the clinicians.

[44] Marziniak M, Brichetto G, Feys P, Meyding-Lamadé U, Vernon K, Meuth SG
The Use of Digital and Remote Communication Technologies as a Tool for Multiple Sclerosis Management: Narrative Review JMIR Rehabil Assist Technol 2018;5(1):e5 URL: https://rehab.jmir.org/2018/1/e5 DOI: 10.2196/rehab.7805 PMID: 29691208 PMCID: 5941090

Level 2 - Aspect: Bladder function
Indicator Group
Level 3 - Group: Patient Reported Outcomes (PROs)
Level 4 – Indicator: OAB-Q - Overactive Bladder Questionnaire (PRO-MS Specific) - Core
Level 3 - Group: eHealth
Level 4 - Indicator: data on the Bladder function collected via App/ICT devices

Level 2 - Aspect: Locomotion
Level 3 - Group: Patient Reported Outcomes (PROs)
Level 4 - Indicator: Walking Scale – 12 PRO on walking ability in MS (PRO-MS Specific) - Core
Level 3 - Group: eHealth
Level 4 - Indicator: data on the Lower-limb dexterity collected via App/ICT devices (e.g. pedometer)

Level 2 - Aspect: Cognitive function
Level 3 - Group: Patient Reported Outcomes (PROs)
Level 4 – Indicator: PRO on Cognitive Function[45]
Level 3 - Group: eHealth
Level 4 - Indicator: data on the Cognitive Functions collected via App/ICT devices

4.4.4 Psycho-social aspects: indicators for Return on Engagement (RoE)

Building on the Public Consultation performed under WP1 activities and the MULTI-ACT Patient Engagement Guidelines[46], a selection of indicators that can be used for assessing the Return on Patient Engagement (RoE) have been identified. The guidelines present indicators to assess the **performance** of patient engagement (i.e. the success of the initiative in terms of participation) and the **effectiveness** of patient engagement (i.e. the success of the initiative in term of real impact of the participation on the research process). The indicators to assess effectiveness of patient engagement that are reported by the patients could be developed into PRO indicators to be included under the PRD.

In particular, three indicators have the potential to be developed into questionnaire and PRO:

- The analysis of whether patients' expectation with respect to the research and mission of the initiative are met;
- Endorsements given by patients to research activities and results;
  Patients' expectation and satisfaction for and with their engagement in research.

4.4.5 Description of RoE Indicators

[45] Currently a PRO on cognitive function is not available, there is a need to develop a PRO on cognition and this aspect could be addressed by FISM in future research activities, also providing opportunity for exploitation. Even if a PRO on Cognition is not available yet, it's important to foreseen an aspect under the PRD on this specific functional domain.

[46] MULTI-ACT Patient Engagement Guidelines, short version v0.1 May 30th 2020, https://www.multiact.eu/project-deliverables/

The table below presents an example on how the indicators included in the guidelines (D1.6) could be integrated into the Digital Toolbox under the PRD as qualitative indicators.

Table 4 Rationale of RoE indicators

Indicator name	Rationale
Mission/agenda aligned to patients' needs.	The indicator provides an analysis of whether patients' expectation with respect to the research and mission of the initiative are met. A questionnaire developed ad hoc for assessing if the mission of the initiative/research meet the need of patients is submitted to patients.
Endorsement of patients	The indicator provides evidence on the endorsements given by patients to research activities and results after their engagement and their influence in the process. A questionnaire developed ad hoc for assessing if the patients endorse the research results is submitted to patients.
Patient engagement: expectation and satisfaction	The indicator provides evidence on the expectation and satisfaction of patients for/with their engagement in the research, including identification of benefits and critical issues (pros and cons). A questionnaire developed ad hoc for assessing if the patients satisfaction with the engagement is submitted to patients.

