
# Value of Treatment for Brain Disorders research project "Case studies on Rare Diseases and Mental Disorders"

## 8 June 2021 – Virtual Synthesis Meeting FINAL AGENDA

## Meeting Afternoon Session (13.00 – 17.30)

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| **OPENING SESSION** | |
| **13.00 – 13.05** | **Video Rare Diseases - What is the Value of Treatment for Brain Disorders project and why is the study so timely?** |
| **13.05 – 13.10** | **Welcome and objectives of the Synthesis Meeting** by the Chair, Ms. Joke Jaarsma, EFNA President |
| **13.10 – 13.15** | **Opening keynote on the Value of Treatment for Brain Disorders and the need for more research** by Prof. Monica Di Luca, EBC President |
| **13.15 – 13.25** | **Opening keynote on primary health care and brain disorders** by Prof. Thomas Frese, WONCA Europe, EGPRN Representative |
| **SESSION 1: Results – Case studies on Rare Diseases** | |
| **13.25 – 13.35** | **Introduction: Addressing the burden of neurological diseases** by Prof. Claudio Bassetti, EAN President<br>**Introduction and research framework: Early intervention, bridging the gaps and achieving seamless, coordinated care** by Prof. Wolfgang Oertel, EBC Vice President |
| **13.35 – 14.05** | **Synthesis – presentation of the results: case studies on rare diseases**<br>**The care pathway analysis and the economic modelling conclusions**<br>- **The case study on Ataxias** by Prof. Paola Giunti and Prof. Steve Morris<br>- **The case study on Dystonia** by Prof. Maja Relja and Prof. Stjepan Oreskovic<br>- **The case study on Phenylketonuria** by Prof. Gregory Pastores and Prof. Steve Morris |
| **14.05 – 14.10** | **Comments: towards an overarching perspective on the care pathway analysis and health economics study for rare diseases** by Prof. Giuseppe Turchetti, Professor of Economics and Management of Innovation in Healthcare, Scuola Superiore Sant'Anna Pisa, Italy |

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| **14.10 – 14.40** | **Panel discussion moderated** by Prof. Wolfgang Oertel, EBC Vice President<br>- Mr. Simone Boselli, Public Affairs Director, EURORDIS<br>- Prof. Holm Grassner, ERN-RND<br>- Prof. Francjan J van Spronsen, MetabERN<br>- Mrs. Luz Fialho, Director of Outcomes Research, ICHOM |
| **14.40 – 15.15** | **Q&A: open discussion with patients and patient associations**<br>**Discussion moderated** by Prof. Sophia Bakhtadze, EPNS Executive Director<br><br>*With the contribution of Dr. Cathalijne Van Doorne (EFNA), Ms Monika Benson (DYSTONIA EUROPE), Dr. Elizabeth Caller* |
| **15.15 – 15.30** | **BREAK – PIANO PERFORMANCE BY Ms OLGA BOBROVNIKOVA** |
| **SESSION 2: Preliminary Results – Case studies on Mental Disorders** | |
| **15.30 – 15.35** | **Video Mental Disorders - What is the Value of Treatment for Brain Disorders project and why is the study so timely?** |
| **15.35 – 15.45** | **Introduction: Addressing the burden of mental disorders** by Prof. Philip Gorwood, EPA Past President<br>**Introduction and research framework: Early intervention, bridging the gaps and achieving continuity of care by** Prof. Patrice Boyer, EBC Vice President |
| **15.45 – 16.15** | **Synthesis – presentation of preliminary results: case studies on mental disorders**<br>**The care pathway analysis and the economic modelling**<br>- **The case study on Anorexia Nervosa** by Prof. Janet Treasure and Prof. Eva Bonin<br>- **The case study on Autism Spectrum Disorder** by Prof. Celso Arango and Prof. Martin Knapp<br>- **The case study on Major Depressive Disorder** by Prof. Allan Young and Prof. Paul McCrone |
| **16.15 – 16.20** | **Comments: towards an overarching perspective on the care pathway analysis and health economics study for mental disorders** by Prof. Judit Simon, Professor of Health Economics, Medical University of Vienna, Austria |
| **16.20 – 17.00** | **Q&A: open discussion with patients and patient associations**<br>**Discussion moderated** by Ms Margaret Walker, EPA Executive Director<br><br>*With the contribution of John Saunders (EUFAMI), Aurélie Baranger (AUTISME EUROPE), Dr. Raluca Nica (GAMIAN Europe), Dr. Mark Ashworth* |
| **17.00 – 17.25** | **Overall remarks**<br>- Prof. Jose Miguel Caldas de Almeida, Lisbon Institute of Global Mental Health, CHRC/Nova Medical School<br>- Pierre Delsaux, Deputy Director General at the European Commission, Directorate General for Health (DG SANTE)<br>- Prof. Patrice Boyer, EBC Vice President |
| **CLOSING** | |
| **17.25 – 17.30** | **Final words and way forward** by the Chair, Ms. Joke Jaarsma, EFNA President |

