



**2<sup>nd</sup> ROUND 2019-2021**  
BRIDGING THE GAPS &  
ACHIEVING SEAMLESS,  
COORDINATED CARE

EBC RESEARCH PROJECT - THE **VALUE OF TREATMENT** FOR BRAIN DISORDERS IN EUROPE

The Value of Treatment for Brain Disorders: Case  
Studies on Rare Diseases & Mental Disorders present  
findings at Synthesis Meeting (8 June 2021)

## Meeting Report and Next Steps

### Table of contents

VOT2 Study Background .....	2
Meeting Introduction.....	4
1. Session 1 - Rare Brain Diseases .....	5
2. Session 2 - Mental Disorders.....	11
VOT2 Research Next Steps.....	17
Annexes .....	18
References.....	39

Meeting attendance: 150 participants (see participants list)

Meeting Master Slides Deck is attached to the Meeting Report

Organizer: EBC – Chair: Ms. Joke Jaarsma, EFNA President and EBC Treasurer Executive Committee: Prof. Patrice Boyer, EBC Vice- President, Prof. Wolfgang Oertel, EBC Vice-President – Meeting support EBC team (Communications, Finance & Office)

Research project coordination and meeting report: Vinciane Quidbach, EBC Research Project Manager, 22/6/2021

## VOT2 study background

**The Value of Treatment for Brain Disorders (VOT)** is a health economics and outcomes research project coordinated by the European Brain Council (EBC). EBC conceptualized in 2015 the Value of Treatment research framework with a first VOT study<sup>1</sup> to address the increasing all-age burden of brain disorders – both neurological and mental alike. Direct healthcare and non-medical costs of brain disorders are high, making up for 60% of the total costs (40% attributable to lost productivity) – which EBC estimated at 800 bln€/year in Europe. All types of costs increase with the severity and the chronification of the disease. Budgetary restrictions across the EU are threatening the sustainability of the European social welfare model as a whole and make it even more important to achieve cost-effectiveness in the use of resources in health systems and its deliverables. In particular, challenges are multiple because of the medical, social and economic impacts of chronic disabling conditions. The long-term and transversal nature of care and treatment for mental and neurological disorders have all served to confound hospital traditional and top-down led responses towards care provided in more than one setting. Together, these emphasize the need for an ambitious patient-empowering research policy and an integrated, multidisciplinary approach to brain disorders looking at payment systems and healthcare digitalization as an innovative boost.

**Risk reduction, preclinical and early detection, and timely intervention are seen as the solutions to help national health systems and society cope.** In 2019, in order for the research to dig deeper into the current unmet needs in health care using a value-based approach, a second round (VOT2) on new therapeutic areas was launched; focusing on The Value of Early Coordinated Care for Rare Diseases (Ataxia, Dystonia and Phenylketonuria) and The Value of Early Intervention and Continuity of Care for Mental Disorders (Anorexia Nervosa, Autism Spectrum Disorder and Major Depressive Disorder).

**The study aims** to examine health gains resulting from optimized healthcare interventions in comparison with current care or inadequate treatment and converge data evidence to policy recommendations on how to improve the care pathway(s). 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. **Seamless, coordinated care is defined as** “a service characteristic which is manifested by coherent treatment plans for individual patients. Each plan should have clear goals and should include interventions that are needed and effective: no more, no less. In particular, by seamless care, we mean the coordination of information and services within an episode of care (both within and between services). Inter-linkages between staff and between agencies over a longer period of treatment, often spanning several episodes are also considered”<sup>ii iii iv</sup>.

**Study scope** focuses on patient needs, early intervention and coordination/continuity of care using the care pathway as a tool recommended at the first step of the research *to understand better the condition from onset to rehabilitation and recovery while identifying the treatment gaps, and to translate clinical practice guideline recommendations into health care processes, sequences for improved outcomes*<sup>v vi</sup>. It is proposed to reach a consensus on optimized care pathways and discuss harmonized datasets (health economics perspective) based on a VOT patient-centred approach (see [figure 1](#)). **Throughout 2020, joint working sessions** aimed to exchange and build synergy between the research-work and the European Commission DG Sante Rare Diseases European Reference Networks (ERN-RND and MetabERN) as well as the EU H2020 PECUNIA project on mental health services. A VOT2 mid-term review took place on 18 May 2020 followed by two meetings to discuss the method which respectively took place on 6 October 2021 and 11 December 2021. **Moving on towards the project last phase (phase 3 “final results and publications”)**, EBC together with its members (EAN, EANS, ECNP, EFNA, EPA, EPNS, EUFAMI, FENS, GAMIAN Europe, IBRO) and experts who are participating in the research convened a meeting on 8 June 2021 to present a synthesis of the VOT2 research project results so far. Both EBC position papers will be released on 7 December 2021 to be followed by scientific publications (Q1 2022). Beyond the research design and considering current context, the impact of Covid-19 on treatment and healthcare transformation will be also further explored.

**Figure 1:** Key touchpoints of the patient care pathway for chronic rare diseases or mental disorders



## Meeting Introduction

### 1. Health systems resilience and today's challenges: the impact of Covid-19 on health services provision for brain disorders

**The COVID-19 pandemic** has put national health systems in Europe and beyond under immense pressure. Health systems were largely unprepared for an outbreak of this magnitude. The crisis tested their resilience, their ability and capacity to absorb, effectively respond and adapt to shocks and structural changes while sustaining day-to-day operations. Many analyses of its impact and the responses adopted have already been published. However, there is a need to look beyond the current pandemic to think about how health systems can prepare better for future crises that threaten the ability to deliver health care.

**There were already treatment gaps to be addressed before Covid-19.** The sanitary crisis exacerbated those gaps and emphasized even more the need for integrated, person-centered care.

**Today EU recommendations target a number of key areas,** including: enhancing workforce training and resilience, reviewing research and development and procurement (especially for innovative medicines), identifying and reducing disinformation, fostering interprofessional and inter-sectoral collaboration with community health workers and informal care givers for example, integrating information and communication technologies across care levels and public health, strengthening primary and mental health care, increasing public health focus on psychological distress, debating methods for Member States to collect and share aggregate health data on ethnicity and socioeconomic status, developing and deploying online trainings for frontline health and social care professionals regarding care provision to vulnerable groups, and finally investing from the European Commission in the development and implementation of comprehensive resilience testing of health systems that use qualitative and quantitative data collection methodologies to generate meaningful, actionable results for health system transformation.

### 2. Burden of brain disorders and primary health care

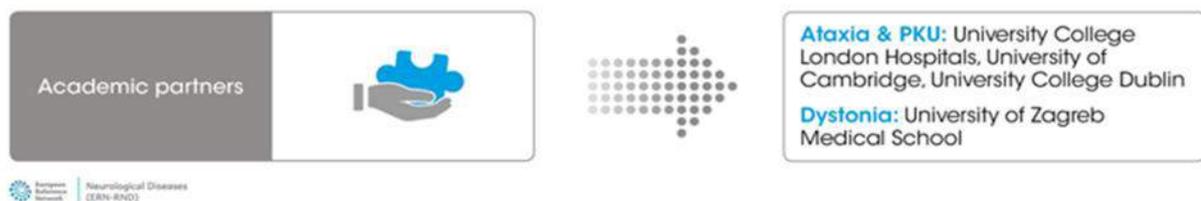
**Disorders of the brain** rank among the world's leading causes of ill-health and disability. Europe, particularly has a high burden and frequency of brain disorders. Early detection and intervention are key to achieve optimal treatment results in individuals at risks and patients. Analyzing the treatment gap and underlying causes along the continuum of care remains central. The role of primary health care is essential (gatekeeping) but need to address several challenges. The chronically ill patients and subjects to co-morbidities, are in special need of coordinated and continuity of care. However, there

are multiple obstacles such as diagnosing rare conditions in a GP-setting. Could case detection be facilitated by technical approaches? Which structures enable fast—track diagnosis and treatment?

**Among the challenges to be addressed:** 1) quality of care varies largely from general practice to general practice; 2) undertreatment has to be identified and addressed on an individual basis; 3) health care providers need to be guided and trained while facilitating communication; 4) re-assessing patient’s needs and priorities while avoiding overtreatment.

**Gaining evidence** is a necessity to improve the diagnostic process for brain disorders. Patients’ needs for long term care should be better recognized and addressed.

## Meeting Session 1 Advancing Patient Outcomes: The Value of Early Diagnosis and Coordinated Care for Rare Brain Diseases (Ataxia, Dystonia and Phenylketonuria)



1. Presentations by Clinicians (WG leaders) and health economics experts: overview of preliminary findings
  - See [Master Slides Deck](#).
  - See [Annex 1A: Ataxia, Dystonia and PKU case studies overview](#)

Motivated by addressing the existing gaps in the care pathways, **the EBC Study on Ataxia, Dystonia and Phenylketonuria (PKU)** aims to assess the benefits of early coordinated care and treatment, multidisciplinary care patterns (also addressing comorbidity) and health care providers education on outcomes to patients and costs.

**Care coordination using the key roles of multidisciplinary teams** is considered important for professionals and patients with complex rare conditions<sup>vii</sup>, yet research addressing its impact is limited<sup>viii ix x</sup>. The study addresses a **research gap** by capturing the views of the patients (surveys and descriptive statistics), clinicians and health economists. An analysis of the cost-consequences of specialist centres (centres of expertise) for managing care of people with ataxia or dystonia in several

European countries; and the cost-consequences of metabolic care unit services for people with phenylketonuria is performed.

The research is ongoing, however:

- **From the results of the Ataxia study**, it emerges very clearly that patients with rare neurological diseases have a better management and treatment of their condition in the specialist centres compared to the one they had previously. Moreover, patients have valued the translational research aspect of these centres, been on the forefront of new diagnostic tools and management and treatment.
- **From the results of the Dystonia study**, medical education about dystonia is needed to increase knowledge of GPs, neurologists to diagnose and manage dystonia, which is probably also the case for many other rare diseases.
- **From the results of the PKU study**, early diagnosis through NBS has enabled timely intervention. However, there are still issues, difficult to address. European guidelines have been delineated, but their implementation is variable across sites (metabolic care unit services) which is characterized by variability in staffing and resources, genotyping of patients and access to novel therapies. Patients deemed most likely to benefit from novel therapies should have access to novel therapies, but this requires attention to close monitoring and determining the added value of treatment, beyond dietary management alone therefore advocating for resources is necessary to meet the added demands on the service.

**Overall**, where no national guidelines exist, European guidelines should be implemented to ensure that people with RDs have access to the support and care they need, see [table 1](#): Clinical Guidelines.

