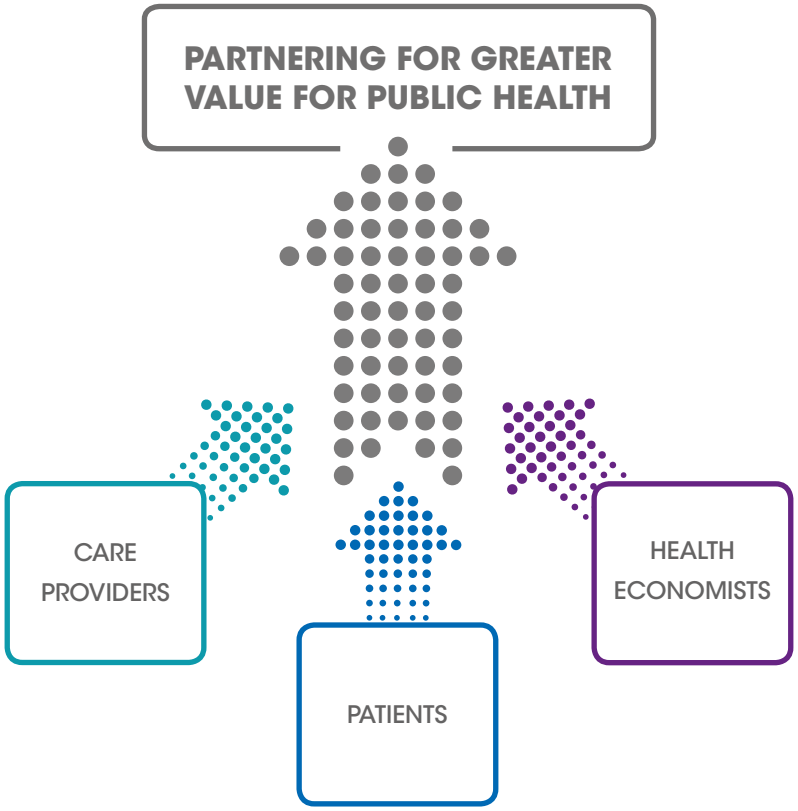
VOT

2nd ROUND 2018-2021
BRIDGING THE GAPS & ACHIEVING SEAMLESS, COORDINATED CARE

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

The Value of Early Coordinated Care for Patients Affected by Rare Neurological Diseases Study

A proposition for consolidating the current research project economic analysis and future perspectives



Document for discussion - May 2020

The European Brain Council (EBC) is a network of key players in the "Brain Area", with a membership encompassing scientific societies patient organisations, professional societies and industry partners.

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VOT Patient-Centered Approach:
A Health Economics and Outcomes Research

Health Economics

Analyses the economic aspects of health and healthcare, with a focus on the costs (inputs) and consequences (outcomes) of healthcare interventions including healthcare services.

Outcomes Resarch

Evaluates the impact of healthcare interventions on patient-related clinical, humanistic, and economic outcomes.

For an improved quality of life for Europeans living with brain conditions

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SUMMARY – OBJECTIVE OF THIS NOTE

Brain disorders, including rare neurological disorders, are among the world's leading causes of poor health and disability[1]. Europe, particularly, has a high burden and frequency of brain disorders [2 3]. The European Brain Council study on *"The Value of Treatment for Brain Disorders in Europe: Bridging the Early Diagnosis and Treatment Gap"* [4] built on a previous EBC Report "The Economic Costs of Brain Disorders in Europe" published in 2005 [5] and updated in 2010 [6 7]. Direct healthcare and non-medical costs of brain disorders make up for 60% of the total costs (40% attributable to lost productivity) – which EBC estimated at 800 bln€/year in Europe[8]. All types of costs increase with the severity and the chronification of the disease. Despite the escalating costs of brain disorders, numerous needs of patients are unmet. Many people living with a brain disorder remain non-treated or inadequately treated although effective treatments exist[4]. The Value of Treatment study, released in June 2017, covered a range of disorders of the brain, from mental disorders (schizophrenia) to neurological disorders (Alzheimer's disease, Epilepsy, Headaches, Multiple Sclerosis, Normal Pressure Hydrocephalus, Parkinson's disease, Restless Legs Syndrome and Stroke). The conclusions highlight the need for more research, early, if possible prodromal, diagnosis and intervention, integrated seamless care underpinning timely care pathways as a solution to address value-based health care in Europe and access to the best treatments available.

In the continuity of these conclusions and in the framework of the VOT research, new projects on new therapeutic areas were launched in 2018 focusing on rare neurological diseases (RNDs). Many of those affected by a rare or complex condition do not have access to diagnosis and high-quality treatment. Expertise and specialist knowledge may be scarce because patient numbers are low. Starting from case studies' data analysis, including Ataxias, Dystonia and Phenylketonuria, the VOT project objectives are to identify treatment gaps (or barriers to care) and causing factors along the care pathway and propose solutions to address them, assess health gains and socio-economic impacts resulting from best practice healthcare interventions, in comparison with current care or no treatment, and converge evidence to policy. Case studies are conducted in collaboration with experts from the EBC network and with the support of academic partners (see annex), applying empirical evidence from different European countries. An EBC final paper and scientific publications are to be released in mid-2021. We aim to analyse patient views and assess the cost-effectiveness/consequences of specialist centres for managing care of people with Ataxias or Dystonia in several European countries. We plan to analyse the cost-effectiveness/consequences of metabolic care units for people with Phenylketonuria to reduce drop-outs, encourage sufferers to strictly follow the phenylalanine-free diet, and improve overall health outcomes. The aim is also to examine the role of national policies and programmes, including National Rare Diseases Plans, on the effective implementation of coordinated comprehensive services targeting Ataxia, Dystonia, and Phenylketonuria.

A mid-term review meeting with experts is taking place on 18 May 2020, firstly to provide a research project update since the last 27th November 2019 researchers meeting, and to discuss research methodology (care pathways, outcome variables measurement including economic analysis), preliminary findings and next steps; and secondly to provide the opportunity to examine the health economics perspective while looking at early intervention and coordinated care, and to reiterate the need to continue building synergies with current EU initiatives such as the European Reference Networks (ERNs) on Rare Diseases and Orphanet (registries and biobanks). This time, particularly in the discussions and fully in alignment with phase 2 of the research (see annex), there will be a major focus on the economic evaluation framework and case studies analysis from both a societal and healthcare perspective (quantitative approach). Privileging cost-effectiveness/consequences analysis, the economic evaluation will include multiple variables, using modelling and valuation methods while examining healthcare interventions. In addition, relevant elements will be taken into consideration with new coordinated care models as well as transmural data sharing and care emphasizing crossborder collaboration. On the one hand, it is essential at national level to demonstrate economic sustainability for innovative interventions with regard to treatment and organisation of care. On the other hand, same opportunities need to be provided to all patients wherever they live. The value of a collaboration at European level is particularly clear in the case of rare and complex diseases. No country alone has the knowledge and capacity to treat all rare and complex conditions. As chronic diseases with diverse symptoms requiring long-term care by a multidisciplinary team, Ataxias, Dystonia and Phenylketonuria have so many parallels with other neurological conditions. Meaning there is much that can be learnt across Europe and inspiration that could be taken by other advocates and clinicians. Optimizing care pathways and rationalizing costs remain key. Furthermore, looking at the current situation and the aftermath of the COVID-19 crisis, health, welfare and economics will continue to be interlinked while addressing unmet needs and treatment gaps, as well as organisational and economic challenges.