The above-mentioned indicators present the opportunity to be developed also in quantitative indicators, as for example Patient Reported Outcomes on Return on Engagement. FISM will assess and include in the MULTI-ACT Exploitation Plan (D8.5) the individual exploitation activities related to this aspect,

The other relevant RoE indicators identified in the D1.6 are included under the dimension of the MSC accordingly to their relevance to the different aspects (e.g. measurement of how patient engagement has influenced the mission = Mission/Efficacy dimension).

4.4.6 Taxonomy of RoE Indicators

The taxonomy below presents the metrics included in the MULTI-ACT Patient Engagement Guidelines (D1.6) elaborated with aspects for their potential integration into the Digital Toolbox.

Aspects related to "Return on patient Engagement"

Dimension: Patient Reported

Aspect: Research's relevance to patients

Indicator Group: Return on Engagement (RoE)

- Indicator: Mission/agenda aligned to patients' needs: The analysis of whether patients' expectation with respect to the research and mission of the initiative are met

Aspect: Patients' endorsement

Indicator Group: Return on Engagement (RoE)

- Indicator: Endorsement of patients: Endorsements given by patients to research activities and results

Aspect: Patients' satisfaction with the engagement

Indicator Group: Return on Engagement (RoE)

- Indicator: Report on Patient Satisfaction with the experience of being engaged in research.

Dimension: Efficacy/Mission

Aspect: Patient engagement according to the mission/agenda

Indicator Group: Return on Engagement (RoE)

- Indicator: Projects involving patients in research activities, according to the needs of the mission

Aspect: Endorsement of patients

Indicator Group: Return on Engagement (RoE)

- Indicator: Changes in the research process according to the review made by patient
- Indicator: Endorsements given by patient organisations

Aspect: Impact on Patient Reported Outcomes (PROs)

Indicator Group: Return on Engagement (RoE)

- Indicator: Projects that include and show an effect on Patient Reported Outcomes (indicator 43 in D3.6 MSC)

Dimension: Social

Aspect: Representativeness and balance

Indicator Group: Return on Engagement (RoE)

- Indicator: Degree of representativeness: the number of the underrepresented population and of the disadvantaged patients involved in the research
- Indicator: Analysis of whether the value of patient contribution if the same as others stakeholders

Aspect: Patient Communication and Dissemination

Indicator Group: Return on Engagement (RoE)

- Indicator: dissemination actions carried out by patients
- Indicator: scientific articles in which patients are co-authors and/or reviewers

5 OPPORTUNITIES FOR EXPLOITATION OF PRD

The integration of the PRD in the Digital Toolbox provides opportunities for exploitation. In particular, the PRO data collection is relevant for R&I purposes and this function could be implemented in the Digital Toolbox providing opportunities for the Exploitation of MULTI-ACT after the end of the project (i.e. MULTI-ACT Digital Toolbox 3.0).

The Digital Toolbox, building on the existing initiatives and database on PROs, could provide the functionality to collect and analyse PRO data.

The MULTI-ACT Digital Toolbox 2.0 (M30), building on the PROMOPRO-MS database, will provide the interface to collect data related to PRO indicators and facilitate the use of the indicators, laying the groundwork for the development and implementation of the data collection algorithm for the Exploitation phase. The algorithm could build on the existing initiatives and database on PROs and relevant FISM results[47].

Following the interesting results published by FISM, the purpose of MULTI-ACT MSC/Co-accountability Model is to evaluate the impact of R&I on outcomes that matter most to patients could be expanded in its version 3.0 by providing tools connected to PRO, such as the monitoring of disease evaluation and progression.

Moreover, the Consortium foresees the possibility to include in the MULTI-ACT MSC/Co-accountability Model eHealth indicators to be collected via ICT devices. Considering that there isn't a standard ICT device or method to collect eHealth data, we expect that each initiative relies on its own method, and thus the indicators related to the eHealth data collection is left to the decision of the initiatives. The additional eHealth indicators could be included in the Digital MSC via a specific function in the Digital Toolbox functionality.