**Case studies - Working Groups Leaders (Clinicians)**

Prof. Celso Arango, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Prof. Paola Giunti, University College London, UK

Prof. Gregory Pastores, The Mater Misericordiae University Hospital, Dublin, Ireland

Prof. Maja Relja, University of Zagreb Medical School, Croatia

Prof. Janet Treasure, King's College London, UK

Prof. Allan Young, King's College London, UK

**Case Studies - Health Economics Experts**

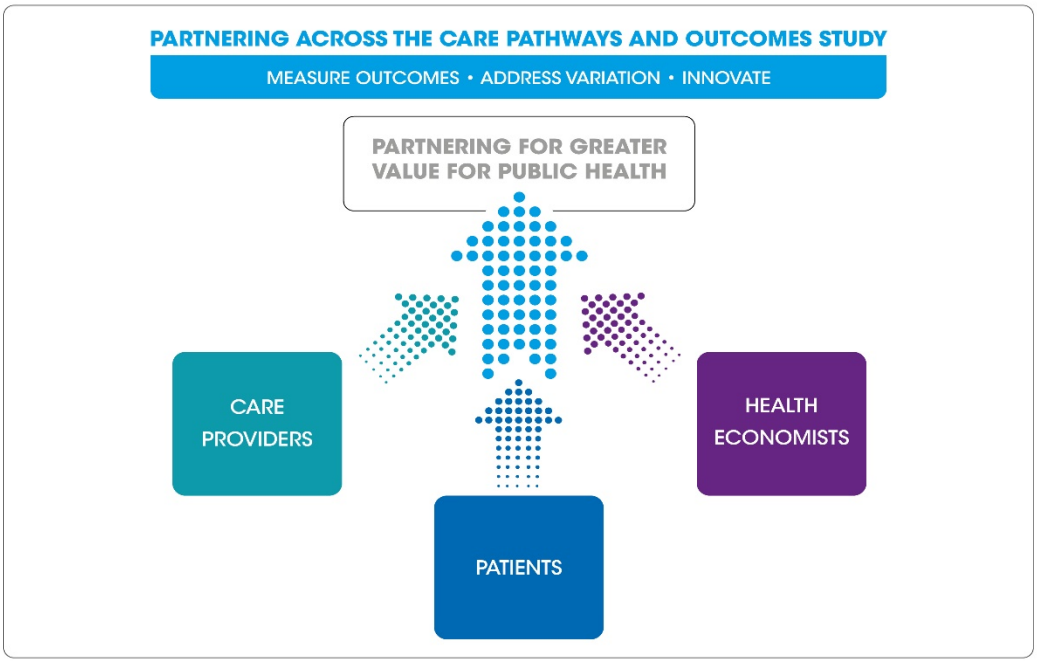
Prof. Eva Bonin, London School of Economics, UK

Prof. Martin Knapp, London School of Economics, UK

Prof. Steve Morris, University of Cambridge, UK

Prof. Paul McCrone, Greenwich University, UK

Prof. Stipe Oreskovic, University of Zagreb, Croatia




## Study background

The Value of Treatment for brain disorders (VOT) is a health economics and outcomes research project addressing all brain disorders and coordinated by the European Brain Council (EBC). Brain disorders - both neurological and mental alike - constitute a major factor, alongside cancers and cardiovascular diseases, driving the overall burden of diseases in Europe[1]-[2]. Neurological and psychiatric disorders across all lifespans are the leading cause of poor health and disability in Europe. The conclusions of the VOT research project first round released in 2017[3] (which included case studies on disorders ranging from schizophrenia to Alzheimer's disease, epilepsy, headache, normal pressure hydrocephalus, Parkinson's disease, multiple sclerosis, restless legs syndrome and stroke) highlighted the need for more research, early, if possible prodromal, diagnosis and intervention, integrated seamless care underpinning timely care pathways as a solution to address value-based health care in Europe and access to the best treatments available[4].