Therefore, and in alignment with the project expected deliverables, the momentum is there to reflect on the consolidation of the health economic assessment for Ataxias, Dystonia and Phenylketonuria and new perspectives such as synergies to be further created with the European Reference Networks, the development of learning healthcare systems (LHS) with clinical management networks and patient engagement. LHS are research areas in which knowledge generationprocesses are embedded in daily practice to produce continual improvement of care. Considering the future conclusions that will come out from the VOT2-RNDs study, digitalisation of clinical data and set-up of networks (patient, clinical, biobanking) will be part of the future niches or strategic prospects of the Value of Treatment research.

The major project building elements for reinforcing the economic analysis and examining future niches or strategic prospects are summarized in this "proposal for discussion, May 2020" that will be presented and debated with its members, EBC VOT Expert Advisory Committee and Industry Partners.

1. BACKGROUND

WHAT ARE RARE NEUROLOGICAL DISORDERS?

Rare neurological diseases (RNDs) collectively exert a public health burden in terms of their manifestations' severity and the total number of people afflicted across their lifespan. According to the European Reference Network on neurological diseases (ERN-RND), 500.000 people are living with RNDs in Europe, 60% of those affected are still undiagnosed due to significant phenotype and genotype heterogeneity in clinical presentation and disease course[9]. Health systems face significant challenges to respond to patients' needs and guarantee equal access to treatment. Most rare disorders are of genetic origin. For many patients, considerable barriers exist in terms of access to appropriate care, delayed diagnosis, and treatment options. When patients are diagnosed, many are unable to access resources such as centres of expertise (or specialist centres), coordinated care, patient support systems, and effective treatment[10]. Treatment of chronic RNDs has become increasingly multifaceted and comprises either disease-modifying drugs with different mechanism of action for some of them, symptomatic therapies or other supportive therapies, and surgical procedures such as deep brain stimulation. Treatment must be highly customized to the needs of the individual. While some countries coordinate their approach to rare disease management using comprehensive specialist centres, many countries do not, either because they have not yet adopted this approach or are employing different strategies[11]. Multidisciplinary specialist centers directed to a particular RND may, in addition to the specialist neurologists and nurses, comprise geneticists, physiotherapists, occupational therapists, nutritionists, and neuropsychologists. These centers may even be cost-effective for the society by maintaining the patient's ability to work and reducing the costs of home help and custodial care by keeping people with an RND independent or minimally so.

See published article (May 2019) VOT2 – rare neurological disorders article on "Toward earlier diagnosis and treatment of rare neurological disorders: the value of coordinated care and specialist centers" - www.ncbi.nlm.nih.gov/m/pubmed/31044588/?i=6&from=croat%20med%20j

Box 1: Ataxias, Dystonia and Phenylketonuria in a word

Ataxias

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

Dystonia

- Dystonia is a neurological movement disorder syndrome in which sustained or repetitive muscle contractions result in twisting and repetitive movements or abnormal fixed postures. Dystonia is often intensified or exacerbated by physical activity, and symptoms may progress into adjacent muscles. Dystonia is a very complex, highly variable neurological movement disorder characterized by involuntary muscle contractions. As many as 250,000 people in the United States have dystonia, making it the third most common movement disorder behind essential tremor and Parkinson's disease.
- The disorder may be hereditary or caused by other factors such as birth-related or other physical trauma, infection, poisoning (e.g., lead poisoning) or reaction to pharmaceutical drugs, particularly neuroleptics.
- Treatment must be highly customized to the needs of the individual and may include oral medications, chemodenervation botulinum neurotoxin injections, physical therapy, or other supportive therapies, and surgical procedures such as deep brain stimulation.

Phenylketonuria (PKU)

- 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 phenylalaline in the body and can further affect the brain.

- Prevalence varies considerably across Europe –around 1/10,000 live births on average. Lifelong impact. PKU is diagnosed as a result of newborn screening. If left untreated, the increased concentration of Phe in blood and brain can lead to neurocognitive deficits – e.g. severe intellectual disability, epilepsy and behavioral problems. Therefore, guidelines are important to improve diagnosis and management of PKU ["Key European guidelines for the diagnosis and management of patients with phenylketonuria" – The Lancet/diabetes-endocrinology – September 2017]. Treatment consists of dietary restriction of phenylalanine and early intervention is key.

Being the seat of many chronic disabling diseases, RNDs are particularly challenging as most are associated with the management of long-term conditions including co-morbidities (physical health, psychiatric), loss of independence, occurrence of acute, relapsing episodes and rehabilitations phases (motor, cognitive). In terms of cost of illness studies, there are limited data on the socio-economic burden of rare neurological diseases in Europe.

Box 2: A Cost of Illness Study Evaluating The Healthcare And Societal Burden of Friedreich's Ataxia In The United Kingdom (2016)[12]

Friedreich's Ataxias (FRDA) is a rare neurological disease with an estimated prevalence of 1/30–50,000, which is equivalent to ~2,000 individuals in the UK [13]. FRDA is an autosomal recessive, multi-system disorder, characterised by a range of severe and debilitating symptoms (Figure 1)[14]. Most notably, patients experience a progressive loss of coordination and mobility, resulting in the majority of patients eventually becoming wheelchair bound [14]. Currently, there are limited data on the economic burden of FRDA in the UK [15].

The study used NHS Reference Costs (2014–2015) and the British National Formulary informed model inputs, in conjunction with patient questionnaires and clinician interviews. The model considered two perspectives: (1) direct costs to the NHS including treatment costs and consultations; (2) indirect societal costs to FRDA individuals and social services. According to the study results, the total COI of FRDA patients to the NHS was £8,038,645 per year, with a mean annual cost per patient of £3,556. Loss of mobility and cardiac abnormalities caused the most substantial direct costs: contributing 35% and 21% respectively. Inclusion of societal costs contributed an additional £7,633,263 per year and an additional mean annual cost of £3,376 per patient. Travel costs and loss of earnings to carers were considerable contributors to societal costs.

WHAT IS THE VALUE OF TREATMENT RESEARCH FRAMEWORK?

From an overarching perspective, the study is looking at value, early intervention and exploring the potential benefits and consequences of coordinated care through the examination of health services, patient outcomes and multidisciplinary care patterns.

Rationale: VOT Research Methodology

Starting with the definition, what do we mean by "treatment gap" and "value"?

Analysing the "treatment gap" has been central in the study: unmet needs are not only within the provision of medicines and medical devices, but also within health care systems and services. A definition of the treatment gap is "the number of people with an illness, disease or disorder who need treatment but do not get it or receive inadequate treatment"[16] or "anytime the care offered to the patient doesn't correspond to his or her needs and/or to the stage of the disease or the lack thereof"[17]. It is used as an outcome measure in health care.

The VOT study addresses the obstacles to optimal treatment which are defined as "missed diagnosis", "delayed" or "inadequate treatment", "non-adherence", "no access to care", "unaffordability", "over-use or under-use" (see fig. 1: possible causes of the treatment gap).