5.1 Machine Learning algorithm applied to PROs

Literature shows that machine learning (ML) technique in brain disease area is mainly used for Detection of Neurological Disorders, and in particular for computer-aided diagnosis (CAD) system trained with patient data, physiological signals and images based on adroit integration of advanced signal processing ML and Artificial Intelligence (AI) techniques[48]. This use can support researchers to produce more efficient research results and clinicians to make better clinical decisions. It is important to note that access to large data sets is needed for the validation of all the developed ML/AI techniques**.** ML applied to patient-reported (PROs) and clinical-assessed outcomes (CAOs) in brain disease patients could favour the shift from the current reactive medicine mode towards a personalized, predictive, preventive and participatory medicine**.** In particular, the application of ML to PROs and CAOs could become the keystone to better detect the rapid changes due to the pathology evolution and, consequently, to pave a timelier, low-cost and patient-centred way for people with MS (PwMS) management. Although, ML approaches have proven to be able to extract meaningful

[47] Brichetto G, Monti Bragadin M, Fiorini S, et al. The hidden information in patient-reported outcomes and clinician-assessed outcomes: multiple sclerosis as a proof of concept of a machine learning approach. Neurol Sci. 2020;41(2):459-462. doi:10.1007/s10072-019-04093-x

[48] Raghavendra U, Acharya UR, Adeli H. Artificial Intelligence Techniques for Automated Diagnosis of Neurological Disorders. Eur Neurol. 2019;82(1-3):41-64. doi:10.1159/000504292

information hidden in the data in a wide range of biomedical applications, their role in analysing PROs and CAOs of PwMS has still to be fully consolidated. Several instrumental measures (e.g. MRI) offer established and well-known biomarkers of disease activity, especially for relapsing-remitting (RR) course of MS; those are currently less useful in detecting the transition from RR to the secondary progressive (SP) form. Thus, ML applied to PROs and CAOs could be valuable to fill this gap or to improve MRI prediction power.

5.2 PRO data collection in the Digital Toolbox

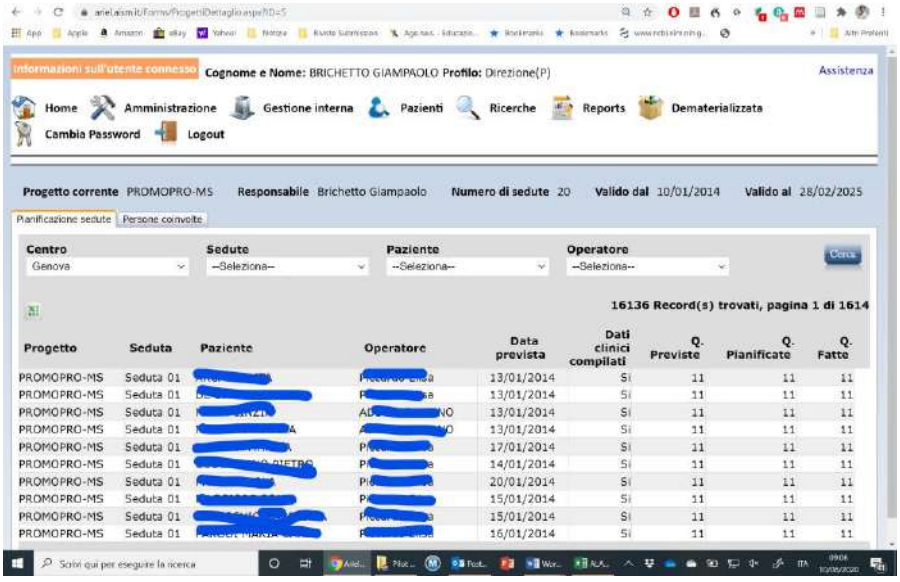
The Consortium will propose an example of the interface for data collection in the Digital Toolbox by developing the interface for the Aspect "Anxiety & Depression", indicator "HADS - Hospital Anxiety and Depression Scale".