In the continuity of these conclusions and in the framework of the VOT research, a second round of case studies (VOT2) have been developed on new therapeutic areas focusing on rare

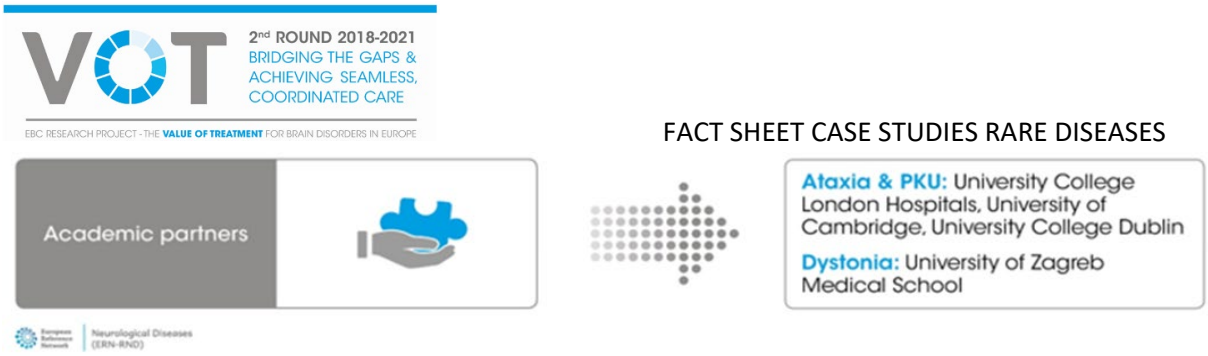
[1] Feigin VL, Vos T, Nichols E, Owolabi MO, Carroll WM, Dichgans M, Deuschl G, Parmar P, Brainin M, Murray C. The global burden of neurological disorders: translating evidence into policy. Lancet Neurol. 2020 Mar;19(3):255-265. doi: 10.1016/S1474-4422(19)30411-9. Epub 2019 Dec 5. PMID: 31813850.
[2] Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry. 2016 Feb;3(2):171–8. doi: http://dx.doi.org/10.1016/S2215-0366(15)00505-2 PMID: 26851330.
[3] The value of treatment policy white paper: towards optimizing research and care for brain disorders. Brussels: European Brain Council; 2017. Available at: https://www.braincouncil.eu/wp-content/uploads/2017/06/EBC_white_policy_paper_DEF26072017_Low.pdf
[4] Bulletin of the World Health Organization 2018;96:298-298A. doi: http://dx.doi.org/10.2471/BLT.17.206599

diseases (Ataxia, Dystonia and Phenylketonuria) and mental disorders (Anorexia Nervosa, Autism Spectrum Disorder, Major Depressive Disorder), see fact sheets in Annex. The study to be finalised in 2021 is focusing on "early intervention, bridging the gaps and achieving seamless, coordinated care", and the objective is to examine health gains resulting from optimized healthcare interventions in comparison with current care or no treatment, and converge data evidence to policy recommendations on how to improve the care pathway(s). Previous joint working sessions aimed to exchange and build synergy between the research-work and DG Sante Rare Diseases European Reference Networks (ERNs) programme and research as well as the PECUNIA project from the EU Framework on mental health and well-being. Beyond the research design and considering current context, the impact of Covid-19 on treatment and healthcare transformation is also explored.

**Meeting objectives**

EBC together with its partners (EAN, EANS, ECNP, EFNA, EPA, EPNS, EUFAMI, FENS, GAMIAN Europe, IBRO) and experts who are participating in the research will convey a meeting to present a synthesis of the results so far. We will examine the most critical issues in brain diseases in Europe from different perspectives including policymakers, innovators, academia and industry, medical professionals and patient organisations.

ANNEX




## Case studies on Ataxia, Dystonia, Phenylketonuria

**THE CHALLENGE**

Rare neurological diseases (RNDs) like ataxia and dystonia collectively exert a public health burden in terms of their manifestations' severity and the total number of people afflicted across their lifespan. According to the European Reference Network on neurological diseases (ERN-RND), 500.000 people are living with RNDs in Europe, 60% of those affected are still undiagnosed due to significant phenotype and genotype heterogeneity in clinical presentation and disease course. Health systems face significant challenges to respond to patients' needs and guarantee equal access to treatment. Most rare disorders are of genetic origin. Phenylketonuria (PKU) is an inherited metabolic disorder which cause significant

cognitive impairment if untreated. For many patients, considerable barriers exist in terms of access to appropriate care, delayed diagnosis, and treatment options. When patients are diagnosed, many are unable to access resources such as centres of expertise (or specialist centres), coordinated care, patient support systems, and effective treatment[5].