Optimizing healthcare processes with an outcomes-based approach: achieving high value for patients is the overarching goal of health care delivery, with value defined as the health outcomes achieved per money spent[13]. Treatment is based on the needs of the patient ("demand") instead of on the offer/supply of treatment structures. Each age group according to disease stage has specific needs to be addressed along the care process (biological, psychological, health care services, social needs)[18]. Care for people with chronic, rare diseases usually involves multiple specialties and numerous interventions, with final outcomes determined by interventions across the full cycle of care. Measuring, reporting, and comparing outcomes are crucial to improve outcomes and make informed choices about how to optimize healthcare and rationalize costs (see fig. 2: measuring value in health care and the patient pathway)[19].

Figure 1: Possible causes of the treatment gap

NATURAL HISTORY OF THE DISEASE

- Asymptomatic phase of illnesses
- Illnesses usually with no symptoms
- Low understanding of the disease aetiology, symptoms, risk and preventive factors

DEFICIENCIES IN HEALTH SERVICE ALONG THE CARE PROCESS (PREVENTION, SCREENING, DIAGNOSIS, TREATMENT, FOLLOW-UP AND REHABILITATION)

- Not available services, systems or policies
- No health insurance
- Limited access to care (primary and secondary care)
- Fragmented, poorly organized or or uncoordinated care
- Lack of primary and secondary prevention programmes
- Delay in detection and diagnosis leading to late treatment
- Drugs not available for whatever reason
- Physician misses detection, diagnosis
- Inadequate treatment
- Low disease awareness in general public and lack of training, expertise from healthcare providers
- No patient empowerment to facilitate adherence, compliance – non-adherence to treatment being intentional or unintentional
- Absence of support for caregivers

ECONOMIC FACTORS

- Costs of treatment
- Limited access to drugs and devices

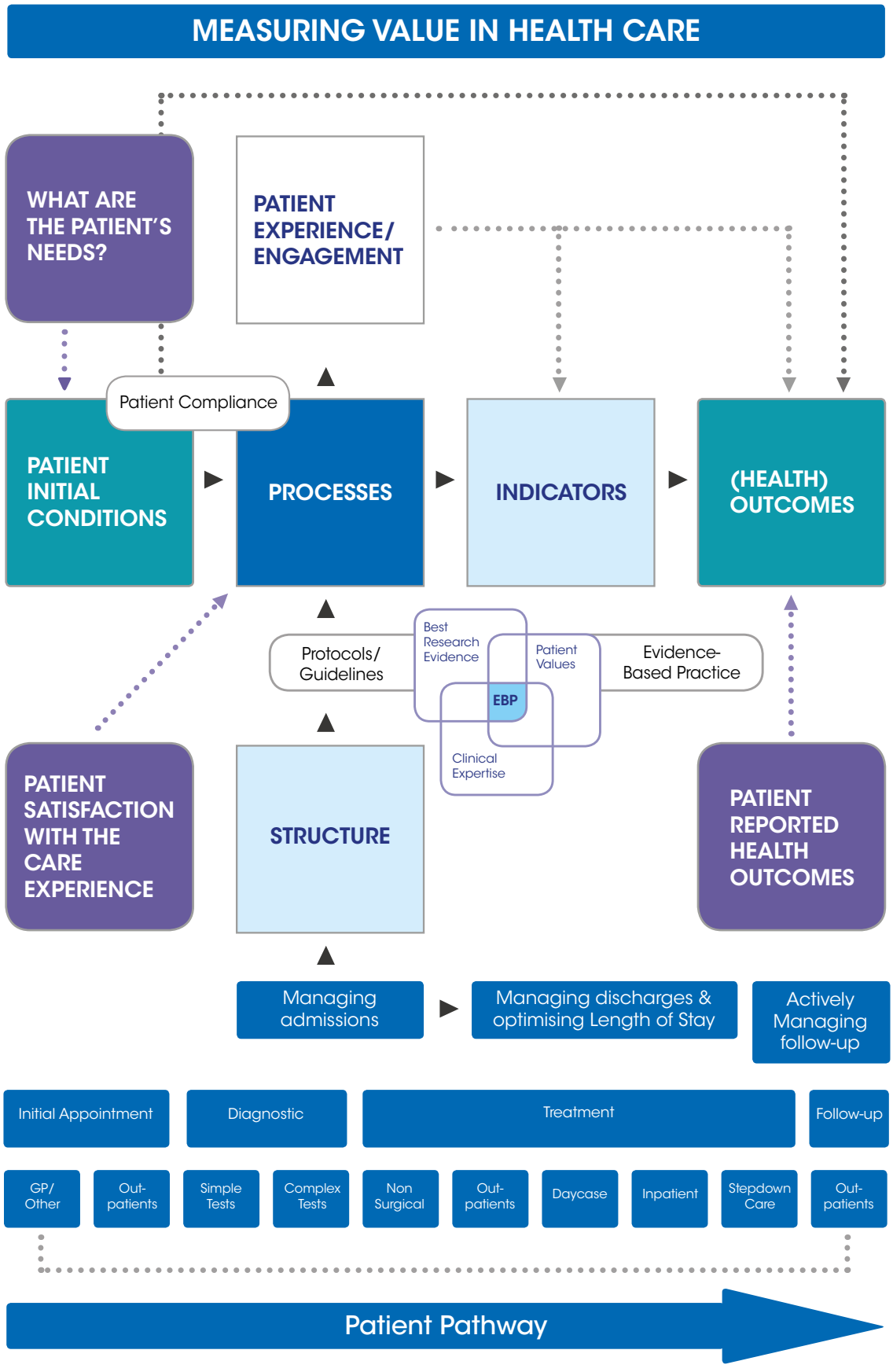
SOCIAL FACTORS

- Fear of disclosure
- Stigma discourages seeking treatment (e.g. epilepsy, mental illnesses)
- Isolation and vulnerability

OTHER FACTORS (unknown because of lack of research)

Source: Adapted from R. Kale. The treatment gap. BMJ. Epilepsia 435supp 6) :31-33, 2002.

Figure 2: Measuring Value in Health Care by achieved outcomes, starting with defining the patient's needs (in-patient care pathway)



This is **the objective of VOT with the case studies analysis: "delivering health care value by improving outcomes"** (see Fig. 3), refining data and indicators, an overarching outline.

Figure 3: Delivering health care value for RNDs by improving outcomes

Outcomes	Rational of measures and data sources
From Deaths	> Mortality and life expectancy • Public health perspective
To Disorders/Diseases	> Prevalence and incidence of disorders/diseases > Outcome measures to capture the reduction in morbidity andfor specific disorder or disease, Quality-Adjusted Life Year (QALY) gained, Healthy Life Years (HLYs) gained. • Medical/clinical perspective > Linking to cost/value • At system level: burden of disease studies • For specific service and interventions: cost-effectivences studies
To Disability	> Outcomes to address the way a health system deals with disabilities • At system level: Disease-Adjusted Life Year (DALY) • At health services: e.g. Resident Assessment Instruments (RAI)
To Discomfort and Dissatisfaction	> Outcomes experienced by patients • PROMs (patient reported outcomes measurement) including EQ5D • PREMs (patient reported experience measurement)

Source: Adapted from OECD delivering health care value by improving outcomes, 2015.