Table 1: Clinical guidelines for Ataxia, Dystonia and PKU

Therapeutic areas	Clinical guidelines
Ataxia	de Silva, R., Greenfield, J., Cook, A. et al. Guidelines on the diagnosis and management of the progressive ataxias. Orphanet J Rare Dis 14, 51 (2019). Posted on the ERN-RND website together with Diagnostic Flowchart for Adult Ataxias.
Dystonia	- Albanese, A, et al. “EFNS Guidelines on Diagnosis and Treatment of Primary Dystonias.” European Journal of Neurology, vol. 18, no. 1, 2011, pp. 5–18. <u>Background</u> : Primary dystonias are chronic and often disabling conditions with a widespread spectrum mainly in young people. - Tamás, Gertrúd, et al. “Quality and Reporting of Guidelines on the Diagnosis and Management of Dystonia.” European Journal of Neurology, vol. 25, no. 2, 2018, pp. 275–283.

PKU	Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis. 2017;12(1):162. October 2017.
-----	---

**Complementary research on the patients' care pathways (PCP)** - as a suggested tool by the EC ERN Programme to increase homogeneity among centres, among countries - will be further conducted in order to 1) design an "optimized" PCP for the three RDs Ataxia, Dystonia, PKU and 2) assess the resources use/economic implication of the adoption of the optimized PCP for the RDs compared to the current ones (lead: Prof. G. Turchetti).

## 2. Discussion: participation of EURORDIS, ERN-RND, MetabERN and ICHOM & participation of patients, patient associations and HCPs

Heterogeneity and low prevalence are the defining characteristics of rare diseases, but also complexity: about 80% of these disorders are of genetic origin, and about 75% have neurological symptoms<sup>xi</sup> (see [Table 2](#): Estimated European prevalence rates of the 22 selected Rare Diseases including Ataxia, Dystonia and PKU).

**Table 2:** Estimated European prevalence rates of the 22 selected Rare Diseases including Ataxia, Dystonia and PKU

	Rare disease name	Estimated prevalence (per 100,000)
	Congenital isolated hyperinsulinism	2.0 <i>BP</i>
	Scleroderma (systemic sclerosis, localised sclerosis)	42.0 <i>P</i>
	Familial QT syndrome (Inc. Romano Ward)	40.0 <i>BP</i>
	Primary systemic amyloidosis	30.0 <i>P</i>
	Retinitis pigmentosa	26.7 <i>P</i>
	Fragile X	32.5 <i>P</i>
	Neurofibromatosis 1	21.3 <i>P</i>
	Marfan syndrome	15.0 <i>P</i>
	Sickle cell anaemia	22.0 <i>P</i>
	Sarcoidosis	12.5 <i>P</i>
<b>Inherited</b>	Haemophilia	7.7 <i>P</i>
	Huntington's disease and rare neurodegenerative disease	2.7 <i>P</i>
<b>Metabolic</b>	Phenylketonuria	10.0 <i>BP</i>
<b>Disorder</b>	22q11.2 Deletion syndrome (DiGeorge syndrome)	37.5 <i>BP</i>
	Duchenne or Becker muscular dystrophy	4.78 <i>P</i> / 1.53 <i>P</i>
	Prader-Willi syndrome	3.1 <i>BP</i>
	Epidermolysis bullosa	2.2 <i>BP</i> *
	Mucopolysaccharidosis (type 2)	10.0 <i>P</i>
<b>RND</b>	Rare ataxias (including Friedreich's)	2.0 <i>P</i> *
	Tuberous sclerosis	12.0 <i>P</i>
	Osteogenesis imperfecta	10.0 <i>P</i>
<b>RND</b>	Motor neuron disease	3.85 <i>P</i>

Estimates provided from the Orphanet Report Series  
*P* = prevalence; *BP* = birth prevalence  
 \*Estimates shown are for epidermolysis bullosa simplex and Friedreich's Ataxia

Byrne, N., Turner, J., Marron, R. et al. The role of primary care in management of rare diseases in Ireland. *Ir J Med Sci* 189, 771–776 (2020).

**Common to almost all rare diseases is that there is no cure and management focuses on timely diagnosis, disease-modifying therapies with different mechanisms of action, symptomatic therapies or other supportive therapies, or surgical procedures such as deep brain stimulation, rehabilitation and social care.** Personalizing and optimizing each of these components can help people adapt to life with the disease. Increasingly, case management goes far beyond reimbursement to include a host of

wraparound services. These services differ for each patient and disease state. Case management can include nurse navigators who assist patients with their therapies, and with obtaining psychosocial support or mental health counseling.

**According to the European Reference Network on rare neurological diseases (ERN-RND)**, in Europe there are 500.000 people living with RNDs, while 60% of those affected are still undiagnosed due to significant phenotype and genotype heterogeneity in clinical presentation and disease course<sup>xii</sup>. **Consequently, healthcare costs have shifted from inpatient care and rehabilitation to outpatient care.** The analysis of the **“treatment gap”** is central in the study with the development of benchmarks while addressing both the obstacles to optimal treatment as well as the deficiencies in health services along the continuum of care. Effective interventions exist. However, **effective implementation of early diagnosis and treatment vary** widely across health systems and many European countries are still lagging behind, with **wide clinical practice variations** even within countries<sup>xiii</sup>.

**At healthcare systems level**, as rare disease patient populations are normally small and scattered across large geographical areas, hospitals can struggle to ensure highly specialised healthcare services that are both financially and clinically sustainable. However, national policies on centralisation of care (and budgets) for rare diseases to regional centres and for highly specialised healthcare for extremely rare diseases to national centres vary between EU Member States, depending on the size of the country and the structure of their health system. Despite volume being a driving factor for quality, **centralisation of care for rare diseases and the designation of centres of expertise** bundled with mandated referrals is a politically sensitive topic in some EU Member States with highly decentralized health systems<sup>xiv</sup> (see [figure 2](#): Coordinated care, designation and evaluation criteria of CE<sup>xv</sup>).

Figure 2: Coordinated care, criteria for the designation and evaluation of centres of expertise (CE)

• DESIGNATION	• EVALUATION	
	Soft values	Hard values
MS establish a procedure to define and approve designation criteria and a transparent designation process	Co-operation with patient organisations	Time to diagnosis
1. Capacity to manage RD patients and provide expert advice; adhere to good practice guidelines for diagnosis and care	Patient-orientated approach	Waiting time
2. Patient access to a multidisciplinary team of experts (integrating medical, paramedical, psychological and social needs)	Improved outcomes	Genetic consultancy
3. Assure quality of care, participation in internal and external quality schemes, propose quality of care indicators	Improved atmosphere	Multidisciplinary approach
4. Proven expertise documented by annual volume of referrals, second opinions, publications, grants, teaching and training activities	Improved quality of life	Co-operation with other centres (clinical and laboratory)
5. Participation in research activities, data collection, clinical trials if applicable	Avoiding unnecessary complications	Registries
6. Organisation of collaborations to assure the continuity of care between childhood, adolescence and adulthood, if relevant	Awareness and knowledge dissemination	Care guidelines and recommendations
7. Organisation of collaborations to assure the continuity of care between all stages of the disease	Information provision to local centres	Quality control
8. Collaboration with laboratories, patient organisations, and other CE at national, European, international levels		International and national networking
		Economic assessment

Centres of Expertise for Rare Diseases,  
 EU Council Recommendation on action in the field of rare diseases (2009)  
 EUCERD recommendations on centres of expertise at nat. level (2013)

## PANEL DISCUSSION AND REMARKS

Priorities have been set up by the **European Commission in the 2009 Council Recommendation on an action in the field of rare diseases**<sup>1</sup> calling for countries to adopt national plan or strategy aimed at guiding and structuring actions in the field of rare diseases within the framework of the health and social systems<sup>xvi</sup>. Considering that most European countries (and countries under study) have adopted such a plan or strategy today<sup>xvii</sup> and building also on the **most recent Clinical guidelines** adopted for Ataxia<sup>xviii</sup>, Dystonia<sup>xx</sup> and PKU<sup>xxii</sup>, the following sub-questions are raised to address unmet needs:

Ataxia, Dystonia and Phenylketonuria all share similar challenges, how best to address delayed diagnosis; barriers to access specialized care and treatment options; and the psychosocial burden affecting most productive part of patient's life?

**See Remarks from Speakers in Annex 1B.**

---

<sup>1</sup>2009/c151/02 - A number of recommendations issued at European level covering areas such as data epidemiology, registries and e-health, adequate identification and coding of rare diseases, care pathways, centres of expertise, practical guidelines, clinical research, disease registries, patient organisations and information services as well as transition from paediatric to adult healthcare provider in RDs have been indicated as priorities to be incorporated into national plans for rare diseases.

### 3. Summary conclusions based on current results

**So far, case studies** highlighted the complexity of care needs for many people living with Ataxia, Dystonia or PKU, and the need for adequate treatment and care coordination both within and across medical domains.

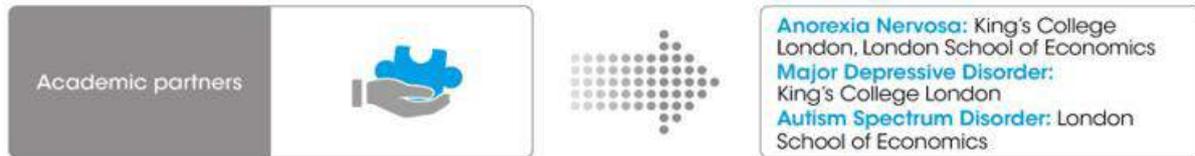
**With drugs currently available for only about 5% of rare diseases**, the future should be wide open for investment in orphan drug development projects in Europe. A European Expert Group on Orphan Drug Incentives (OD Expert Group) has been established in 2020 to discuss and bring forward innovative proposals to stimulate innovation and foster research into therapies for rare diseases<sup>xxiii</sup>. **With the general consultation for the Orphan Medical Products and Paediatric Regulation recently opened (May 2021)**, recommendations in that regard to be followed-up will be released in the context of the review on the EU legislation for Rare Diseases.

#### **At research level:**

- It is essential to invest in more (basic, clinical, translational) neuroscientific research to understand the causes and reasons for progression of rare diseases and to develop new treatments that can improve quality of life, functioning and reduce associated direct and indirect costs.
- In exploring opportunities to provide more systematic care coordination, consideration should be given to Clinical Guidelines and Centres of Expertise or multidisciplinary specialist centres for Rare Diseases - while ensuring smooth transition from paediatric to adult care - as well as medical education for GPs, general neurologists and specialist nurses.
- Addressing prevention and timely intervention as a priority based on needs, consideration of validated MTD care models/ care pathways with primary care and incentives will help ensure patients with RNDs or metabolic disorders receive holistic, and well-integrated medical care.

**At macro level**, a new European policy framework for rare diseases is needed to bridge progress from the last decade and to innovate based on patient needs. Crucially, this framework would bring together a refreshed concerted strategy across research, digital, healthcare and social welfare complementing existing legislations; to guide the implementation of national plans for rare diseases with the same measurable objectives; and to foster collaboration with European Reference Networks for Rare Diseases such as ERN-RND and MetabERN.