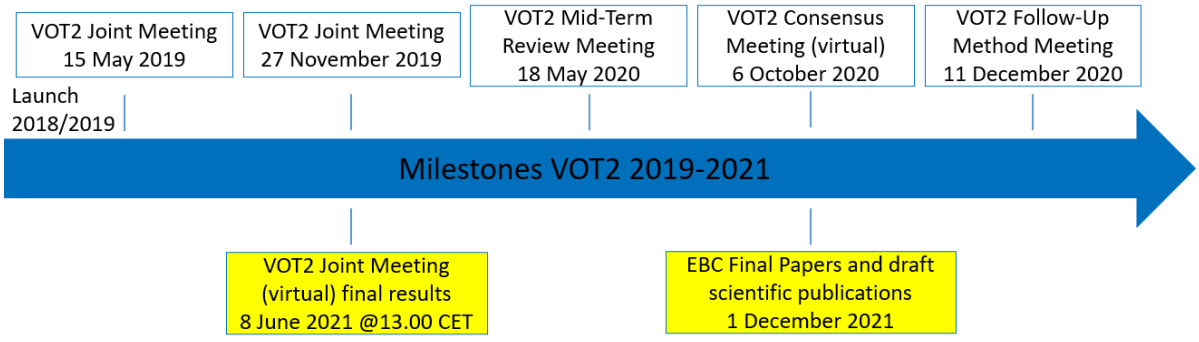
**MISSION**

The European Brain Council (EBC) initiated a three-year research project (results will be released in 2021) on the Value of Treatment for Brain Disorders for more equitable access to care all around Europe "Bridging the gaps and achieving seamless, coordinated care for people affected by rare diseases". The project includes case studies on Ataxia, Dystonia and Phenylketonuria. Discussions on health care focus too often on the increase in per-person health care cost rather than on the benefits of better health. It is therefore important to emphasize the need for more value-based and patient-centred care, and the scaling-up of high-quality underpinning sustainable care models for rare diseases.

Treatment gaps—the proportion of people who require detection and treatment but do not receive these or receive inadequate care—pose the biggest barriers to improved diagnosis, treatment and care across Europe. Effective interventions exist. Strategies of early diagnosis and treatment to ensure adequate care, which are proving to be cost effective in the long run, are key. The study's research framework includes the development of a series of qualitative and quantitative benchmarks to identify treatment gaps and causal factors along the continuum of care in a patient care pathway analysis (in alignment with the EC RarERNPath approach). The study is also assessing the socioeconomic impact and health gains from optimal health-care interventions with an economic evaluation and final evidence-based policy recommendations. Case studies are analysed in collaboration with experts from the European Brain Council's scientific societies in line with the research framework, applying empirical evidence from different European countries.

**PLANNING AND END DATE :**

December 2021




[5] VOT2 – rare neurological disorders article (CMJ 2019) on "Toward earlier diagnosis and treatment of rare neurological disorders: the value of coordinated care and specialist centers". Link to PubMed:
https://www.ncbi.nlm.nih.gov/m/pubmed/31044588/?i=6&from=croat%20med%20j

**Contact person :** Vinciane Quoidbach, EBC Research Project Manager

## VOT2 Case Study on Ataxia

Aim of the Ataxia study is to understand differences in care between specialist ataxia centres compared with non specialist care for progressive ataxia in adults.

***Box 1*: Ataxia in a word**

Ataxia is a heterogeneous group of chronic rare neurological disorders, characterized by a lack of muscle coordination which may affect speech, eye movements, the ability to swallow, walking, and other voluntary movements. Amongst the different types of progressive ataxias in Europe, the most common are inherited Friedreich's ataxia and cerebellar ataxia. Diagnosis has generally been a long process because of the complexity of the different ataxias. The management of these conditions is also challenging and requires clinical expertise and evidence-based practice. Although there are no disease modifying treatments for the majority of progressive ataxias, there are many aspects of the conditions that are treatable, therefore the importance of guidelines to improve diagnosis and management of the ataxias ["Management of the ataxias towards best clinical practice", third edition July 2016, Ataxia UK]. Early intervention in both the diagnosis and in management of patients with the ataxia is critical in slowing progression of disability and maintaining functional ability.