Box 3: Realising the true value of integrated, coordinated care: Beyond COVID-19

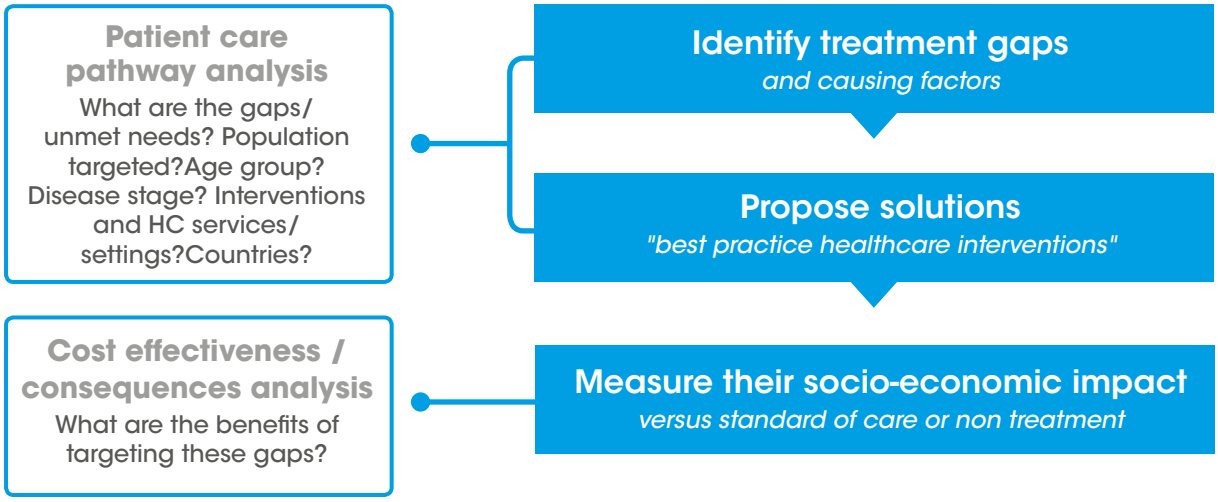
COVID-19 presents an opportunity to reset fragmented health and care systems so that they are integrated, driven by people and communities and resilient in the face of future systemic shocks.

Seizing the opportunity to think how systems transformation and design will lead to improving population health and wellbeing and ensure we are better equipped to respond to future crises, this will require a paradigm shift for health systems, moving on from a hospital-centric focus and a disease specific approach to multimorbidity and transmural coordinated care patterns.

The case studies research combined methodology encompasses 1) patient care pathway analysis (qualitative research) followed by 2) economic evaluation of specific clinical interventions across different rare neurological diseases, assessing their impact on costs and outcomes (quantitative research) see figure 4: VOT research methodology).

Figure 4: VOT research methodology

Case studies analysis aims to:



From an overarching perspective, the study is looking at value, early intervention and exploring the potential benefits and consequences of coordinated care through the examination of health services, patient outcomes and multidisciplinary care patterns. Outcomes measurement/indicators are defined accordingly (starting with a care pathway analysis followed by the economic evaluation). It is crucial to harmonize datasets for the three case studies on RNDs based on a standardized approach.

Box 4: VOT Research methodology framework 1

Guidelines – a patient care pathway analysis from both patient and clinician perspectives (qualitative approach)

The aim is to map the patient experience and treatment gaps, describing patient needs and issues along the whole care process from prevention, prodromal, early detection to disease management. The results of the analysis are built based on epidemiology analysis, available evidence-based diagnosis and treatment guidelines, quality standards and other information such as expert and patient opinions. Gaps are assessed along a set of indicators defined (such as access, adherence, satisfaction, QoL, EQ5D e.g. pain or fatigue) and recommendations are proposed on how these can be improved. Tools: patient survey and statistical analysis based on survey

Box 5: VOT Research methodology framework 2

Guidelines - Economic evaluation framework and case study analysis from both a societal and healthcare perspective (quantitative approach)

- The aim of the proposed economic case study is to make more and better economic evidence on the value of treatment in rare neurological disorders [Ataxia, Dystonia, Phenylketonuria] available to policy decision making. The analyses are built on previously published research in the field, particularly where it has generated evidence on effectiveness, and use methods successfully employed in published studies to explore the economic case for closing treatment gaps in the therapeutic area under study.

- The quantitative case study analysis aims at producing a compendium of the economic evidence of treatment gaps in the therapeutic area under study. It examines the economic case for the best healthcare intervention proposed and the treatment gaps previously identified via the patient care pathway analysis.

- Mathematical modelling, such as a simple decision tree, can be populated with data from the literature, previous randomised or quasi-experimental studies, observational studies or routine management information systems (secondary data). Models are simulations of what might happen in reality, tracing pathways through care for individuals with particular characteristics/ treatment gaps, estimating the associated outcomes and costs, and then comparing them in order to better understand whether one is more cost-effective than the other.

2. RESEARCH STUDY PROTOCOLS

Here is an overview of the research study protocols for the case studies on the investigations of healthcare delivery to patient, w/Ataxias, Dystonia or Phenylketonuria.

VOT2 Proposed Value of Treatment Study on Ataxias

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

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 SAC and those who have not.
METHOD AND EXPECTED RESULTS	• **Patient care pathway and treatment gaps/unmet needs analysis of individuals with progressive ataxias (survey population from 16+ years old)** • Patient survey (Costello Medical report UK patients, Sep 2019) data collected and analysed – survey is being extended to Germany (survey disseminated and data collection ongoing) and Italy (survey translated and will be disseminated soon online). Data collected on 1) diagnosis; 2) Management of the ataxias; 3) costs and consequences of specialist ataxia centres • UK survey questions (64 questions, n=277 participants) focused on: 1) the length of time to get a diagnosis; 2) number, length, reason for hospital admission; 3) attendance at specialist centres; 4) utilisation of other primary and secondary health care services; 5) patients satisfactions with services used; 6) out-of-pocket expenses incurred when receiving care. • Statistical analysis based on UK data: some results will be presented on the 18th of May which relates to 1) Demographics, 2) Diagnosis & co-morbidity by attendance to SAC according to stratification, 3) Patient pathway (referral), 4) Symptoms management and care satisfaction and 5) economics analysis for management and care.

METHOD AND EXPECTED RESULTS	Regression analysis will be used and other complementary tests to achieve statistical significance. • **Cost consequences analysis**: use of the UK survey data to measure the costs and consequences (analysis done) of attending a specialist ataxia centre, further impact analysis based on statistics analysis to be conducted. A similar analysis will be carried on for Germany and Italy.

VOT2 Proposed Value of Treatment Study on Dystonia

Aim of the Dystonia study is to examine the potential benefits of coordinated care combining effective team care and patient-centred planning.