## Meeting Session 2 Advancing Patient Outcomes: The Value of Early Intervention and Continuity of Care for Mental Disorders (Anorexia Nervosa, Autism Spectrum Disorder and Major Depressive Disorder)



### 1. Presentations by Clinicians (WG leaders) and health economics experts: overview of preliminary findings

- See [Master Slides Deck](#).
- See [Annex 2A: Anorexia Nervosa, Autism Spectrum Disorder, Major Depressive Disorder case studies overview](#)

Motivated by addressing the existing gaps in the care pathways, **the EBC Study on Anorexia Nervosa (AN), Autism Spectrum Disorder (ASD) and Major Depressive Disorder (MDD)** aims to assess the benefits of improved detection, early continuity of care and treatment, and collaborative care patterns (also addressing mental health problems with comorbid medical conditions) on outcomes to patients and costs.

**Care continuity across age groups and services** is considered particularly important for patients with long-term conditions and subjects to co-morbidities, yet research addressing its impact is limited<sup>xxiv xxv xxvi xxvii</sup>. The study addresses a **research gap** by capturing the views of the patients (surveys and descriptive statistics), clinicians and health economists. Different analysis - cost-saving (AN); cost-consequences and cost-effectiveness (ASD and MDD) of proposed interventions/models are performed.

The research is ongoing, however:

- **From the results of the Anorexia Nervosa (AN) case study**, it is proposed to optimize care pathways for adults by improving detection in primary care to improve access to treatment; reducing waiting times to enter specialist treatment and avoiding delay; increasing the effectiveness of routine treatment through a) a triage system and b) augmentation; bridging the transition from inpatient treatment and increasing support in the community; providing rehabilitation and new treatments for those not responding to available treatments. In

addition, families would prioritize for all (children, youth and adults): an increase in specialist ED services, an increase of inpatient beds and improvements in GP training.

- **From the results of the Autism Spectrum Disorder (ASD) case study**, it is proposed while optimizing care pathways for ASD and epilepsy to reduce the time to access specialists and early intervention, to improved epilepsy screening in children diagnosed with ASD and to improve paediatrician and GP awareness of comorbidities such as epilepsy and ASD. Improving coordination among professionals remain essential through MTD care units. Supporting transitions from inpatient and outpatient services, and creating specific guidelines on the management of ASD and epilepsy should also be considered.
- **From the results of the Major Depressive Disorder (MDD) case study**, while there is a good evidence base to support the use of medication and different types of psychological therapy in the treatment of MDD, it is well-known that there are gaps in detecting MDD and the provision of effective treatment and continuity of care. If these gaps are reduced, there are likely to be impacts on healthcare and societal costs and patient outcomes.

Overall, reference to clinical guidelines remains essential, they strengthen the role of the GP, emphasizing the need for early detection and active follow-up to people with mental disorders, see [Table 3](#): Clinical Guidelines for AN, ASD, MDD.

[Table 3](#): Clinical guidelines for AN, ASD, MDD referred in the VOT2 study

Therapeutic areas	Clinical guidelines
Anorexia nervosa	Survey indicates that while most countries have guidelines for treatment in place (8/12), surveillance systems are immature, with only about half having data on incidence and prevalence available, and two having information on outcomes – although the latter is not routinely collected. clinical guidelines for treatment of Anorexia. One example is the NICE guidance for England. There are guidelines in most countries. But there is not a lot of empirical evidence to assess whether these guidelines are actually in place.
Autism spectrum disorder	- Care pathway for ASD (J. Green, Journal of Child Psychology and Psychiatry, 2019) <sup>xxviii</sup> . - NICE guideline on pharmacological treatments for children with focal epilepsy was used as applicable to <i>autistic</i> children with focal epilepsy, see Epilepsies: diagnosis and management, NICE Clinical Guideline (2012) <sup>xxix</sup> .
Major depressive disorder	Gold standard “stepped care” NICE depression management guidelines (2009) <sup>xxx</sup> .

The importance of intersectoral impacts including families, educational sector, employment is particularly highlighted across case studies. Families are often supporting high care and treatment

costs correlated to patient high needs. **Harmonizing datasets (health economics perspective) based on a VOT patient-centred approach was proposed:** discussions amongst the groups were held aiming to exchange and build synergy between the research cost analysis and the EU H2020 PECUNIA project - Programme in costing, resource use measurement and outcome valuation for use in multi-sectoral national and international health economic evaluations related to mental health services in Europe<sup>xxxii</sup>.

## 2. Discussion: participation of EUFAMI, AUTISME Europe, GAMIAN Europe and HCPs & overall remarks

**Table 2: GBD 2010 Mental, Neurological, and Substance Use Disorders, Estimated Disability Weights, and Prevalent Cases<sup>xxxii</sup>**

Disorders	Disability weights	Prevalent cases (to the nearest 100,000)
<b>Neurological disorders</b>		
Alzheimer's disease	mild: 0.082 (0.055–0.117); moderate:0.346 (0.233–0.475); severe:0.438 (0.299–0.584)	43,000,000
Parkinson's disease	mild: 0.011 (0.005–0.021); moderate:0.263 (0.179–0.360); severe:0.549 (0.383–0.711)	5,100,000
Epilepsy	treated, seizure free:0.072 (0.047–0.106); treated, with recent seizures:0.319 (0.211–0.445); untreated:0.420 (0.279–0.572); severe:0.657 (0.464–0.827)	28,300,000
Multiple sclerosis	mild: 0.198 (0.137–0.278); moderate:0.445 (0.303–0.593); severe:0.707 (0.522–0.857)	1,800,000
Migraine	0.433 (0.287–0.593)	1,014,000,000
Tension-type headache	0.04 (0.025–0.062)	1,432,500,000
<b>Substance use disorders</b>		
Alcohol dependence	mild: 0.25(90.176–0.359); moderate:0.388(0.262–0.529); severe:0.549(0.384–0.706)	94,800,000
Opioid dependence	0.641 (0.459–0.803)	15,500,000
Cocaine dependence	0.376 (0.235–0.553)	6,900,000
Amphetamine dependence	0.353 (0.215–0.525)	17,200,000
Cannabis dependence	0.329 (0.223–0.455)	13,100,000
<b>Mental disorders</b>		
Major depressive disorder	mild: 0.159 (0.107–0.223); moderate:0.406 (0.276–0.551); severe:0.655 (0.469–0.816)	298,700,000
Dysthymia	0.159 (0.107–0.223)	105,700,000
Bipolar disorder	manic: 0.480 (0.323–0.642); depressive: 0.406 (0.276–0.551); residual: 0.035 (0.021–0.055)	58,900,000
Schizophrenia	acute: 0.756 (0.571–0.894); residual:0.576 (0.399–0.756)	21,500,000
Anxiety disorders	mild: 0.03 (0.017–0.048); moderate:0.149 (0.101–0.210); severe: 0.523 (0.365–0.684)	272,100,000
Eating disorders	Anorexia nervosa: 0.223 (0.151–0.313); Bulimia nervosa:0.223 (0.150–0.310)	Anorexia: 9,400,000 Bulimia: 8,600,000
Autism	0.259 (0.177–0.362)	14,900,000
Asperger's syndrome	0.11 (0.073–0.157)	35,500,000
Attention-deficit hyperactivity disorder	0.049 (0.031–0.074)	36,400,000
Conduct disorder	0.236 (0.031–0.074)	48,700,000
Idiopathic intellectual disability	mild: 0.031 (0.018–0.049); moderate:0.08 (0.053–0.114); severe:0.126 (0.085–0.176); profound: 0.157 (0.107–0.221)	30,800,000

According to recent OECD estimates<sup>xxxiii</sup>, more than one in six people across EU countries have a mental health issue, among them anorexia nervosa, autism or major depressive disorder. **Treatment includes the careful use of medication, non-pharmacological approaches, and social support.** Positive outcomes can be achieved by a recovery approach that attends to all aspects of the person's health. However, unmet medical and non-medical needs are growing and much more can be done to early detect and manage mental disorders.

**Treatment gaps**—the proportion of people who require detection and treatment but do not receive these or receive inadequate care—can range to **60% of people with anorexia or autism across Europe<sup>xxxiv xxxv</sup>**. The duration of untreated illness for **anorexia nervosa** is high, at an average of 18

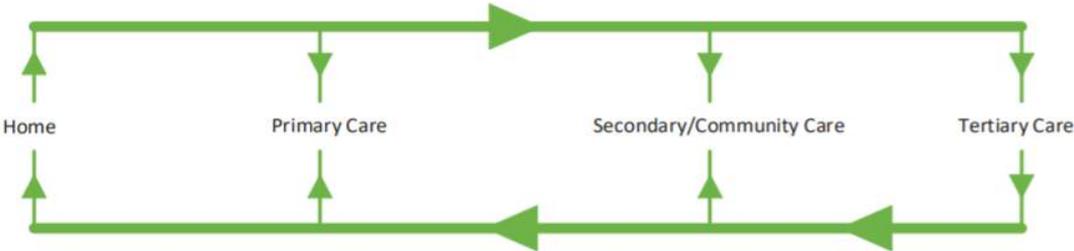
months or more, highlighting the importance of a stepped care model/care pathway with primary care will help ensure patients receive holistic and well-integrated medical care. **Autism** is a lifelong, complex neurodevelopmental condition affecting brain development and behaviour. In exploring opportunities to provide more systematic continuity of care, consideration should be given to clinical guidelines and collaborative care between primary care and specialist care - while ensuring smooth transition from paediatric to adult care. Proportion of undetected depression (50%) is more or less the same than for anorexia and autism. Many individuals with **major depressive disorder** are not receiving treatment at any one time and it is known that both duration of untreated illness and the number of ineffective treatments trialled are risk factors for poorer long-term outcomes. Together, these phenomena demonstrate a need for improved management of MDD. The most common treatments used to manage depression are antidepressants, electroconvulsive therapy (ECT) and psychosocial interventions.

The analysis of the “treatment gap” is central in the study with the development of benchmarks while addressing both the obstacles to optimal treatment as well as the deficiencies in health services along the care pathway. Effective interventions exist. However, **effective implementation of early detection and treatment as well as continuity of care** vary widely across health systems and many European countries are still lagging behind, with **wide clinical practice variations** even within countries.

The shift towards community mental health care “out-patient care” as encouraged by mental health deinstitutionalization reforms across Europe in the last decades has raised concerns about continuity<sup>xxxvi xxxvii</sup>. **The criterion for best quality care** has become the degree to which care delivered and information shared by separate services (in-patient psychiatry and out-patient mental health community services) and professionals (mental health and primary care providers) are continuous and well-coordinated<sup>xxxviii xxxix xl</sup>. The World Health Organization optimal mix of services pyramid framework for mental health pleads for a **comprehensive care offer integrating mental health care into primary health services**<sup>xli</sup>. Several trials of collaborative care models have attempted to maximize the cost-effectiveness of collaborative care by using a process described as “**stepped care**”<sup>xlii xliii</sup>. According to the staging approach to mental health care<sup>xliv</sup>, stepped care usually begins with relatively low-intensity interventions, such as antidepressant medications prescribed by a primary care provider and care management provided in the primary care clinic. Under the supervision of a consulting psychiatrist or other appropriate mental health specialist, patients who are not helped by such initial treatments are shifted to progressively more intensive treatment approaches, including referral to specialty mental health care as needed.