The development of the data collection function for the PRD, will take advantage from the PROMOPRO-MS database (see *Figure 12 FISM PROMOPRO-MS Database Interface*[49]).

The next steps for exploiting the data collection function will be dedicated to:

- Merging of two data sets FISM-iConquerMS in order to identify metadata that could facilitate patient reported dimension calculation (Figure 13 Merging the PROMOPRO-MS and I Conquer MS databases): the output will be the identification of common functional domains (metadata) that could be used in the ML model to test the effect of an initiative or of a research project.
- Inclusion of the data in the Digital Toolbox, taking into consideration the type of input data and characterization
- Testing of the metadata analysis on a user case (*Figure 14 User case for data collection interface: Anxiety & Depression*)

Figure 12 FISM PROMOPRO-MS Database Interface (Italian language)



[49] The actual interface of the FISM PROMOPRO-MS Database is for Italian patients therefore it is in Italian language. FISM will deploy a multiple language interface when the data will be merged with those of the iConquerMS Database.

Figure 13 Merging the PROMOPRO-MS and I Conquer MS databases

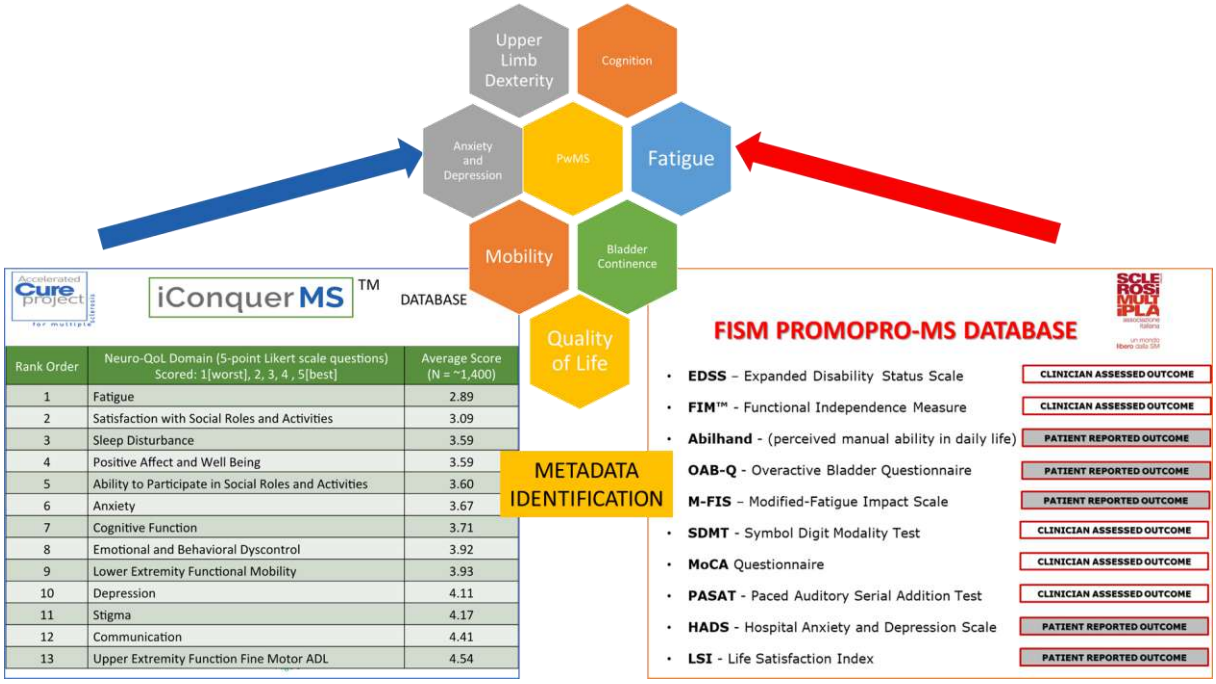
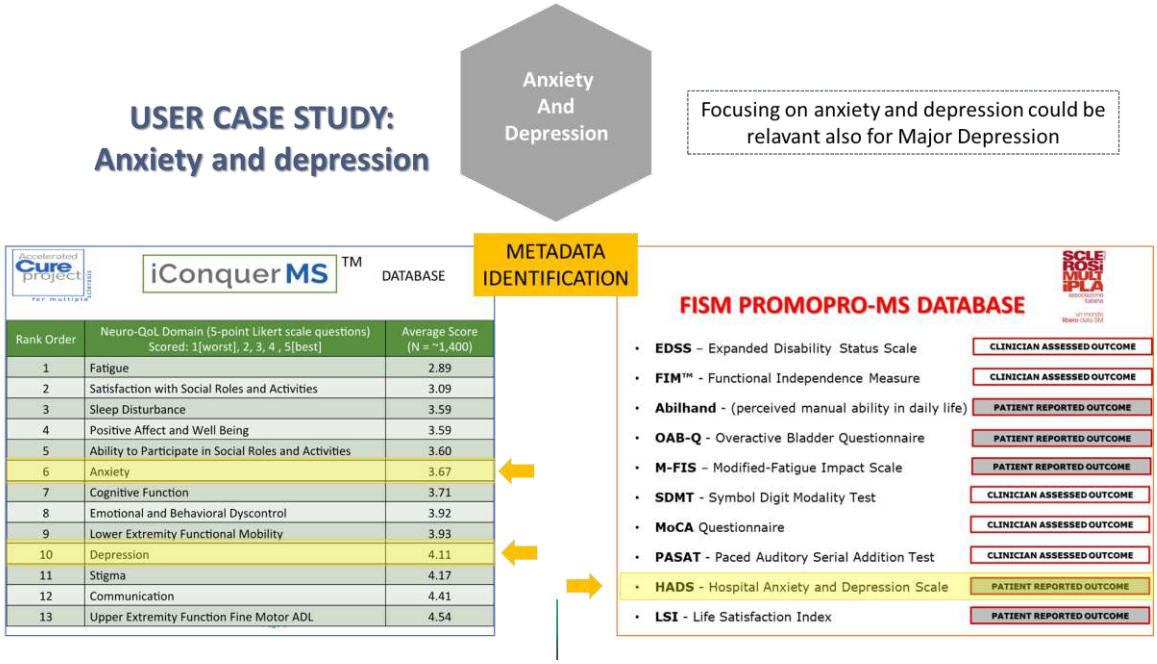