**STUDY OBJECTIVES**

Ataxia patients require complex care by a multidisciplinary team (MDT), including appointments with numerous health care professionals such as neurologists, general practitioners (GP) and physiotherapists. Specialist ataxia centres (SAC) can provide the necessary coordinated care and therefore address the specific needs of ataxia patients. The aim of the study, survey and analyses are to gain an understanding of ataxia patient care in the UK and other European countries. Of particular interest are any potential differences in the patient experience between patients who have attended a Specialist Ataxia Centre and those who have not.

**METHOD AND EXPECTED RESULTS**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with progressive ataxia: survey population from 16+ years old including statistical analysis
- Cost-consequences analysis
- Sites : specialist Ataxia centres (UK, Germany, Italy)

## VOT2 Case Study on Dystonia

Aim of the Dystonia study is to examine how different training levels and structured, accredited postgraduate, or sub-specializing movement Disorders (MD) training is related to dystonia diagnosis, treatment and improvement of the quality of life. It is also looking at the potential benefits of coordinated care combining effective team care and patient-centred planning.

***Box 2* : *Dystonia in a word***

Dystonia is a neurological movement disorder syndrome in which sustained or repetitive muscle contractions result in twisting and repetitive movements or abnormal fixed postures. Dystonia is often intensified or exacerbated by physical activity, and symptoms may progress into adjacent muscles. Dystonia is a very complex, highly variable neurological movement disorder characterized by involuntary muscle contractions. Although an underdiagnosed condition, with an estimated prevalence rate in Europe of 15.2/100 000 for primary dystonia and 11.7/100 000 for focal forms, dystonia syndrome is the third most common movement disorder behind essential tremor and Parkinson's disease. The disorder may be hereditary or caused by other factors such as birth-related or other physical trauma, infection, poisoning (e.g., lead poisoning) or reaction to pharmaceutical drugs, particularly neuroleptics. Treatment must be highly customized to the needs of the individual and may include oral

medications, chemodenervation botulinum neurotoxin injections, physical therapy, or other supportive therapies, and surgical procedures such as deep brain stimulation.

**STUDY OBJECTIVES**

What are the new research developments in early intervention to improve (primary and secondary) prevention and treatment of dystonia, knowing that, as of today, there is no cure? The study is looking at potential benefits of integrated, coordinated care combining effective team care and patient-centred care planning and how different training levels and structured, accredited postgraduate, or sub-specializing movement disorders (MD) training is related to dystonia treatment and improvement of the quality of life.

**METHOD AND EXPECTED RESULTS**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with dystonia : survey population including statistical analysis
- Cost-consequences analysis
- Sites : specialist Dystonia centres (Croatia, Germany, Italy, UK)

## VOT2 Case Study on Phenylketonuria

Aim of the Phenylketonuria (PKU) study is to identify the care pathways for patients accessing PKU services, and how these vary by provider and country and to evaluate the quality of life and care-related costs per patient associated with PKU, and how these vary by patient characteristics, provider and country.

***Box 3** : Phenylketonuria (PKU) in a word*

PKU is a rare genetic disorder, under the umbrella of inborn errors of metabolism, a disorder in which the body is not able to break down a type of protein called phenylalanine (Phe). [Phenylalanine is one of the amino acids that help in protein formation in the body. However, in PKU as the body is unable to process this amino acid, it begins to build up in the body and be harmful]. This leads to improper digestion of proteins and accumulation of phenylalanine in the body and can further affect the brain. Prevalence varies considerably across Europe – around 1/10,000 live births on average. Lifelong impact. PKU is diagnosed as a result of newborn screening. If left untreated, the increased concentration of Phe in blood and brain can lead to neurocognitive deficits – e.g. severe intellectual disability, epilepsy and behavioral problems. Therefore, guidelines are important to improve diagnosis and management of PKU ["Key European guidelines for the diagnosis and management of patients with phenylketonuria" – The Lancet/diabetes-endocrinology – September 2017]. Treatment consists of dietary restriction of phenylalanine and early intervention is key.

**STUDY OBJECTIVES**

Identify challenges in delivering care to patients with PKU, including access to monitoring services and provision of support to achieve optimal outcome (using Phe level as a surrogate).