Figure 3 relates to interactions and continuity across primary, community, secondary, tertiary, and forensic mental health services. This is central to the acuity of the condition and the pathway to resilience and recovery<sup>xlv</sup>.

**Figure 3:** The seamless system of continuity of care



PANEL DISCUSSION AND REMARKS

Building on the **most recent Clinical Guidelines adopted for Anorexia Nervosa, Autism and Major Depressive Disorder**, the study will at the same time examine the role of national policy and programs, including National Mental Health Plans on the effective implementation of collaborative care patterns, the following sub-questions have been addressed.

Anorexia Nervosa, Autism Spectrum Disorder and Major Depressive Disorder all share similar challenges: how best to address delayed detection; barriers to access specialized care and treatment options and a high psychosocial burden – burden increasing with the severity of disability?

See Remarks from Speakers in Annex 2B.

### 3. Summary conclusions based on current results

**So far, case studies highlighted the complexity of care needs** for many children, adolescents living with anorexia nervosa or autism spectrum disorder, as well as for adults living with major depressive disorder, and demonstrated the need for early diagnosis, adequate treatment and continuity of care both within and across medical domains.

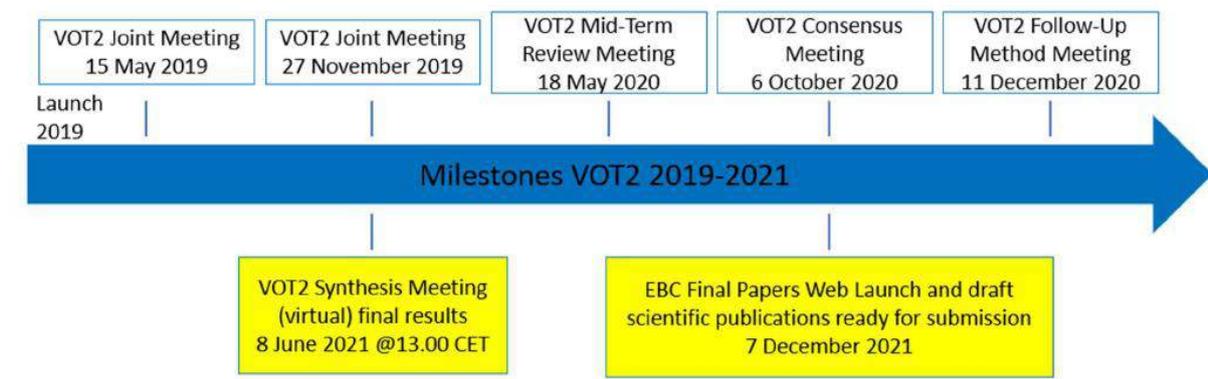
#### **At research level**

- It is essential to invest in mental health, promoting a life course approach “big change starts small”.
- In exploring opportunities to provide more systematic continuity of care, consideration should be given to Clinical Guidelines and collaborative care between primary care and specialist care - while ensuring smooth transition from pediatric to adult care.
- Consideration of a stepped care model/ care pathway with primary care will help ensure patients with mental disorders receive holistic, and well-integrated medical care

**At macro level, a new European policy framework for mental disorders** is needed to bridge progress from the last decade and to innovate based on patient needs. Crucially, this framework would:

- Develop/update mental health policy aiming at moving away from institutional care to integrated and well coordinated community-based mental health care, including inpatient treatment in general hospitals and comprehensive community-based services for each catchment area, according to local and national needs;
- Promote actions that ensure the efficient use of available resources and those to be reallocated from long-stay psychiatric hospitals to community-based services.

## VOT2 Next Steps



Deliverables and by whom	Deadline
Final posters (care pathway analysis + economic evaluation) - GROUPS	1 October 2021
1 <sup>st</sup> Draft EBC Papers for consultation – EXPERTS (J. SIMON & G. TURCHETTI) + EBC (V. QUOIDBACH)	15 October 2021
Final Draft EBC Papers – EXPERTS (J. SIMON & G. TURCHETTI) + EBC (V. QUOIDBACH)	15 November 2021
<b>Web Launch of EBC final papers MDs and RDs – EBC</b>	<b>7 December 2021</b>
Manuscripts for scientific journals – final draft – GROUPS	15 December 2021
Manuscripts for scientific journals – start submission (EBC) on behalf of the GROUPS	17 January 2022
VOT2 & Covid-19 manuscripts MDs and RDs – final draft – ACADEMIC PARTNERS + EBC	17 January 2022
VOT2 & Covid-19 manuscripts for scientific journals – start submission (EBC) on behalf of the GROUPS	31 January 2022
Revision process of manuscripts – back and forth	1st semester 2022

**Next VOT2 research update meeting with each group will take place between 2 July – 9 July 2021.**

**Note - The VOT2 current research design beyond COVID-19**, two additional papers covering the therapeutic areas under study (rare diseases and mental disorders) will examine the impact of the pandemic and true value of integrated, coordinated/continuity of care for patients. Technologies enable real-time, long-term follow-up of the patient, whatever the setting, in care or otherwise. This has been highlighted during the Covid-19 crisis. Some hospitals are today already monitoring a substantial amount of patient data through the Electronic Health Record (EHR). The gradual shift towards more extra-muros care, either at home or in intermediary care settings (such as rehabilitation centres), and the need and ability to follow the patient when he is not “in treatment”, will require investments in e-health/integrated health data ecosystem and reforms of healthcare systems.

# Annex 1A

## Rare diseases – Overview case studies

### ATAXIA CASE STUDY ACCORDING TO POSTERS AND PRESENTATION

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 [Guidelines on the diagnosis and management of the progressive ataxias (2019)]. The guidelines are aimed predominantly at HCPs in secondary care (such as general neurologists, clinical geneticists, physiotherapists, speech and language therapists, occupational therapists, etc.) who provide care for individuals with progressive ataxia and their families, and not ataxia specialists. 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

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with progressive ataxia: survey population from 16+ years old (patient stratification: patients with no comorbidity/with comorbidity) including statistical analysis
- Cost-consequences analysis
- Sites: Ataxia Specialist Centres
  - UK (London Centre and Sheffield Centre) – Patient survey UK data only reported (n=277 respondents)
  - Germany: the survey was circulated through numerous german sites– ongoing research
  - Italy (Charity name) – ongoing research

Treatment gap (cat.)	Treatment gap breakdown	Summary of current results & recommendations
Detection & treatment Access to primary care Access to secondary/general neurology services	Rates of ataxia not detected Delays in reaching diagnosis 40% of respondents	- Primary care services play an important role in the management and care of ataxia patients. Yet the knowledge of ataxia is poor, a leading role in education of this condition in primary care health services is necessary.

	Lack of understanding of ataxia in primary care (HCPs education)	- Increase the awareness of Ataxia Specialist Centres in the UK in order to have more timely referrals.
Access to tertiary/specialist services and multidisciplinary care team (MTD)	<p>Coordinated care</p> <p>Rates of referral to tertiary services (Specialist Ataxia Centres) +/- 50%</p> <p>Travel to specialist centre SAC is too far away for 30% respondents</p> <p>Rates/frequency of follow-up contact for care and treatment by MTD 77% of the respondents received care from a MTD and satisfied about MTD care being effective for the management of their symptoms</p>	<ul style="list-style-type: none"> <li>- Coordinated care by SAC recommended</li> <li>- Implementation of Whole Genome Sequencing in SAC in order to achieve timely genetic diagnosis of the rare ataxias</li> <li>- Patients reported a better overall treatment and care in SAC</li> <li>- Especially for patients with complex needs and co-morbidities (markers of severity)</li> <li>- More patients with ataxia should attend MDT clinics.</li> <li>- Implementing telemedicine in existing centres to increase the number of patients who can be seen and increase the number of centres when possible.</li> <li>- The centres need to have an interest in translational research so the treatment will be more evidence based for these rare conditions, and they can be sites for clinical trials.</li> <li>- High correlation between patient satisfaction and SAC (chi square test) in comparison with non SAC</li> <li>- COSTING: SAC is slightly more expensive considering MTD management, complex needs (disease severity) and comorbidity than non SAC but demonstrated benefits for patients.</li> </ul>

#### DYSTONIA CASE STUDY ACCORDING TO POSTERS AND PRESENTATION

Dystonia is a very complex, highly variable neurological movement disorder characterized by involuntary muscle contractions. Although an underdiagnosed condition, 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, chemodeneration botulinum neurotoxin injections, physical therapy, or other supportive therapies, and surgical procedures such as deep brain stimulation; therefore the need for guidelines [EFNS Guidelines on Diagnosis and Treatment of Primary Dystonias (2011)].

#### 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**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with dystonia: survey population including statistical analysis
- Cost-consequences analysis
- Sites : Dystonia Specialist Centres

Patient survey: Management and QoL of dystonia patients in Europe using patients’ online questionnaire (n=3120 respondents to the survey from 30 countries) – Study performed by Dystonia Europe (Maja et al., EAN Oslo, 2019). A previous study was performed by the European Network for the Study of Dystonia, Network of the Study of Dystonia (Valadas et al. Eur J Neurol 2016)<sup>xlvi</sup> which reported a lack of specific training in dystonia by GNs, GPs and health professionals.

- Croatia (Medical School Zagreb University)
- Germany (Movement Disorders Section, Department of Neurology, Hannover Medical School, Hannover)
- Italy (University Hospital (Movement Disorders Centre)
- UK (St George’s University of London)

Treatment gap (cat.)	Treatment gap breakdown	Summary of current results & recommendations
Detection & treatment Access to primary care Access to secondary/general neurology services	Delays in reaching diagnosis	<ul style="list-style-type: none"> <li>- 27% of respondents only obtain a correct diagnosis within 1 year after first symptom. 14% had to wait longer than 10 years.</li> <li>- 45% of patients received botulinum toxin as the most common type treatment followed by drugs and DBS. However only 30% of patients are satisfied with treatment.</li> <li>- Only 16% of respondents had GPs recognized their symptoms and referred to an appropriate specialist.</li> <li>- Dystonia affects working status in 59 % of patients</li> <li>- Limited knowledge about DS - different types of dystonia (general dystonia, focal dystonia, segmental dystonia), different procedures: 1) DBS surgical procedures (specialist centres) and 2) out-patient care for others/injections.</li> <li>- Lack of training of GN and GPs lead to delayed diagnosis and therapy, and in fine decreased QoL</li> </ul>
Access to tertiary/specialist services and multidisciplinary care team (MTD)	Coordinated care Medical education	<ul style="list-style-type: none"> <li>- To facilitate access to specialized care, especially for surgery/DBS</li> <li>- To promote locally, in each country, the creation of multidisciplinary teams for the management of dystonia patients could provide the basis for improving all aspects of dystonia management across Europe and to promote Internationally,</li> </ul>

	<p>collaboration in training, advanced diagnosis, treatment and research of DS and to develop specific trainings for GNs, GPs, nurses led by specialist neurologists in order to overcome the disparity in education of medical professionals</p> <ul style="list-style-type: none"> <li>- High correlation demonstrated between management of dystonia patients and HCPs medical education (chi square test) especially GPs and general neurologists in comparison with HCPs not receiving medical education. Physiotherapists also play an important role.</li> <li>- So far, limited COSTING analysis with regards to the economic impact of medical education and specialist centres however, if there are budgetary restrictions in national health systems, it is better to allocate funding to medical schools to compensate the lack of financing in health systems.</li> </ul>
--	---

#### PKU CASE STUDY ACCORDING TO POSTERS AND PRESENTATION

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. Lifelong impact. PKU is diagnosed as a result of newborn screening. Treatment consists of dietary restriction of phenylalanine and early intervention is key. 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. PKU can also compound mental health issues, like feelings of isolation, anxiety, depression and stress. Therefore, guidelines are important to improve diagnosis and management of PKU from a multidisciplinary care approach [The complete European guidelines on phenylketonuria: diagnosis and treatment (2017)]. These guidelines are intended to be used by metabolic physicians, dieticians, obstetricians, midwives, psychologists, social workers, biochemists and other professionals involved in the treatment of patients with PKU.