Figure 14 User case for data collection interface: Anxiety & Depression



The data collection interface will be developed under the activities of WP2, whereas the detailed methodology that will be followed has been documented in D2.5. Report describing the methodology & design principles of the MULTI-ACT Toolbox.

To support this data collection feature, questionnaires related to individual PRD indicators will be implemented in the Toolbox in order to be transformed into web forms that can be distributed via web surveys. The promoter will beforehand populate the list of emails of participants that will partake in the surveys, and no other personal information will be collected. Upon commencing a new data

collection process all recipients receive a notification email containing tokenized links to the web-forms hosted at the Toolbox. This tokenization apart from further ensuring the anonymity of the collected data, guarantees that all participants will be able to undertake the survey only once.

The promoter during the period of the process has the ability to view analysis of the ongoing participation, whereas upon the completion of the survey are able to view statistical analysis of the collected data, compared with older results, and provide detailed graphs portraying the chronological progress of the indicator's impact.

5.2.1 Data protection and processing measures

The GDPR regulation will be applied with respect to PRO data protection and processing measures. Informed Consents are as usual a pre-requisite to proceed with data collection.
As in PROMOPRO-MS database, the data sharing aspects will be carefully taken into consideration by anonymizing all the data sets. All the stakeholders involved in data collection will be invited to give approval to a dedicated informed consent form and a specific information sheet will be available in order to explain how all their data will be treated and stored, for what purpose they will be collected, for how long they will be retained and the contact points of the Data Protection Officers for users to communicate with in case of any question or objection. The MULTI-ACT templates of the informed consent forms and information sheets are collected and details in Deliverable "D10.3 POPD - H - Requirement No. 3". They are written in language and terms intelligible to the participants and clearly address the "legitimate use" that third parties must demonstrate in order to have access to sensitive data and how these may affect the patient's interests. Information Sheet and Informed Consent templates will be adapted for each specific use and purpose[50].

[50] Information on the collection and processing of personal data in the MULTI-ACT project are included in Deliverable "D10.2 – POPD - Requirement No. 2" and Deliverable "D8.4 - MULTIACT Data Management Plan (DMP)". The procedures detailed in the deliverables provides a preliminary direction for the exploitation activities related to the PRO data collection and will be customized for the purpose.

6 CONCLUSION

The PRD is of outmost importance to evaluate the impact of R&I on outcomes that matter most to patients and maintain patients and stakeholders engaged along the R&I continuum. The PRO data collection provides opportunity to exploit the outcomes of MULTI-ACT and it's of utmost importance for the research & healthcare community, for research outcomes evaluation (e.g. use of PROs in clinical trials or observational studies), R&I impact assessment, but also in healthcare for monitoring of disease progression and evolution.

The next steps will be directed to implement the PRD into the Digital Toolbox 2.0 (available by September 2020) and to seek for exploitation opportunities. A dedicated exploitation plan will be developed and included in D8.5.

Preliminary exploitation opportunity could be:

- PRO data collection function and machine learning algorithms implementation into the Digital Toolbox 2.0
- Development and validation of PROs questionnaire on Return on Patient Engagement, building on the indicators included in the MULTI-ACT Patient Engagement Guidelines.

The MULTI-ACT framework and its PRD, aim to support RRI and produce positive impact on society by providing a model to assess R&I from a multi-stakeholder's perspective and to monitor that it is really impacting on the aspects and outcomes that most matter to patients.

APPENDIX 1 – Patient Reported Dimension Master Scorecard

Excel file with PRD indicators in the form of D3.6 MSC database – see Excel file MULTI-ACT_D1.8_APPENDIX_1_PRD_MSC_20200731_v0.3

APPENDIX 2 – PROMs

Examples of PROMs scale are presented below.