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? What about the potential benefits of integrated, coordinated care combining effective team care and patient-centred care planning. How different training levels and structured, accredited postgraduate, or sub-specializing movement disorders (MD) training is related to dystonia treatment and improvement of QoL
DESIGN|METHOD	A questionnaire for dystonia patients was developed in Croatia (2010) to investigate the effects of specific training of dystonia in postgraduate medical education. The questionnaire was composed of 30 questions divided into three parts (part I. general questions as name, age, etc; part II. specific questions as disease duration, type of DS, time to correct diagnosis, who made correct diagnosis, experience with first visit to GP etc; part III. Availability of therapy, type of therapy, therapy side effects, effects on social life, working capacity, QoL). After validation in Croatia, we are using this questionnaire in European countries to investigate the QoL, treatment availability, socio-economic impact etc. in Europe. For VoT treatment project 4 countries on different level of development (Croatia, Germany, Italy, UK) should be analized additionaly to investigate the influence of integrated, coordinated care, well developed center and structured, accredited postgraduate, sub-specializing MD training on early diagnosis, treatment and socio-economic impacts of dystonia.

SITES	University of Zagreb, Medical School, Croatia (with Germany, Italy,UK)
ANALYTICAL APPROACH , EXPECTRD RESULTS	Correlation between the relative number of MD experts, DBS centers, BTX centers and\or clinical specialized MD centers and Surve Survey results from 4 each 4 countries will be analyzed. Could we confirm the potential benefits of integrated, coordinated care combining effective team care and patient-centred care planning? Could we see the positive socio-economic impact of structured, accredited postgraduate, or sub-specializing MD training and developed organized centres? Answers would have the great impact on Value of Treatment of dystonia in Europe and should be important for planning healthcare and organisation of specialized, well defined centres and accredited clinical training for dystonia treatment in Europe. Statistical analysis will be performed with $P < 0.05$ considered as statistically significant. For example: Descriptive statistics will be used for continuous variables (Survey results level, eg, gender, age, disease duration, therapy, QoL etc.) Pearson correlation test will be used to determine the relationship between Survey results and education components as well as rel number of MD centres, MD experts, DBS and BTX units, etc.

VOT2 Proposed Value of Treatment Study on Phenylketonuria (PKU)

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

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	In the first instance, a review of PKU Clinic structure and processes will be undertaken: Current Metabolic Unit staffing, available resources and workload will be examined across participating centres through two surveys, a follow-up phone call and a Webex video conference; sharing experience and defining challenges. Separately, a designated patient advocate/representative (liaising with their respective patient associations/support groups from the participating countries) will be requested to provide information, based on a survey of patients within their respective associations/ support groups: What are deemed to be unmet medical needs and patients' expectations/preferences regarding delivery of care and their understanding of how well they are managing their condition. Patients will also be asked to complete self-report questionnaires to investigate the impact of PKU on their quality of life.These questionnaires include: HADS (Hospital Anxiety and Depression Scale), EQ-5D-5L (Euroqol), VAS (Visual Analogue Scale), and the FNS (Food Neophobia Scale). It is proposed a retrospective review of medical records of PKU patients scheduled to attend clinics over 4 consecutive months would be undertaken: Examining scheduled appointments against actual attendance (or DNAs), and among attendees during this period looking at Phe levels to identify those meeting targets, and also characterize the population demographics, and most importantly resource utilization (e.g., interaction with named staff, lab testing, etc), co-morbidities and concomitant medications, if any; and the extent to which the latter impact on their overall healthcare managements and other considerations relevant to PKU (appendix 3) Access to supplements and targeted therapies will also be evaluated.

METHOD	**Data collection will focus on**

Centre-based Unit audit:

1. Characterization of staffing (Medical, Nursing, Dietetic), clinic resources and workload, and model of care (mapping actual patient journey), including Laboratory support services and ancillary health care providers (Clinical Psychologist and Medical Social Worker support, Dietetic Assistant).
2. Identify no. of PKU patients cared for, guidelines followed and adherence to targets (based on no. of blood samples sent, frequency of visits, and proportion of values meeting target Phe < 600 µmol/L).
3. Survey of Dieticians working with Children or Adults to explore their treatment of PKU patients.

N.B. Data will be examined in relation to overall metabolic program, proportion of PKU patients in relation to overall clinical load, and WTE and experience of staff dedicated to PKU-related efforts.

Patient data collection:

1. Assessment of patient satisfaction with current delivery of care and challenges in their management.
2. Completion of HADS, EQ-5D-5L, and the FNS.

Centre-based audit of medical records of PKU patients (individuals who attended during 4 consecutive months' clinic visits):

1. Demographic data: Age- and gender- distribution, ethnicity, highest educational achievement, employment status, IQ (if available); for females of reproductive age: gravida/parity
2. BMI, height, weight, lipid profile, co-morbidities and concomitant medications (if any)

SITES	Three sites across three countries (Ireland/UK/Spain)
INCLUSION CRITERIA	Patients with a confirmed diagnosis of PKU who are above 12 years of age at date of enrolment and who are scheduled to attend clinic appointments over 4 consecutive months.
EXCLUSION CRITERIA	1. If non-verbal and deemed unable to satisfactorily complete self-report questionnaires/patient satisfaction survey. 2. If in residential care and not actively followed by wthe respective site 3. If has a serious comorbidities or life-limiting illness
ANALYTICAL APPROACH	Descriptive statistics will be performed for continuous variables (eg, Phe level), and frequency distribution to define the distribution of categorical variables (eg, gender, test scores). Independent sample test will be used to find the difference in means between groups (eg, Phe levels within or outside target); paired t test will be used to find the difference in means within groups. One way analysis of variance will be used to determine whether there is any significant difference in mean among various groups. Pearson correlation test will be used to determine the relationship between duration of symptoms and HADS scoring. SPSS V.25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). will be used to perform the statistical analysis and any test with $P < 0.05$ was considered as statistically significant.
ASSESSMENTS	Patients will complete HADS, EQ-5D-5L, VAS, and the Food Neophobia Scale (See Method section).

3. HEALTH ECONOMICS STUDY: TOWARDS COST-EFFECTIVENESS/CONSEQUENCES ANALYSIS

It is proposed to conduct a robust health economic evaluation by collecting information on the costs and consequences of best practice health care interventions and its comparator(s). The practice generally considers to design a cost cost-utility analysis (CUA), a single summary ratio which provides information on the incremental cost per quality adjusted life year (QALY) gained of a new technology compared to current best practice. A CUA is generally recommended due to the definitive methodology for calculating QALYs, hence facilitating the comparison of results across programmes of work [20]. A CUA though is not always possible or practical, particularly when information about morbidity, such as a quality of life questionnaire like the EuroQol 5-D, is not available to be able to calculate QALYs, as is the case with routinely collected patient data.

Cost-consequences analysis (CCA) is a form of economic evaluation in which the outcomes (of which a variety of measures are normally presented) are reported separately from costs. Cost-consequences analysis presents the costs and consequences of numerous intercessions. CCA is comparable to CEA in that results chosen are calculated in a natural unit of effect. This is usually done using a descriptive table to present the effectiveness results (primary and secondary outcomes) in a disaggregated format, together with the estimates of the mean costs with appropriate measures of dispersion associated with each intervention [21] (see example 1).