#### 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

- Patient care pathway and treatment gaps/unmet needs analysis of individuals (paediatric and adults) with PKU : patient survey including statistical analysis and a review of PKU Clinic structure and processes will be undertaken
- Cost-consequences analysis
- Sites : PKU Metabolic Units
  - Ireland (Dublin) - adults
  - Spain (Santiago) - both
  - UK (Birmingham) – paediatrics

Treatment gap (cat.)	Treatment gap breakdown	Summary of current results & recommendations
<p>Detection &amp; treatment Access to primary care Access to secondary/general neurology services</p>	<p>Drop-outs Incompliance</p>	<ul style="list-style-type: none"> <li>- Newborn screening programme (NBS) has enabled early diagnosis and early intervention (major role of pediatricians) in the form of a “phenylalanine (Phe)-free” diet.</li> <li>- However, this diet is highly restrictive, unpalatable, and can substantially affect patients’ and caregivers’ time and quality of life. As patients affected by phenylketonuria reach adolescence and adulthood, between 70 to 80% of them are not fully compliant with the prescribed diets<sup>xlvii</sup>.</li> </ul>
<p>Access to tertiary/specialist services and multidisciplinary care team (MTD)</p>	<p>Coordinated care including monitoring Phe levels</p>	<ul style="list-style-type: none"> <li>- Risk factors: 1) psychosocial issues - anxiety, and depression - which in combination with challenges in their imposed dietary restriction has a significant impact on quality of life.</li> <li>2) comorbidities - despite close interaction with metabolic dieticians, it is worth noting a proportion of patients are overweight and/or obese; the potential clinical relevance of which with aging necessitates close tracking.</li> <li>- Only 12% of patients in Europe have access to a multi-disciplinary team consisting of specialist physicians, nutritionists, specialty nurses, psychologists and clinical biochemists<sup>xlviii</sup>.</li> <li>- Variability in staffing and resources with regards to the implementation of the European guidelines, genotyping of patients, monitoring Phe levels (blood tests), and access to novel therapies =&gt; Patients deemed most likely to benefit from novel therapies should have access, but this requires attention to close monitoring and determining the added value of treatment, beyond dietary management alone.</li> <li>- COSTING – the cost of health service contacts for people affected by PKU are modest compared with the costs of the protein diet and treatment with KUVAN.</li> <li>“At the Irish site, the medication has been approved; but interestingly there was no provision for enhancement of the service to implement the new service/drugs, as this is the responsibility of another health service executive branch. It is mentioned the cost of running the service relative to the novel therapies. So we can advocate for</li> </ul>

		resources to meet the added demands on the service”.
--	--	--

## Annex 1B

### Rare diseases - Remarks from Speakers and overview of statements

#### 1. EURORDIS

- The case studies on Ataxia, PKU and Dystonia reveal, if it was needed, the similarity in challenges across diseases - lack or delayed diagnosis due to limited knowledge of the diseases, limited treatment options, inequalities and difficulties in accessing established care pathways (where existing), thus resulting in reduced quality of care.

- In EURORDIS most recent surveys, it is noted that there is much more satisfaction with care in centres affiliated with European Reference Networks (ERNs) - continuing in supporting (politically as well as financially) adequately the work being done in terms of clinical guidelines development, training of healthcare professional, meaningful involvement of patients in the co-creating efficacious care pathways.

- While there has been great progress for people living with a rare disease in Europe since the adoption of the Council Recommendation on European Action in the field of Rare Diseases in 2009, the reality is that for 30 million people in Europe unmet needs remain and current policies are no longer fit for purpose. For people living with a rare disease in Europe:

- It still takes on average four years to receive a diagnosis
- Only 6% have access to a treatment for their disease
- 52% of patients and carers say their disease has a severe or very severe impact on daily life

- As per 95% of rare diseases, dedicated and centrally authorised treatment are lacking; even where they are present and indicating efficacy, often opaque and uneven decision-making processes coupled with potentially budget-threatening prices create inequalities in access to treatment.

- When those treatments are not present, research efforts should be increased with further financial investments in the area that are most in need of therapies.

- All in all, even more similar studies are needed for a great number of conditions or group of conditions, as it is often the case in rare diseases only collecting data collectively we can advocate for change.

## 2. ERN-RNDs

- Expertise centres that provide MDT based diagnosis and care/treatment coordination contribute a significant added value to the care of RND patients (all ERNs centres should be reachable to patients).
- For complex (genetic) rare diseases next generation sequencing should be made available and applied very early in the diagnostic process.
- Diagnostic expert centres for RND should have an established link to diagnostic research.
- Harmonization, coordination and collaboration across the expertise centres is needed for RND – this is what ERN-RND provides.
- For ataxias and dystonia no curative therapies are available – so disease expertise driven non-pharmacological treatments (physiotherapy, speech therapy, etc.) should be provided close to where the patient live (local, regional level).
- Highly specialized treatments such as deep brain stimulation and (eventually) genetic therapies should only be provided by qualified expertise centres.
- Access to treatment should be equal across the EU.
- RND education should address all those healthcare providers who are involved in the healthcare provision including GPs, specialist practitioners, physiotherapists, etc.
- Education, care and treatment standards should be harmonised across the EU – the best possible vehicle for this are ERNs – and then be adapted to the specifics of the national healthcare systems.

## 3. MetabERN

- PKU history is a history of success, thinking we have done the job, making clinicians “lazy”.
- Some clinicians still think treatment is not necessary during adulthood if no urgent matter arises like pregnancy, blindness, encephalopathy, not acknowledging the existence of other issues.
- There are still issues, but we seem not that well in capturing them. The diet has brought us a lot of good things but at the same time, other therapies should be found.
- What is needed from VOT initiatives is projects that:
  - Really start to try to understand the issues of PKU patients at various ages
  - Cooperate at an international level to find the balance between the necessary strictness of the treatment and its drawbacks.
  - Continue searches for doable and affordable treatments

#### 4. ICHOM

- Patient-reported outcome measures (PROMs) are a crucial element of the VOT approach and need to be standardised in an evidence-based manner. The VOT project is clearly doing excellent work in this direction and is of tremendous value, particularly in these areas, which have been somewhat neglected.
- Work done by ICHOM (international level) as well as the Common Measures Board in the UK (a Wellcome Trust and NIMH joint initiative) has helped to drive forward the standardisation of PROMs in this field.
- In fact, following these initiatives, Lancet Psychiatry have updated their Guide to Authors and now require the Methods section of all Research Articles to include a brief paragraph sub-titled "Choice of primary outcome measure". In this section, authors should place their primary measure into context for editors, reviewers, and readers, and briefly describe why they have chosen the measure, how widely used it is, how accessible, how burdensome to implement, whether it has been translated, and how to clinically interpret its change scores. The journal published an Editorial in October last year (see [here](#)), highlighting the central importance of harmonizing outcome metrics to allow for meaningful comparisons and interpretation of research findings.

#### 5. Dystonia Europe

- The results of the dystonia survey and the case study show that:
  - Dystonia symptoms are not recognized and patients are misdiagnosed, or it takes a long time to have correct diagnosis and access to treatment.
  - Work and family life is affected (productivity loss, income loss, need for social benefits)
  - The multi-disciplinary teams are missing and patients very often have to search for additional therapies themselves, such as psychologic support and physiotherapy.
  - Treatment is not always effective and many patients suffer from disability.
- In addition to VOT, there is another initiative that is supporting the one voice of rare neurological disease patients, that is the European Reference Network for Rare Neurological Diseases established in 2017 which is a very important European initiative for rare neurological disease patients and health care professionals. There are today about 60 centers that are members across Europe. It cannot be enough emphasized how crucial it is that this initiative continues and is further developed to benefit patients living with rare neurological diseases. The success of this Network depends on its sustainability and it has the potential to be the hub for knowledge, treatment, and research of rare neurological diseases in Europe. One of the activities the Reference Network is involved in is education and training.

- Unfortunately, treatment does not work for all. In the dystonia survey only 30% were satisfied with the treatment. Therefore it must be a priority with more basic research into rare neurological diseases to find the causes in order to develop new drugs and molecular therapies. Better therapies will have an impact on patients's well-being and quality of life.

## 6. Clinical Psychologist

- This research is valuable in highlighting the psycho-social – as well as medical - burden of a lifelong disease, for example in PKU the difficulties of lifelong adherence to diet, the impact (for some people) of non-adherence to diet on mood, cognitive function. Hopefully this research will help ensure psycho-social support is provided as part of the coordinated care pathway for patients.

- Coordinated care within specialist Metabolic MDT is especially important for patients with more complex combinations of bio-psycho-social issues. In my experience some systems can help to support this, e.g. using case discussion to make sure staff from different disciplines have a shared understanding of patient's issues, so all staff respond to the patient in a way that considers their psychological needs.

- Coordinating inter-agency working can be a difficult issue for rare disease teams (e.g. if refer a patient to local mental health services, or if a patient with PKU and LD requires a support worker support to help them manage their diet, or DBS). Rareness of disease can mean clinicians in other agencies feel de-skilled, or patients' needs don't fit well with usual service provision.

- It is helpful to have clear, evidence-based guidance about what leads to better outcomes re wellbeing, and economically, to offer to other services. This helps both services to be clear what is required.

- However, for guidance to be useful in clinical practice, it needs to strike a balance between being concrete and clear, and being flexible. So, it is known from the research that there is a lot of variability about what is available between countries, areas, and teams. Guidance that is too specific and prescriptive may be fit poorly with this variability and be less helpful. For example, from a clinician's point of view it is more helpful to be told what outcome to aim for (e.g. measure working memory) than what tool to use, because people with PKU have a wide range of skills and needs, and different services have different tools and budgets available to them.