**METHOD AND EXPECTED RESULTS**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with PKU : survey population including statistical analysis and a review of PKU Clinic structure and processes will be undertaken
- Cost-consequences analysis
- Sites : Metabolic Units (Ireland, UK, Spain)






## Case studies on Anorexia Nervosa, Autism Spectrum Disorder, Major Depressive Disorder

**THE CHALLENGE**

Mental health is critical to individual well-being, as well as for social and economic participation. Yet, according to recent estimates (OECD Health At A Glance 2018), more than one in six people across EU countries had a mental health issue in 2016, equivalent to about 84 million people. The economic and social costs of mental illness are substantial. The total costs of mental ill-health are estimated at more than 4% of GDP – or over EUR 600 billion – across the 28 EU countries. EUR 190 billion (or 1.3% of GDP) reflects direct spending on health care, another EUR 170 billion (1.2% of GDP) is spent on social security programmes, while a further EUR 240 billion (1.6% of GDP) represents indirect costs to the labour market due to lower employment and productivity. The heavy individual, economic and social burdens of mental illness are not inevitable. Many European countries have in place policies and programmes to address mental illness at different ages. However, much more can be done to manage and promote mental health.

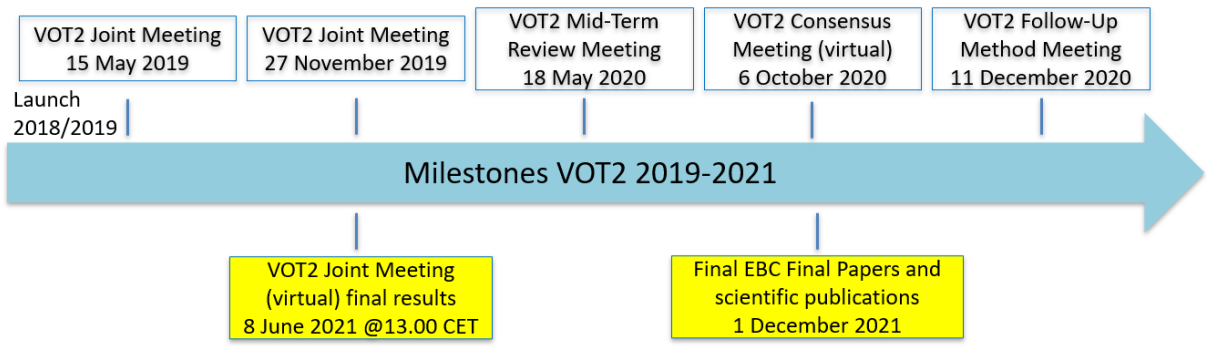
**MISSION**

The European Brain Council (EBC) initiated a two-year research project (2019-2021) on the Value of Treatment for Brain Disorders for more equitable access to care all around Europe "Bridging the gaps and achieving continuity or transition of care for patients affected by mental disorders". The project includes case studies on Anorexia Nervosa, Autism Spectrum Disorder and Major Depressive Disorder. Discussions on health care focus too often on the increase in per-person health care cost rather than on the benefits of better health. It is therefore important to emphasize the need for more value-based and patient-centred care, and the scaling-up of high-quality underpinning sustainable care models for mental disorders.

Treatment gaps—the proportion of people who require screening and treatment but do not receive these or receive inadequate care—pose the biggest barriers to improved diagnosis, treatment and care across Europe. Effective interventions exist. Strategies of early diagnosis and treatment to ensure adequate care, which are proving to be cost effective in the long run, are key. The study's research framework will include a consensus on a comprehensive care model and the development of a series of qualitative and quantitative benchmarks to identify treatment gaps and causal factors along the continuum of care in a patient care pathway analysis (harmonization across case studies using the EU Horizon 2020 Pecunia project tools as examples). The study will also estimate the socioeconomic impact and health gains from optimized health-care interventions with an economic evaluation. Case studies are analysed in collaboration with experts from the European Brain Council's scientific societies in line with the research framework, applying empirical evidence from different European countries.

**PLANNING AND END DATE :**

December 2021



**Contact person :** Vinciane Quoidbach, EBC Research Project Manager

## VOT2 Case Study on Anorexia Nervosa

The overarching aim of the "value of treatment" study is to develop evidence-based policy recommendations on improving the care pathway(s) for anorexia nervosa in Europe.