Example 1: Cost consequences analysis: example of summary costs and effects

	Intervention 1	Intervention 2	Difference
Costs	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Cost of intervention	€ (€, €)	€ (€, €)	€ (€, €)
NHS secondary care	€ (€, €)	€ (€, €)	€ (€, €)
Informal care	€ (€, €)	€ (€, €)	€ (€, €)
Social care	€ (€, €)	€ (€, €)	€ (€, €)
Costs to patient	€ (€, €)	€ (€, €)	€ (€, €)
Welfare payments	€ (€, €)	€ (€, €)	€ (€, €)
Cost of productivity loss	€ (€, €)	€ (€, €)	€ (€, €)
Outcomes			
Primary clinical outcome	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Secondary outcomes	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
QALYs using EQ-5D-5L	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
QALYs using SF-6D	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Quality of life	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Patient satisfaction	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)

Source: NICE 2013 - How NICE measures value for money in relation to public health interventions.

CCAs have been recommended for complex interventions that have multiple effects for example public health interventions which have an array of health and non-health benefits that are difficult to measure in a common unit (NICE 2013)[21]. CCAs are not restricted to any viewpoint and decision makers can see the impact of their decisions on patient costs or on other sectors such as social care[22]. Similarly, outcomes including also indicators to measure coordination of care are not restricted to health outcomes such as QALYs and can include other measures of wellbeing such as patient, or HCPs, satisfaction. These non-health considerations are becoming increasingly relevant to national health systems decision makers. CCA may be of particularly value to stakeholders that are more concerned with patient-orientated outcomes and intervention costs (particularly those with less focus on final stage randomized control trials but still providing an opportunity to pilot instruments used to collect economic data such as resource use and health-related quality of life).

Box 6: Estimating cost-effectiveness in public health: modelling and valuation methods

Beyond the fact that economic evaluation methods as they have been developed for Health Technology Assessment do not capture all the costs and benefits relevant to the assessment of public health interventions", Marsh et al. 2012 paper for instance reviews methods that could be employed to measure and value the broader set of benefits generated by public health interventions[23]. They propose that two key developments are required if this vision is to be achieved. First, there is a trend to modelling approaches that better capture the effects of public health interventions. This trend needs to continue while consider a broader range of modelling techniques than are currently employed to assess public health interventions. The selection and implementation of alternative modelling techniques should be facilitated by the production of better data on the behavioural outcomes generated by public health interventions. Second, economists are currently exploring a number of valuation paradigms that hold the promise of more appropriate valuation of public health interventions outcomes. These include the capabilities approach and the subjective well-being approach, both of which offer the possibility of broader measures of value than the approaches currently employed by health economists. These developments require health, economic and social value judgements. Such a link would have the benefit of ensuring that the methods developed are useful for decision makers.

4. BRAINSTORMING: CONSOLIDATE THE RESEARCH PROJECT ECONOM

Consolidating the research project economic analy

GANTT Chart: Research project current planning and proposed research project conso

VoT2 - RNDs case studies - Timeline 30 months starting in 2018	Phase1 - "Scoping and kick-off"			Phase2 - "Development, qualitative and quantitative research"								
Month	M3 Jul	M4	M5 Sep	M6 Oct	M7	M8	M9 Jan	M10	M11	M12	M13 May	M14 Jun
A1. Scoping meeting	Start	End										
A2. Define scope, research questions and methodology including WG	Start		End									
A3. "Data collection, analysis and interpretation" via literature review, landscape assessment and survey				Start								
A4. Consultation and reporting												Start
A5. Economic evaluation based on care pathways analysis							Start feas.				Start CEA	
A6. Final results, posters and summaries												
A7. EBC Policy Paper and scientific publications												

VoT2 - RNDs: Final case study deliverables
Month
A1. Results data collection, analysis and interpretation via literatu and survey + Economic evaluation based on care pathways and POSTER AND SUMMARY FOR EBC FINAL PAPER
A2. EBC FINAL PAPER with Part 1 and Part 2 (posters and summar
A3. Case study full article: JOINT SCIENTIFIC PUBLICATION

Legend

A "Activity": Phase 1 defined under A1, A2 - Phase 2 defined under A3, A4, A5 - Phase 3 defined under A6, A7