## 7. ESPKU/DIG PKU

- Late- and undiagnosed PKU: Once again forgotten? PKU is not a paediatric phenomenon, it requires lifelong care. Late- and undiagnosed patients tend to be forgotten in the shadow of the repeatedly told success stories of PKU treatment. We should make the invisibles visible. We must grant them access to care for their underlying condition untreated PKU, rather than only looking at their disabilities.

- Adult PKU care - Patients don't think symptoms like obesity are PKU-associated comorbidities. They are man-made consequences of inadequate adult care and enduring systemic failure. Within the next 10/15 years, the first early diagnosed adult PKU patients will become seniors older than 65. Based on the experiences with transition from paediatric into adult care, we are deeply concerned about the upcoming transition from adult to geriatric care. Service provision resources for adult patients do not match with the growing needs. Here are some facts from Germany:

- There are 31 metabolic units located at children hospitals or paediatric departments, and just 7 units at adult clinics. Several hundred adults are highly depending on paediatricians who are committed far beyond duty.

- For just 3 years (since 2018), nutritional counselling for adult metabolic patients is covered by mandatory health insurance. However, only a few dietitians have yet become registered service providers.

- It is just one year ago (2020) that a Chapter on nutritional medicine has been added to the German regulation on medical education and training.

- German legislation provides specialist care explicitly for children with congenital metabolic disorders, and our call for inter-generational justice is still being ignored.

- Importance of nutrition in the healthcare systems - Healthcare systems still underestimate the importance of nutrition. The PKU diet is a medically indicated and proven therapy and it is cost-effective. Because the German health insurance initially doesn't feel responsible for nutrition and food, there are more issues with reimbursement of amino acid supplements, than with the cost of a pharmaceutical enzyme replacement therapy, which is at least 10 times more expensive. Nevertheless, patients also need access to pharmaceutical options such as BH4 and PEG-PAL, as the nutritional therapy is not only associated with economic but also with socio-psychological burdens.

## Annex 2A

### Mental disorders – Overview case studies

#### ANOREXIA NERVOSA CASE STUDY ACCORDING TO POSTERS AND PRESENTATION

Estimates are that yearly over 3.3 million healthy life years worldwide are lost because of eating disorders. In contrast to other mental disorders, in anorexia nervosa and bulimia nervosa years lived with disability (YLDs) have increased. EDs are frequent in adolescents and even more in young adults and are sometimes severe. They may lead to multiple psychiatric and somatic complications and are likely to have an impact in terms of quality of life and even mortality. Indeed, individuals with ED share significantly elevated mortality rates, in particular with anorexia nervosa (AN)<sup>xlix</sup>.

Despite treatment advances, mortality rates of anorexia nervosa and bulimia nervosa remain very high: those who have received inpatient treatment for anorexia nervosa still have a more than five times increased mortality risk. Mortality risks for bulimia nervosa, and for anorexia nervosa treated outside the hospital, are lower but still about twice those of controls. In people with an eating disorder, quality of life is reduced, yearly healthcare costs are 48% higher than in the general population, the number of offspring is reduced, and risks for adverse pregnancy and neonatal outcomes are increased<sup>l</sup>.

#### STUDY OBJECTIVES

A care pathways analysis will identify current treatment gaps and patient needs along the care trajectory sequences, 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”).

One overarching model of the entire care pathway is developed, 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 detection 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

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with anorexia: evidence review (data synthesized) and mapping survey on a sample of ED experts in 12 countries
- Cost effectiveness analysis and cost saving analysis
- Countries selected based on data availability: Germany, Spain, UK

Treatment gap (cat.)	Treatment gap breakdown	Summary of current results & recommendations
Detection & treatment Access to primary care Access to secondary/general services	Delays to the detection and treatment of AN Waiting time Duration of untreated illness	<ul style="list-style-type: none"> <li>- Other potential contributors to delayed or inadequate treatment are GPs lacking confidence and skills in treating AN</li> <li>- The duration of untreated illness is high as a result, at 14.6 months.</li> <li>- To improve GP training</li> </ul>
Access to tertiary/specialist services and multidisciplinary care team (MTD)	Continuity/transition of care Dropouts Unplanned hospital admission	<ul style="list-style-type: none"> <li>- a lack of availability of inpatient beds or specialist services, and regional differences in the availability of specialist care</li> <li>- High quality ED services should entail “well-coordinated care delivered by a knowledgeable and specialist treatment team centered around the patient and their social support”. Research informed by patient priorities is more likely to focus on early intervention and recovery, and supporting carers can enhance and improve treatment for AN</li> <li>- Proposed recommendations to optimize care pathways for adults (Treasure, Oyeleye, et al., 2021):               <ul style="list-style-type: none"> <li>• Improving detection in primary care to improve access to treatment;</li> <li>• Reduction in waiting times to enter specialist treatment and avoiding delay;</li> <li>• Increasing the effectiveness of routine treatment through a) a triage system and b) augmentation;</li> <li>• Bridging the transition from inpatient treatment and increasing support in the community;</li> <li>• Rehabilitation and new treatments for those not responding to available treatments.</li> </ul> </li> </ul> <p>In addition, families would prioritize for all (children, youth and adults): an increase in specialist ED services, an increase of inpatient beds and improvements in GP training</p> <p>- Costing:            Three broad categories of interventions were modelled over a 2-year period (Markov cycle: weeks), using the NICE care pathway as a basis for improvements, and compared to a base case scenario (1):</p>

		<p>(2) <b>Reducing the duration of untreated illness:</b> Average time to treatment reduces from 21 months (Austin et al., 2021) to 8 months (Andrés-Pepiñá et al., 2020), leading to an increase of the proportion in remission and therefore reduction in the number of second courses of treatment.</p> <p>(3) <b>Expanding the availability of specialist treatment:</b> Assuming everyone is offered specialist treatment following referral (House et al., 2012), leading to a reduction in the proportion hospitalised.</p> <p>(4) <b>Improving specialist treatment by offering transition support for patients and carers:</b> Assuming the effectiveness of specialist treatment (SSCM and MANTRA) in terms of re-admissions is increased by 50% compared to current data.</p> <p>Finally, a scenario combining all three improvements was modelled (5).</p> <p>=&gt; In this model, implementing all three improvements to the care pathway result in a cost reduction of almost 40%. Additional savings from reduced wider service use and service use of caregivers, as well as improvements in quality of life are likely to match or exceed this figure. This is predicated on the assumption that early and effective treatment can change the trajectory of the illness and avoid it becoming protracted. <b>More information on transitions between treatments and individual patterns of treatment over the life course is needed to create a more accurate model. An optimized care pathway needs to be implemented, supported by effective interventions, to reap these potential benefits.</b></p>
--	--	--

**AUTISM SPECTRUM DISORDER ACCORDING TO POSTERS AND PRESENTATION**

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. There are huge economic costs. Autism is associated with a wide range of co-occurring developmental, mental, and physical health conditions, including intellectual disability (ID), epilepsy, attention-deficit hyperactivity disorder (ADHD), anxiety, depression, behavioral disturbances and tics, abnormal sleep patterns, motor difficulties, eating and elimination disorders, diabetes, hypertension, obesity, and cardiovascular disease. Each individual with autism has a unique life experience with different onset, combinations, severities, and persistence of ASD symptoms and co-occurring

conditions. Accordingly, there is no one-size-fits-all healthcare approach, and healthcare must be agile, responsive, and, above all, accessible.

The study will look at the analysis of treating epilepsy as comorbidity in autistic children, looking at impacts on healthcare providers and children’s families. 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**

- Patient care pathway and treatment gaps/unmet needs analysis of individuals with autism spectrum disorder: evidence review (data synthesized) and survey
- Cost consequences analysis and cost effectiveness analysis of 2 major treatment gaps
- These analyses will be conducted in four countries:
  - Ireland
  - Italy: analysis underway
  - England
  - Spain: analysis underway

Treatment gap (cat.)	Treatment gap breakdown	Summary of current results & recommendations
Detection & treatment Access to primary care Access to secondary/general services	Delays in screening and diagnosis, delays in intervention/treatment of ASD and comorbid-epilepsy	- Inappropriate screening/detection and treatment for autistic children, even more for autistic children with epilepsy.
Access to tertiary/specialist services and multidisciplinary care team (MTD)	Continuity/transition of care Specialist visits	<p>- Referring to the sequential intervention model for the optimized care pathway</p> <p>- Costing: economic model</p> <p>=&gt; Impacts on HCPs (UK, Ireland): comparison children receiving monotherapy (15 years)   children receiving adjunctive therapy (15 years)</p> <p>Effectiveness: response to (proportion who are seizure-free) and no response or withdraw (due to adverse events) from monotherapy or adjunctive therapy; Quality Adjusted Life Years (QALYs).</p> <p>Comparison of alternatives: cost-consequence approach in alignment with other VOT case studies; plus incremental cost-effectiveness ratios (ICER per QALY) as in NICE guideline.</p> <p>Time horizon and sample: 15 years for a hypothetical cohort of 6-year-old children with newly diagnosed focal seizures.</p>

		<p>=&gt; Impacts on families (Ireland): <b>comparing</b> samples (families with a 6-year-old autistic child on epilepsy medication vs autistic children without epilepsy)</p> <p>Including family costs for autistic children on epilepsy medication is important when considering the cost-effectiveness of anti-epileptic medication and the impact that extra caring demands place on a family's time and resources.</p>
--	--	---

### MAJOR DEPRESSIVE DISORDER ACCORDING TO POSTERS AND PRESENTATION

According to the World Health Organization, depression is the leading cause of disability (WHO, 2017) in part due to its high prevalence (which exceeds 300 million) and often enduring nature, with significant negative impacts on activities of daily living, quality of life, cognitive function, and employment status and work productivity<sup>ii</sup>. The aetiology of depression is multifactorial and recent research suggests it is caused by a combination of genetic, biological, environmental and psychological factors. More than 50% of people who experience a first episode of depression will experience a second episode, and after the second and third episode of depression risk of relapse rises to 70% and 90% respectively. The high rates of recurrence, chronicity and treatment-resistance indicate that MDD is treated suboptimally despite a multitude of effective interventions and well-regarded best-practice treatment guidelines. Many individuals are not receiving treatment at any one time and it is known that both duration of untreated illness and the number of ineffective treatments trialled are risk factors for poorer long-term outcomes. Together, these phenomena demonstrate a need for improved management of MDD. The most common treatments used to manage depression are antidepressants, electroconvulsive therapy (ECT) and psychosocial interventions.

#### 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”).

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 the NICE guidelines.