***Box 1*: Anorexia nervosa in a word**

Anorexia Nervosa is characterized by significantly low body weight without medical explanation. Prevalence: 0.6% (0.9% F; 0.3% M). There is a problem to recruit patients to trials, meaning difficulty to compare effectiveness of intervention assessing inpatient and outpatients and little knowledge about optimal interventions.

**STUDY OBJECTIVES**

A care pathways analysis will identify current treatment gaps and patient needs along the care trajectory sequences, analyze the underlying causes and identify existing or propose potential solutions. The economic study proposed here will build on this analysis, and the objectives are to: 1) estimate the costs (including impact on quality of life) associated with treatment gaps ; 2) estimate the potential savings from closing or reducing them by implementing existing or proposed solutions ("case studies"). While the aim should be to construct one overarching model of the entire care pathway, it is acknowledged that a lack of data may mean this is not feasible. If this is the case, branches of the care pathway may be modelled separately, i.e. for each proposed care study.

Available evidence will be combined using economic modelling techniques. The economic study will focus on three aspects of the treatment gap: 1) Improving diagnosis and early treatment; 2) Reducing waiting times or providing alternative interventions during waiting times; 3) Improving the effectiveness of different approaches to inpatient and outpatient treatment. Specific interventions will be selected following the mapping of pathways and the evidence review. For each of these three areas, an economic model will be developed to estimate the costs associated with the status quo. Evidence will be gathered on existing or potential interventions to improve on the status quo, and potential resulting savings will be estimated.

**METHOD AND EXPECTED RESULTS**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with anorexia: evidence review (data synthetized) and survey
- Cost effectiveness analysis and cost saving analysis
- Countries: Germany, Spain, UK

## VOT2 Case Study on Autism Spectrum Disorder

The overarching aim of the study is to investigate early interventions to paediatric patients with autism spectrum disorder.

***Box 2* : Autism spectrum disorder (ASD) in a word**

ASD is a lifelong, complex neurodevelopmental condition affecting brain development and behaviour. Prevalence (0.7% -1%), sex 4.5M/1F. Reduced life expectancy by 30 years. ASD used to be a rare disorder. Broadening diagnosis - not always intellectual disabilities. There are huge economic costs. Costs also are much supported by families. ASD impacts on education and participation in society.

**STUDY OBJECTIVES**

The objective is to map common care pathway(s) for ASD for each country and develop an 'enhanced' model of continuity of care to assess and conduct economic evaluations in two important areas:

1) Early detection/intervention for autistic children and families
2) Treatment of epilepsy as a comorbidity for autistic children and/or adolescents.

The economic study proposed will build on the care pathway analysis.

**METHOD AND EXPECTED RESULTS**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with autism spectrum disorder: evidence review (data synthetized) and survey
- Cost consequences analysis and cost effectiveness analysis
- These analyses will be conducted in four countries: Ireland, Italy, England and Spain.

## VOT2 Case Study on Major Depressive Disorder

The overarching aim of the "value of treatment" study is to investigate access to psychological therapies and pharmacological treatments for adults with severe depression and develop evidence-based policy recommendations on improving the care pathway(s) for major depressive disorder in Europe.

***Box 3* : Major depressive disorder in a word**

Depression overall 1 year prevalence (European region): 12% (WHO, 2017). Global prevalence high in all age groups. Ranked by WHO as the single largest contributor to global disability (7.5% of all years lived with disability, 2015) and the disability burden is growing.

**STUDY OBJECTIVES**

A care pathways analysis will identify current treatment gaps and patient needs along the care pathway; analyse the underlying causes; and identify existing or propose potential solutions.

The economic study proposed here will build on this analysis, and the objectives are to

1) Estimate the costs (including impact on quality of life) associated with treatment gaps;

2) Estimate the potential savings from closing or reducing them by implementing existing or proposed solutions ("case studies").

While the aim should be to construct one overarching model of the entire care pathway, it is acknowledged that a lack of data may mean this is not feasible. If this is the case, branches of the care pathway may be modelled separately, i.e. for each proposed case study.

The objective is to produce a model for ~6 countries spanning Europe to provide an international representation of current and best practices in the detection and management of depression. Available evidence will be combined using economic modelling techniques, referring to a schematic stepped care pathway for MDD, as recommended by NICE guidelines.

**METHOD AND EXPECTED RESULTS**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with major depressive disorder: evidence review (data synthetized) and survey
- Cost consequences analysis and cost effectiveness analysis
- Countries based on availability of data: UK, Germany, Hungary, Sweden, Italy, Portugal.