Start **End** **Milestone**

IC ANALYSIS & FUTURE PERSPECTIVES

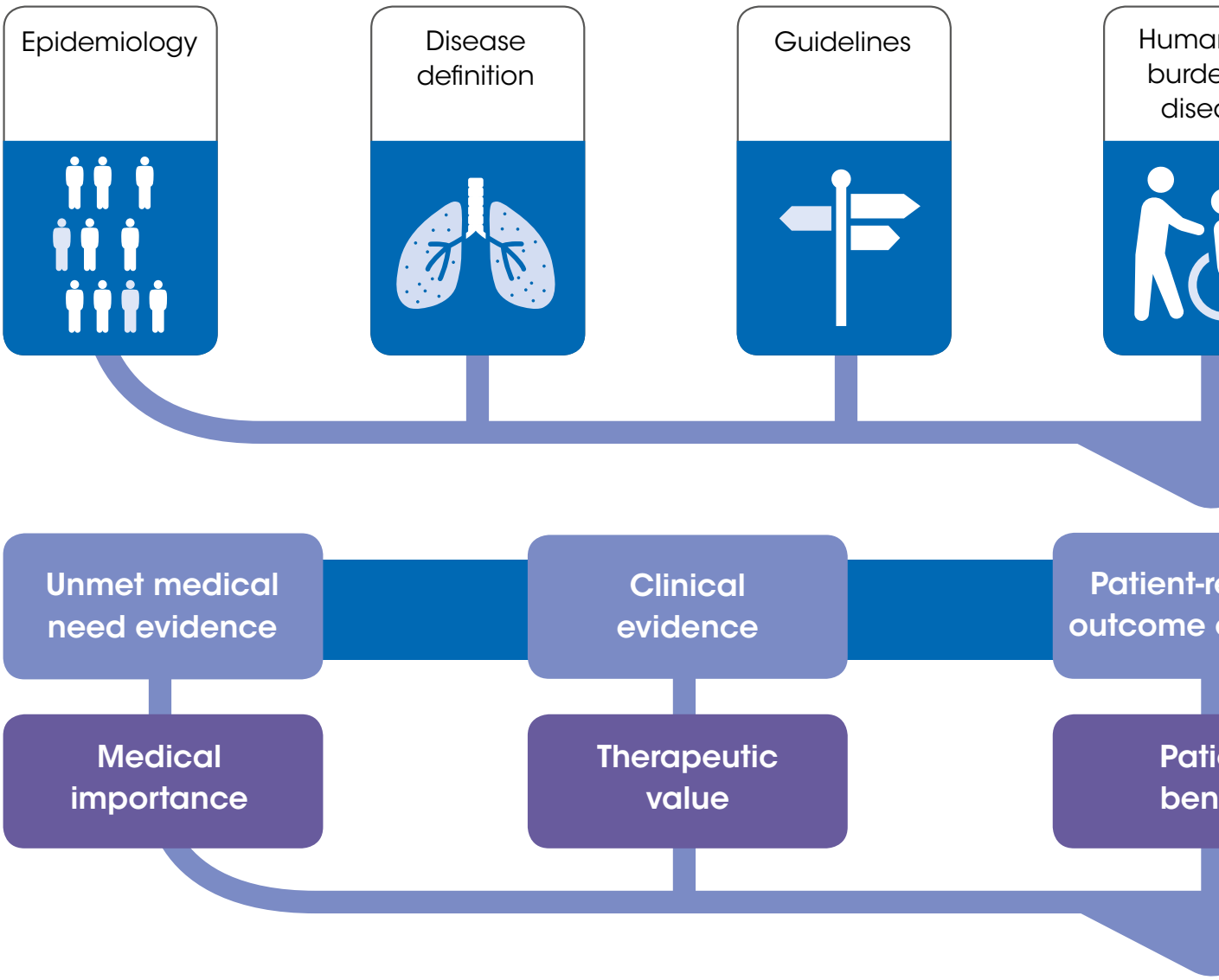
ysis and strategic positioning

olidation of 6 months

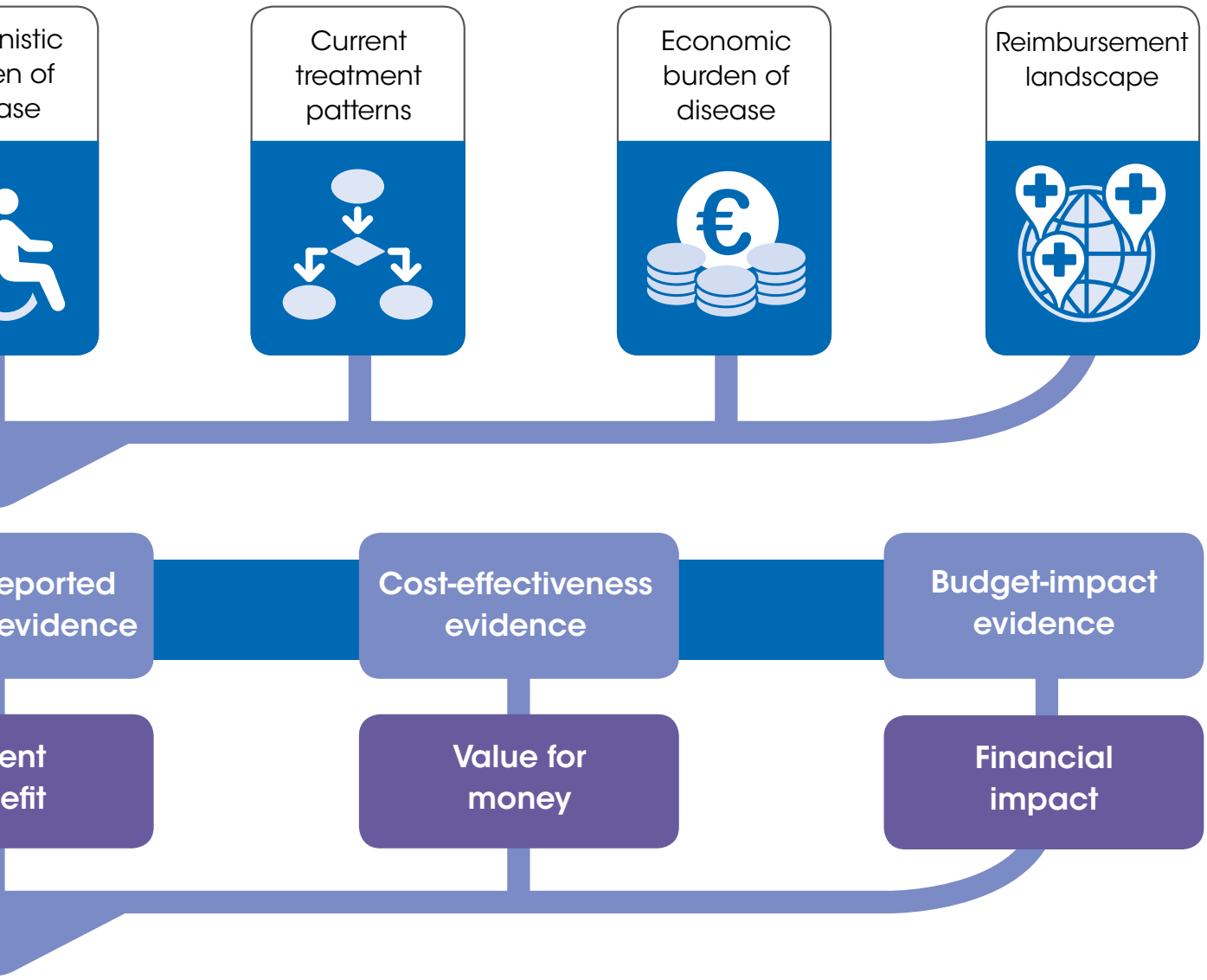
Oct 2018 - Jun 2020 (21 Months)												Phase3 - "Final results and publications Jul 2020 - Dec 2020 (6 months)					
M15	M16	M17	M18	M19	M20 Dec	M21 Jan	M22	M23	M24 Apr	M25	M26 Jun	M27 Jul	M28	M29 Sep	M30	M31	M32 Dec
											End						
														End			
														End			
															Start		End
															Start		End

	Phase 3 "Final results and publications" Dec 2020 - June 2021 (project last 7 months)						
	Dec	Jan	Fev	Mars	April	May	Jun
ure review, landscape assessment alysis: INDIVIDUAL CASE STUDY	End						
ies)							End
							End

Summary approach for consolidating the current res



search project economic analysis



ing the current research project

n Makers (HCDMs)