#### METHOD

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

Treatment gap (cat)	Treatment gap breakdown	summary of current (pre-covid)	summary of current results & recommendations
detection & treatment access to primary care	Rates of depression not detected	approximately 50% of depression not detected	increase availability of primary care appointments
	Delays to the detection of depression	average time to detection (or treatment) likely between 1-5 years depending on definition used and country	integrate e-tools to increase access as above to integrate self-depression screening with GP records access
	Rates of (community) treatment with pharmacological and non-pharmacological therapies	(any) treatment rates likely between 25-50% depending on definition / country. Much lower for psychological than pharmacological treatment.	integrate prescribing-support tools with existing electronic health records to increase detection increase availability of psychological therapies
	(Delays to treatment after detection of depression)	(merged with 2.; delays to treatment)	encourage patient preference shared care arrangements i.e. nursing staff to co-manage with GPs better info. provided to patients about treatment
continuity of care	Rates / frequency of follow-up contacts after treatment in primary care	between one third and two thirds of patients followed up within three months of starting treatment (fairly limited data)	screen for risk factors indicating need for more intensive follow-up increase availability of appointments to remove barriers to COC integrate e-mental health tools for patients to record symptoms and side effects to inform follow-up care automatic appointment scheduling to help ensure follow up
access to secondary / psychiatric services	Rates of referral to secondary services	likely average accessing secondary care between 5-25%	early screening for patients at risk of needing specialist treatment earlier in care pathways
	(Duration / number of contacts within secondary services)	limited or no data	integration of psychiatrists in primary care training for GP specialism in mental health
access to tertiary / specialist services	Rates of referral to tertiary services	limited or no data	resource to create more specialist mood disorders centres enhance training programmes for training psychiatrists
<p>Cost-effectiveness analysis (CEA) is performed based on proposed scenario if reduced detection and treatment gaps: the CEA reveals significant increase in ICER but with increased QALYs. It can be seen that each of these scenarios would be cost-effective with proposed models of care.</p>			

## Annex 2B

### Mental disorders - Remarks from Speakers and overview of statements

#### 1. EUFAMI

- The role of family members and carers is important to the progress of recovery in all health situations. The progress of recovery is dependent on family dynamics. Families can do more than provide care and are central to the continuity of care. They are deliverers of expertise in the absence of professionals. For example, in autism, provision of appropriate environment and communication or in depression, providing good social and personal environment. In addition, families are central to the continuity of care<sup>lii</sup>.

#### 2. Autisme Europe

Around 1% population on the autism spectrum. Targeted actions are needed to address their specific needs. Key to involve autistic people and their families to set the policy and research agenda. Access to early detection/intervention and to adequate medication is a matter of rights (UNCRPD)

- Early detection/intervention

Common challenges identified across Europe in relation to early detection/intervention for autistic children and families: waiting times, lack of training and resources, etc. Key recommendations: EU guidelines, promotion of early detection programs, training of professionals, awareness-raising, mutual recognition of diagnosis across Europe to ensure freedom of movement

- Epilepsy

Just 1% of the general public has epilepsy vs 20–40% in autistic people. Leading cause of death in people with autism and a learning disability - they are at particularly high risk and their epilepsy can be difficult to manage. People with autism spectrum may have a different pattern of seizures in the brain. It may be harder to treat their epilepsy with drugs that work in the general population. Other points to highlight:

- Lack of knowledge regarding drugs that are effective for autistic people with epilepsy. Some may be harmful.

- Research studies involving autistic people with and without epilepsy are needed to increase our understanding of how to manage symptoms and prevent early deaths.

#### 3. GAMIAN Europe

Patients with severe depression need long term bio-psycho-social support on a long-term basis. Only a low number of patients with severe depression receive comprehensive care. Community mental health care should be delivered for patients with severe depression in order to support their recovery oriented care.

#### 4. GP Depression

- Depression is common in primary care but under-detected. In particular, the detection and treatment of depression seems particularly low in deprived and ethnic minority communities.

- Depression is an important component of multimorbidity; it may be both cause or consequence. It is associated with a large increase in healthcare utilisation rates.

#### 5. Lisbon Institute of Global Mental Health, CHRC/Nova Medical School

- Combining a care pathway analysis together with an economic evaluation of current care in comparison with “gold standard” intervention is a good strategy. There are key barriers to care that the reforms should focus on for better outcomes.
- Reducing treatment gaps + other gaps (continuity, quality, prevention) is essential
- Involved in the MDD case study: there are significant gaps and unmet needs in MDD
- Reorganisation of MH services at country level: the main denominator across disorders is how to improve the care pathway
- Collaborative care between primary care and specialist care is recommended. It is unexistent in a majority of countries.
- For the modelling and economic analysis, there are encouraging results. If we can reduce some gaps, this is good value.
- Calling for evidence-based policy based on results for MOH
- Covid 19 represents a window of opportunity : new data to proof/demonstrate that MH is crucial.

#### 6. European Commission, Directorate General for Health (DG SANTE)

- Mental health is being addressed as a matter of priority in our support to Member States’ health policies. Through the Steering Group on Promotion and Prevention, Member States’ health ministries prioritised mental health for the purpose of best practice implementation, and identified those specific practices that were of most relevance to them.

- Co-funded via the third Health Programme’s 2020 Annual Work Plan, we will now support implementation of their ‘top three’ actions:
  - a mental health system reform focusing on strengthening client-centred community-based services;
  - a multi-level national suicide prevention programme;
  - and a step-wise intervention programme to tackle depression.
- The COVID-19 pandemic has put the issues of mental and neurological health firmly in the spotlight. As many as one third of COVID-19 patients are diagnosed with neurological and psychiatric complications within six months of being infected with COVID-19.
- Meanwhile, people with pre-existing mental health or neurological disorders are more vulnerable to the virus itself and to its mental health impact.
- To explore the considerable and complex impact of the COVID19 pandemic on mental health, our Commissioner hosted an online high-level Conference last month.
- To take stock of what we know and need to understand better, share promising approaches, look at the impact of the lives of our citizens and on care providers, give a voice to those most affected, and discuss ways to ensure that our health systems are well-equipped to meet the increasing demand for mental health services.
- Even as we are making good strides to contain the virus itself, the mental health significances of our fight will resonate within our societies for times to come.
- This pandemic has also led us to re-evaluate our existing framework for action in the area of health at the EU level. We need to be honest that no-one was prepared for this unprecedented global health crisis. We managed to be flexible, find solutions, and work in solidarity, with countless examples of this throughout the last year. These include joint procurements for medicines, cross border care, sharing of best practice and expertise, and authorisation of medicines and vaccines.
- But we now need to put long term structural solutions in place. Our proposals for a European Health Union are precisely this. They are a package of measures that will give us a more comprehensive toolbox for preparedness, surveillance, risk assessment and early warning and response.

- Integrated care. This has an ambition to cover as broadly as possible the whole process from health promotion and disease prevention to treatment and rehabilitation, for both physical and mental health. Somatic and psychiatric conditions need comprehensive approach and cannot be treated separately.
- There are neurodegenerative diseases that we are not able to prevent or treat fully. However, we can slow down their progress. One way is when people are involved in their communities, when they interact with those around them and are active in their own care processes. Integrated care provides this opportunity by allowing people to be active in the community while also receiving the necessary care.
- The European Commission has supported integrated care initiatives for years. The European Innovative Partnership on Active and Health Ageing brought together many actions on integrated care. Its work has been taken further by the Joint Action on implementation of digitally enabled integrated person-centred care, which aims to promote and scale up best practices in integrated care all over Europe.
- All these initiatives have ageing, mental health or community care as key components. They stem from the recognition of equal importance of somatic and mental conditions, and a strong believe they should be treated together.

#### 7. Final remark by EBC

To reduce the burden of Rare Disorders and of Mental Conditions alike, we are facing similar challenges:

- lack or delayed diagnoses
- difficulties for patients to access the right pathways to care (including the access to expert centers when existing)
- fragmentation of services offering the different treatment options
- lack of collaboration between these services
- disruption in the continuity of care along the course of the diseases (and along the life span as well).

To adequately address these different challenges, solutions do exist:

- medical education and tools to help for the diagnosis
- dissemination of information regarding the most efficient treatment

- implementation of the current optimal pathways to care (health care systems have to be trained into this direction and to adapt themselves accordingly)
- mandatory exchanges and collaboration between services
- adequate follow-up of patients, having in mind the danger of any discontinuity of care

And the last take-home message is that doing so, not only the quality of outcomes and the degree of satisfaction will increase, but the societal and economic impact of these conditions will be quite significantly reduced.

## References

- <sup>i</sup> The value of treatment policy white paper: towards optimizing research and care for brain disorders. Brussels: European Brain Council; 2017. Available at: [http://www.braincouncil.eu/wp-content/uploads/2017/06/EBC\\_white\\_policy\\_paper\\_DEF26072017\\_Low.pdf](http://www.braincouncil.eu/wp-content/uploads/2017/06/EBC_white_policy_paper_DEF26072017_Low.pdf)
- <sup>ii</sup> Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. *Orphanet J Rare Dis*. 2017;12:63. doi: 10.1186/s13023-017-0618-0.
- <sup>iii</sup> S. Puntis, J. Rugkåsa, A. Forrest, A. Mitchell, and T. Burns, Associations between continuity of care and patient outcomes in mental health care: a systematic review. *Psychiatr Serv*, 66 (2015), 354-363.
- <sup>iv</sup> Kristensen, Mette & Sølvhøj, Ida & Kusier, Amalie & Folker, Anna. (2019). Addressing organizational barriers to continuity of care in the Danish mental health system – a comparative analysis of 14 national intervention projects. *Nordic Journal of Psychiatry*. 73. 1-8. 10.1080/08039488.2018.1551929.
- <sup>v</sup> Rotter T, de Jong RB, Lacko SE, et al. Clinical pathways as a quality strategy. In: Busse R, Klazinga N, Panteli D, et al., editors. *Improving healthcare quality in Europe: Characteristics, effectiveness and implementation of different strategies* [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2019. (Health Policy Series, No. 53.) 12. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK549262/> Accessed: May 1, 2021
- <sup>vi</sup> Rotter T; Kinsman L; James E; Machotta A; Gothe H; Willis J; Snow P; Kugler J (March 2010). "Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs". *The Cochrane Database of Systematic Reviews*
- <sup>vii</sup> Auvin S, Bissler JJ, Cottin V, Fujimoto A, Hofbauer GFL, Jansen AC, Jóźwiak S, Kerecuk L, Kingswood JC, Moavero R, Torra R, Villanueva V. A step-wise approach for establishing a multidisciplinary team for the management of tuberous sclerosis complex: a Delphi consensus report. *Orphanet Journal of Rare Diseases*. 2019; 14/91.
- <sup>viii</sup> Simpson, A., Bloom, L., Fulop, N.J. et al. How are patients with rare diseases and their carers in the UK impacted by the way care is coordinated? An exploratory qualitative interview study. *Orphanet J Rare Dis* 16, 76 (2021). Available from: <https://doi.org/10.1186/s13023-020-01664-6>. Accessed : May 1, 2021.
- <sup>ix</sup> Walton, H, Hudson, E, Simpson, A, Ramsay, ALG, Kai, J, Morris, S, Sutcliffe, AG and Fulop, NJ, 2020. Defining Coordinated Care for People with Rare Conditions: A Scoping Review. *International Journal of Integrated Care*, 20(2), p.14. DOI: <http://doi.org/10.5334/ijic.5464>.
- <sup>x</sup> Continuity and coordination of care: a practice brief to support implementation of the WHO Framework on integrated people-centred health services. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
- <sup>xi</sup> The Lancet Neurology Editorial 2017. Rare advances for rare diseases. Available from: [https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422\(16\)30352-0.pdf](https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422(16)30352-0.pdf). Accessed: May 1, 2021.
- <sup>xii</sup> European Reference Networks – ERN on neurological diseases (ERN-RND); 2017. Available from: <http://www.ern-rnd.eu/>. Accessed: May 1, 2021.
- <sup>xiii</sup> Di Luca M. et al. Towards earlier diagnosis and treatment of disorders of the brain. *Bulletin of the World Health Organization* 2018;96:298-298A. Available from: doi: <http://dx.doi.org/10.2471/BLT.17.206599>. Accessed May 1, 2021.
- <sup>xiv</sup> EURORDIS recommendations to achieve a mature ERN system in 2030 (December 2020). Available from : [http://download2.eurordis.org/documents/pdf/EURORDIS\\_vision\\_on\\_mature\\_ERNs\\_FINAL.pdf](http://download2.eurordis.org/documents/pdf/EURORDIS_vision_on_mature_ERNs_FINAL.pdf). Accessed: May 1, 2021.
- <sup>xv</sup> Centres of Expertise for Rare Diseases, EU Council Recommendation on action in the field of rare diseases (2009), EUCERD recommendations on centres of expertise at nat. level (2013). Available from: [https://www.eurordis.org/sites/default/files/publications/factsheet\\_Centres\\_Expertise.pdf](https://www.eurordis.org/sites/default/files/publications/factsheet_Centres_Expertise.pdf)
- <sup>xvi</sup> Council recommendation on an action in the field of rare diseases (2009/C 151/02) June 2009. Available from <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF>. Accessed : May 1, 2021.
- <sup>xvii</sup> Rodwell C, Aymé S. Rare disease policies to improve care for patients in Europe. *Biochim Biophys Acta*. 2015 Oct;1852(10 Pt B):2329-35. doi: 10.1016/j.bbadis.2015.02.008. Epub 2015 Feb 25. PMID: 25725454.
- <sup>xviii</sup> de Silva, R., Greenfield, J., Cook, A. et al. Guidelines on the diagnosis and management of the progressive ataxias. *Orphanet J Rare Dis* 14, 51 (2019). Available from : <https://ojrd.biomedcentral.com/articles/10.1186/s13023-019-1013-9>. Accessed : May 1, 2021.
- <sup>xix</sup> Diagnostic Flowchart for Adult Ataxias. Available from: [http://www.ern-rnd.eu/wp-content/uploads/2019/08/ERN-RND-Diagnostic-FlowchartAtaxia\\_FINAL.pdf](http://www.ern-rnd.eu/wp-content/uploads/2019/08/ERN-RND-Diagnostic-FlowchartAtaxia_FINAL.pdf). Accessed: May 1, 2021.