A2.1 ABILHAND - Manual Ability Measure

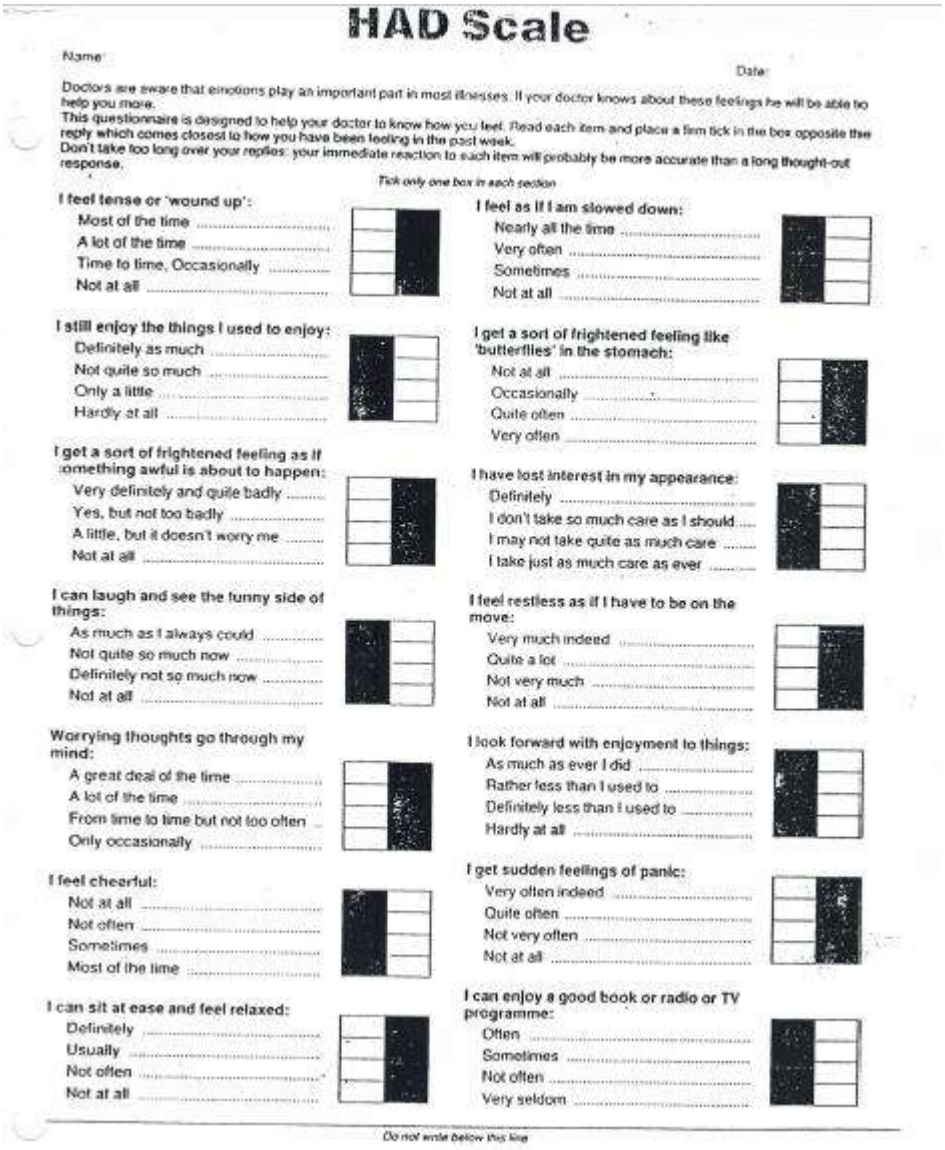
ABILHAND - Manual Ability Measure
English version

Patient _____ **Date** _____

	How DIFFICULT are the following activities?	Impossible	Difficult	Easy	?
1.	Pulling up the zipper of trousers				
2.	Peeling onions				
3.	Sharpening a pencil				
4.	Taking the cap off a bottle				
5.	Filing one's nails				
6.	Peeling potatoes with a knife				
7.	Buttoning up trousers				
8.	Opening a screw-topped jar				
9.	Cutting one's nails				
10.	Tearing open a pack of chips				
11.	Unwrapping a chocolate bar				
12.	Hammering a nail				
13.	Spreading butter on a slice of bread				
14.	Washing one's hands				
15.	Buttoning up a shirt				
16.	Threading a needle				
17.	Cutting meat				
18.	Wrapping up gifts				
19.	Fastening the zipper of a jacket				
20.	Fastening a snap (jacket, bag, ...)				
21.	Shelling hazel nuts				
22.	Opening mail				
23.	Squeezing toothpaste on a toothbrush				

Université catholique de Louvain, Laboratory of Rehabilitation and Physical Medicine order 1

A2.2 Anxiety and Depression Scale (HADS)



HAD Scale

Name: Date:

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more.
This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.
Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':
- Most of the time
- A lot of the time
- Time to time, Occasionally
- Not at all

I still enjoy the things I used to enjoy:
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I can laugh and see the funny side of things:
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

Worrying thoughts go through my mind:
- A great deal of the time
- A lot of the time
- From time to time but not too often
- Only occasionally