Regulators

ents

Payers

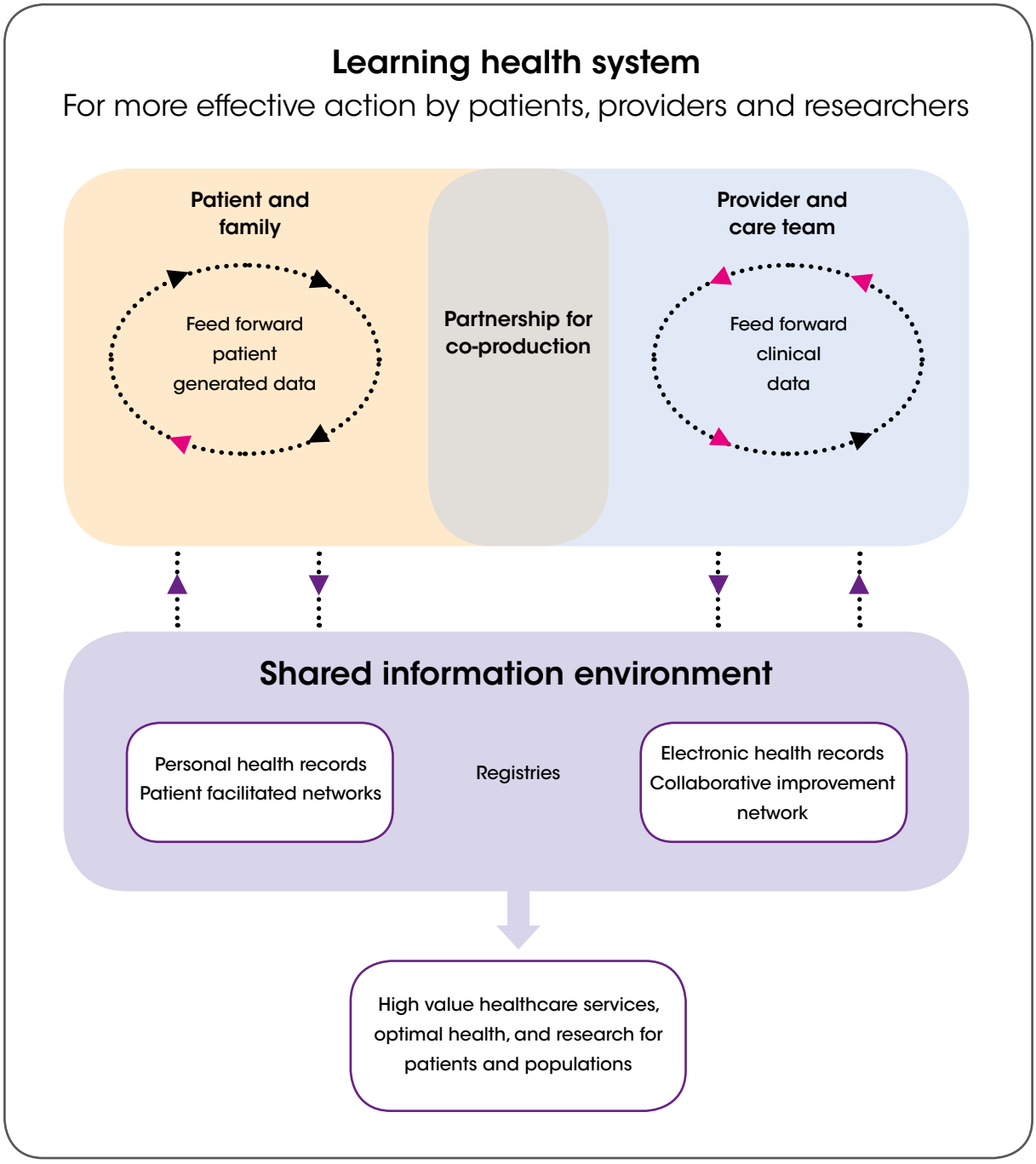
Looking at future perspectives

Fully in alignment with phase 2 of the research (see annex) and from now on, there will be a major focus on the economic evaluation framework and case studies analysis from both a societal and healthcare perspective (quantitative approach). Privileging cost-consequences/effectiveness analysis, the economic evaluation will include multiple variables, using modelling and valuation methods while examining healthcare interventions. In addition, relevant elements will be taken into consideration with new coordinated care models as well as transmural data sharing and care emphasizing cross-border collaboration. On the one hand, it is essential at national level to demonstrate economic sustainability for innovative interventions with regards to treatment and organisation of care. On the other hand, same opportunities need to be provided to all patients wherever they live. The value of a collaboration at European level is particularly clear in the case of rare and complex diseases. No country alone has the knowledge and capacity to treat all rare and complex conditions. As chronic diseases with diverse symptoms requiring long-term care by a multidisciplinary team, Ataxias, Dystonia and Phenylketonuria have so many parallels with other neurological conditions. Meaning there is much that can be learnt across Europe and inspiration that could be taken by other advocates and clinicians. Optimizing care pathways and rationalizing costs remain key. Furthermore, looking at the current situation and the aftermath of COVID-19 crisis, health, welfare and economics will continue to be interlinked while addressing unmet needs and treatment gaps, as well as economic and organisational challenges.

Therefore, and in alignment with the project expected deliverables, the momentum is there to reflect on the consolidation of the health economic assessment for Ataxias, Dystonia & Phenylketonuria, and new perspectives such as synergies to be further created with the European Reference Networks and Orphanet (registries and biobanks), the development of learning healthcare systems (LHS) with clinical management networks and patient engagement (see figure 5: Towards Learning Healthcare System). LHS are research areas in which knowledge generation processes are embedded in daily practice to produce continual improvement of care[24 25 26].

Considering the future conclusions that will come out from the VOT2-RNDs study, digitalisation of clinical data and set-up of networks (patient, clinical, biobanking) will be part of the future niches or strategic prospects of the Value of Treatment research.

Figure 5: Towards Learning Healthcare System



Sources: Learning health system adapted from Nelson et al. 2016[27]

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ANNEX

VOT

2nd ROUND 2018-2021
BRIDGING THE GAPS & ACHIEVING SEAMLESS, COORDINATED CARE

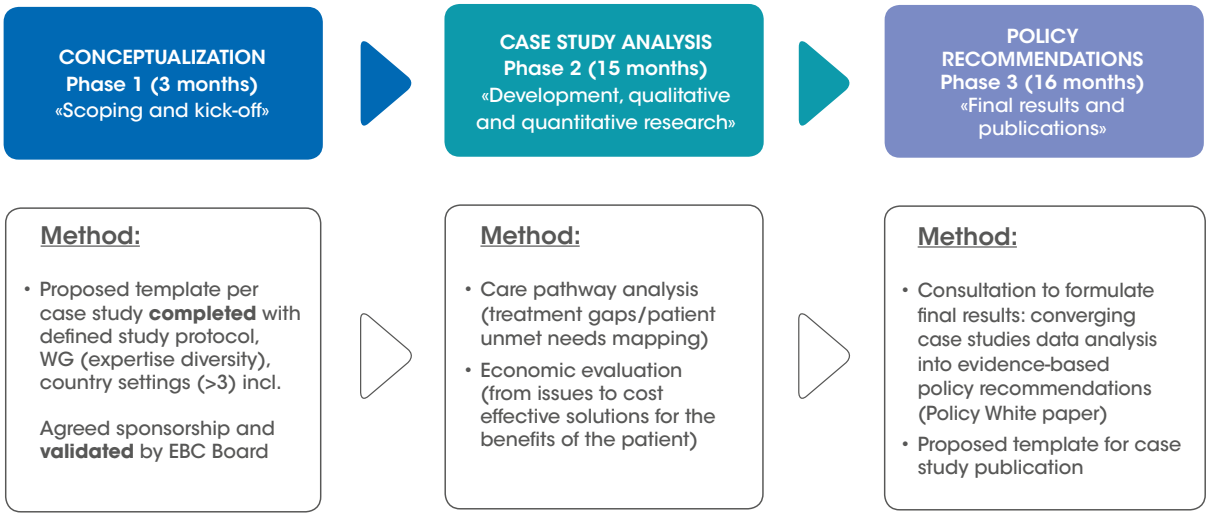
VoT2 RESEARCH PROJECT - RARE NEUROLOGICAL DISORDERS

Working Groups	**Ataxias:** final **Dystonia:** final **PKU:** final
Care pathway analysis Economic evaluation (cost consequence analysis)	**Case studies overarching theme:** role of multidisciplinary, coordinated care (specialist centres) and its impact on health service use and patient outcomes
Academic partners	**Ataxias & PKU:** University College London Hospitals, University of Cambridge, University College Dublin **Dystonia:** University of Zagreb Medical School

European Reference Network | Neurological Diseases (ERN-RND)

Funding: We have received sponsorship from Takeda, Reata (Ataxias case study), Ipsen (Dystonia case study), and Biomarin (Phenylketonuria case study).

Research three phases:



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