- 
- <sup>xx</sup> Albanese, A, et al. "EFNS Guidelines on Diagnosis and Treatment of Primary Dystonias." *European Journal of Neurology*, vol. 18, no. 1, 2011, pp. 5–18. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1468-1331.2010.03042.x>. Accessed: May 1, 2021.
- <sup>xxi</sup> Tamás, Gertrúd, et al. "Quality and Reporting of Guidelines on the Diagnosis and Management of Dystonia." *European Journal of Neurology*, vol. 25, no. 2, 2018, pp. 275–283. Available from: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/ene.13488>. Accessed: May 1, 2021
- <sup>xxii</sup> Wegberg AMJ, MacDonald A, Ahring K, et al. The complete European guidelines on phenylketonuria: diagnosis and treatment. *Orphanet J Rare Dis*. 2017;12(1):162. October 2017. Available from: <https://orjrd.biomedcentral.com/articles/10.1186/s13023-017-0685-2>. Accessed: May 1, 2021.
- <sup>xxiii</sup> European Expert Group on Orphan Drug Incentives (OD Expert Group), see information: <https://od-expertgroup.eu/>. Accessed: May 1, 2021.
- <sup>xxiv</sup> Kaufman EA, McDonnell MG, Cristofalo MA, et al: Exploring barriers to primary care for patients with severe mental illness: frontline patient and provider accounts. *Issues in Mental Health Nursing* 33:172–180, 2012 6.
- <sup>xxv</sup> Sweeney A, Davies J, McLaren S, et al. Defining continuity of care from the perspectives of mental health service users and professionals: an exploratory, comparative study. *Health Expect*. 2016;19(4):973–987. doi:10.1111/hex.12435
- <sup>xxvi</sup> Dieterich M, Irving CB, Bergman H, Khokhar MA, Park B, Marshall M. (2017). Intensive case management for severe mental illness. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD007906. doi: 10.1002/14651858.CD007906.pub3.
- <sup>xxvii</sup> Biringer et al. Continuity of care as experienced by mental health service users - a qualitative study. *BMC Health Services Research* (2017) 17:763 DOI 10.1186/s12913-017-2719-9
- <sup>xxviii</sup> J. Green, *Journal of Child Psychology and Psychiatry*. [Editorial Perspective: Delivering autism intervention through development \(wiley.com\)](https://onlinelibrary.wiley.com/doi/10.1111/jcpp.12435)
- <sup>xxix</sup> Epilepsies: diagnosis and management, NICE Clinical Guideline (2012). Available from: <https://www.nice.org.uk/guidance/cg137/>
- <sup>xxx</sup> Stepped-care model for treating depression, NICE Clinical Guideline (2009). Available from :<https://www.guidelinesinpractice.co.uk/mental-health/nice-has-modified-its-stepped-care-model-for-treating-depression/309471.article>
- <sup>xxxi</sup> EU Pecunia Project. Available at: <https://www.pecunia-project.eu/>
- <sup>xxxii</sup> Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T (2015) The Global Burden of Mental, Neurological and Substance Use Disorders: An Analysis from the Global Burden of Disease Study 2010. *PLOS ONE* 10(2): e0116820. <https://doi.org/10.1371/journal.pone.0116820>  
<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116820>
- <sup>xxxiii</sup> OECD Health At A Glance 2018  
[https://ec.europa.eu/health/sites/default/files/state/docs/2018\\_healthatglance\\_rep\\_en.pdf](https://ec.europa.eu/health/sites/default/files/state/docs/2018_healthatglance_rep_en.pdf)
- <sup>xxxiv</sup> EUROPEAN COMMISSION EU COMPASS FOR ACTION ON MENTAL HEALTH AND WELL-BEING Access to Mental health in Europe Consensus Paper 2016. Available from: [https://ec.europa.eu/health/sites/default/files/mental\\_health/docs/ev\\_20161006\\_co04\\_en.pdf](https://ec.europa.eu/health/sites/default/files/mental_health/docs/ev_20161006_co04_en.pdf)  
Accessed: May 1, 2021.
- <sup>xxxv</sup> Malik-Soni, N., Shaker, A., Luck, H. et al. Tackling healthcare access barriers for individuals with autism from diagnosis to adulthood. *Pediatr Res* (2021). Available from: <https://doi.org/10.1038/s41390-021-01465-y>. Accessed: May 1, 2021.
- <sup>xxxvi</sup> G. Thornicroft, M. Tansella. The balanced care model: the case for both hospital- and community-based mental healthcare. *The British Journal of Psychiatry* 2013, 246–248. doi: 10.1192/bjp.bp.112.111377
- <sup>xxxvii</sup> Macdonald, A., Adamis, D., Craig, T., & Murray, R. (2019). Continuity of care and clinical outcomes in the community for people with severe mental illness. *The British Journal of Psychiatry*, 214(5), 273-278. doi:10.1192/bjp.2018.261.
- <sup>xxxviii</sup> Weaver, Nicholas & Coffey, Michael & Hewitt, J. (2017). Concepts, models and measurement of continuity of care in mental health services: A systematic appraisal of the literature. *Journal of Psychiatric and Mental Health Nursing*.
- <sup>xxxix</sup> Continuity and coordination of care: a practice brief to support implementation of the WHO Framework on integrated people-centred health services. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
- <sup>xl</sup> Caldas-de-Almeida JM. Four reflections on the new global mental health priorities. *Epidemiology and Psychiatric Sciences* 2019 1–4. Available at: <https://doi.org/10.1017/S2045796019000726>
- <sup>xli</sup> WHO Pyramid Framework. Available from: [https://www.who.int/mental\\_health/policy/services/2\\_Optimal%20Mix%20of%20Services\\_Infosheet.pdf](https://www.who.int/mental_health/policy/services/2_Optimal%20Mix%20of%20Services_Infosheet.pdf)

- 
- <sup>xliii</sup> Katon W, Von Korff M, Lin E, et al: Rethinking practitioner roles in chronic illness: the specialist, primary care physician, and the practice nurse. *General Hospital Psychiatry* 23:138–144, 2001.
- <sup>xliiii</sup> Unützer J, Schoenbaum M, Druss B, Katon Wayne (2006). Transforming Mental Health Care at the Interface With General Medicine: Report for the Presidents Commission. *Psychiatric services* (Washington, D.C.). 57. 37-47. 10.1176/appi.ps.57.1.37.
- <sup>xliv</sup> Patel and al., *Lancet* Report October 9, 2018. Available from: [http://dx.doi.org/10.1016/S0140-6736\(18\)31612-X](http://dx.doi.org/10.1016/S0140-6736(18)31612-X).
- <sup>xlv</sup> Evidence-scoping review – service transitions for mental health and addiction. Report for the Health Quality & Safety Commission 2018
- <sup>xlvi</sup> Valadas, A, et al. “Management of Dystonia in Europe: a Survey of the European Network for the Study of the Dystonia Syndromes.” *European Journal of Neurology*, vol. 23, no. 4, 2016, pp. 772–779.
- <sup>xlvii</sup> van Spronsen FJ, van Wegberg AM, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. *Lancet Diabetes Endocrinol.* 2017;5:743–56. doi: 10.1016/S2213-8587(16)30320-5.
- <sup>xlviii</sup> Blau et Al. Management of phenylketonuria in Europe: Survey results from 19 countries. *Molecular Genetics and Metabolism* 99 (2010) 109–115.
- <sup>xlix</sup> Galmiche, Marie & Déchelotte, Pierre & Lambert, Gregory & Tavalacci, Marie-Pierre. (2019). Prevalence of eating disorders over the 2000-2018 period: a systematic literature review. *The American journal of clinical nutrition.* 109. 1402-1413. 10.1093/ajcn/nqy342.
- <sup>l</sup> van Hoeken D, Hoek HW. Review of the burden of eating disorders: mortality, disability, costs, quality of life, and family burden. *Curr Opin Psychiatry.* 2020;33(6):521-527. doi:10.1097/YCO.0000000000000641
- <sup>li</sup> Malhi GS and Mann JJ. Depression. *Lancet.* 2018; 392(10161):2299-312.
- <sup>lii</sup> EUFAMI. The Cost of Caring Research Study, February 2021. Available from: <http://eufami.org/resources/the-value-of-caring-resources-are-now-available/>.