I feel cheerful:
- Not at all
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed:
- Definitely
- Usually
- Not often
- Not at all

I feel as if I am slowed down:
- Nearly all the time
- Very often
- Sometimes
- Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance:
- Definitely
- I don't take so much care as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as if I have to be on the move:
- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things:
- As much as ever I did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic:
- Very often indeed
- Quite often
- Not very often
- Not at all

I can enjoy a good book or radio or TV programme:
- Often
- Sometimes
- Not often
- Very seldom

Do not write below this line

A2.3 Life Satisfaction Index (LSI)

LIFE SATISFACTION INDEX

	I agree	I dont't know	I disagree
This is the dreariest time of my life			
I am just as happy as when I was younger			
My life could be happier that it is now			
There are the best years of my life			
Most of the things I do are boring or monotonous			
I expect some interesting and pleasant things to happen to me in the future			
I feel old and somewhat tired			
As I look back on my life, I am fairly well satisfied			
I would not change my past life even if I could			
I have made plans for things I'll be doing a month or a year from now			
I've gotten pretty much what I expected out of life			

A2.4 Modified Fatigue Impact Scale (MFIS)

MFIS-1

Patient's Name: _____ Date: ____/____/____ month day year

ID#: _____ Test#: 1 2 3 4

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks....

		Never	Rarely	Sometimes	Often	Almost always
1.	I have been less alert.	0	1	2	3	4
2.	I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3.	I have been unable to think clearly.	0	1	2	3	4
4.	I have been clumsy and uncoordinated.	0	1	2	3	4
5.	I have been forgetful.	0	1	2	3	4
6.	I have had to pace myself in my physical activities.	0	1	2	3	4
7.	I have been less motivated to do anything that requires physical effort.	0	1	2	3	4

A2.5 NeuroQoL – Example of search online

Fatigue – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
	I felt exhausted	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I felt that I had no energy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I felt fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I was too tired to do my household chores	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I was too tired to leave the house	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I was frustrated by being too tired to do the things I wanted to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I felt tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	I had to limit my social activity because I was tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English
March 6, 2014

A2.6 Twelve Item MS Walking Scale (MSWS-12)

Twelve Item MS Walking Scale (MSWS-12)

Record form

Subject ID Number | Subject Initials | Date Questionnaire Completed: Day | Month | Year

If you cannot walk at all, please tick this box ☐

In the past two weeks, how much has your MS ...	Not at all	A little	Moderately	Quite a bit	Extremely
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limited how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (eg holding on to furniture, using a stick, etc.)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (eg using a stick, a frame, etc.)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your walking?	1	2	3	4	5

From the numbers you circle against these questions, your healthcare professional can calculate your MSWS-12 score. This is done by adding the numbers you have circled, giving a total out of 60, and then transforming this to a scale with a range from 0 to 100. Higher scores indicate a greater impact on walking than lower scores.

To be completed by the healthcare professional

Total score _____ out of 60

Percentage _____ %

biogen idec © 2010 Biogen Idec GmbH Date of preparation: February 2011

Mobility Matters in MS

A2.7 OAB-q Over Active Bladder Function (QAB-q)

OAB-q

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please circle the number that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

During the past 4 weeks, how bothered were you by. . .	Not at all	A little bit	Some what	Quite a bit	A great deal	A very great deal
1. Frequent urination during the daytime hours	1	2	3	4	5	6
2. An uncomfortable urge to urinate	1	2	3	4	5	6
3. A sudden urge to urinate with little or no warning	1	2	3	4	5	6
4. Accidental loss of small amounts of urine	1	2	3	4	5	6
5. Nighttime urination	1	2	3	4	5	6
6. Waking up at night because you had to urinate	1	2	3	4	5	6
7. An uncontrollable urge to urinate	1	2	3	4	5	6
8. Urine loss associated with a strong desire to urinate	1	2	3	4	5	6

The above questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please circle the number that best answers each question.