VOT

EBC RESEARCH PROJECT

THE **VALUE OF TREATMENT** FOR BRAIN DISORDERS

"Bridging the early diagnosis and treatment gap: exploring the potential clinical and socioeconomic impact of targeting unmet needs - reflections on new research developments including the benefits of alternative approaches such as seamless, integrated care in the prevention and treatment of brain disorders"

DISCUSSION PAPER 2 - FEBRUARY 2017

CONTENT

A MULTIPLE GOAL

Bridging the early diagnosis and treatment gap:
- **Target unmet needs towards achieving high value for patients**
- **Reflect on new research developments**
- **Conduct cost-effectiveness analysis in health care (comparing costs and values of
  defined interventions) and assess benefits of coordinated care in the prevention and
  treatment of brain disorders**

A BOTTOM-UP METHOD WITH CASE STUDIES ANALYSIS

DISCUSSION PAPER 2 (EBC BOARD MEETING, 8-9 FEBRUARY 2017)

Synthesis of 18 January 2017 plenary meeting: working groups case studies preliminary
results presentation and experts roudtable

Setting the scene: early intervention as a common denominator

From case studies data analysis towards evidence-based policy recommendations

EBC VALUE OF TREATMENT MANAGEMENT TEAM:

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Giovanni Esposito, Research Project Manager

The European Brain Council (EBC) is a non-profit organisation gathering
patient associations, major brain-related societies as well as industries.
Established in March 2002, its mission is to improve the lives of those living
with brain disorders by advancing the understanding of the healthy and
diseased brain through bringing together science and society.

ACKNOWLEDGEMENTS AND DISCUSSION PAPER 2 OBJECTIVES

The European Brain Council would like to thank sincerely its Academic Partners, Working Groups Experts, External Experts and Patients Associations' Representatives for their constructive insights. The list of participants to the Value of Treatment Meeting of 18 January 2017 is in the Annex.

EBC Discussion Paper 2 as a synthesis focuses on

- addressing the **burden of diseases** and **issues** in the current healthcare, the health services delivery & care pathways design

- proposing **evidence-based** and **cost-effective solutions** to achieve high value for patients

Results of a literature review, this synthesis report builds on

- case studies key preliminary results analysis and interpretation

- consultations with experts

Wednesday 18 January 2017 - The Value of Treatment Plenary Meeting brought together Working Groups members, partners and external experts.
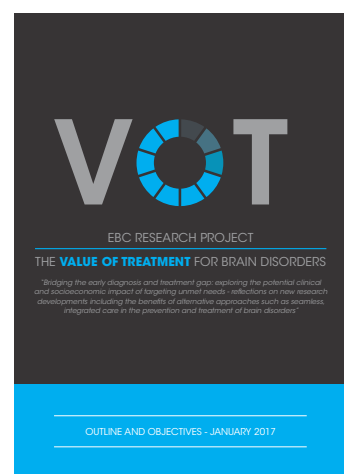
Aim of the meeting was to present case studies preliminary results and to complement the presentations with consultations (experts roudtable) based on meeting Outline **"Bringing the early diagnosis and treatment gap for brain disorders - Towards EBC Policy White Paper"**. **Concept and evidence were highlighted so far around early intervention.**

Link to EBC Meeting Outline - January 2017

We are approaching the end of the research project phase 2 "case studies analysis"
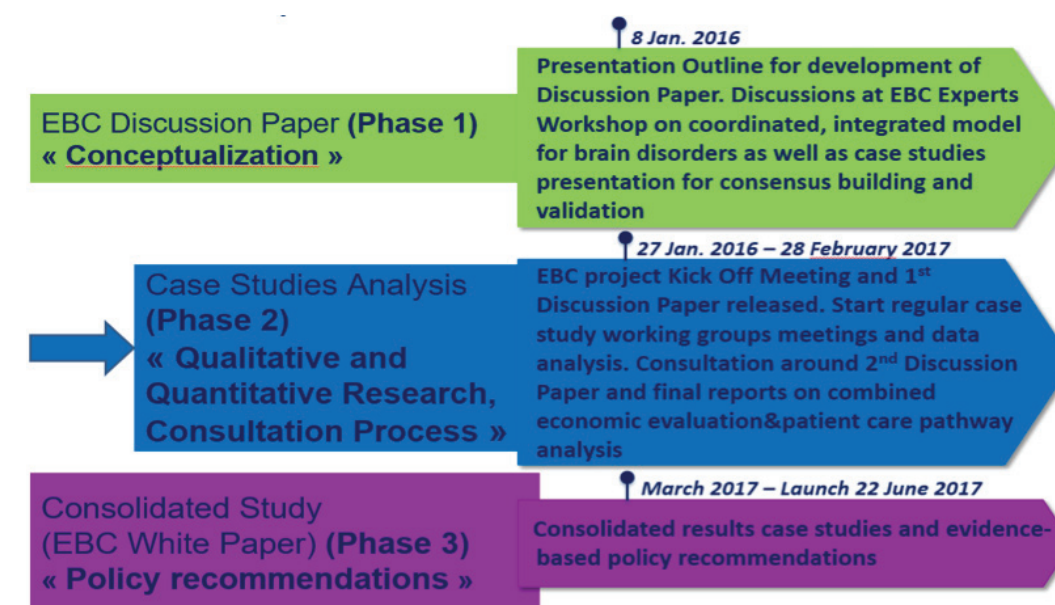*(see fig.1: EBC Value of Treatment research phases and deliverables)*

It is therefore important to start **harmonizing pre-results based on case studies methodology and standardized approach developed, and reporting requirements. An overarching healthcare model for brain disorders** (based on common denominators that could link diseases) **and research conclusions should then be defined for further policy recommendations.** This discussion paper will support the final reporting due by 15 May 2017.

22 June 2017: EBC will launch a Policy White Paper at final conference under the auspices of the Maltese EU Presidency.

The Policy Document will be **addressed to the Ministers of Health and Social Affairs, Ministers of Labour and other involved Ministers, to the European Commission, OECD, WHO, other international institutions and key involved stakeholders.**

Scientific publications will also be released during the first semester of 2017.

Figure 1: EBC Value of Treatment three expected deliverables *(see detailed planning with milestones in the section on next steps at the end of the report, p. 51)*

EBC Discussion Paper **(Phase 1)** **« Conceptualization »**

8 Jan. 2016
Presentation Outline for development of Discussion Paper. Discussions at EBC Experts Workshop on coordinated, integrated model for brain disorders as well as case studies presentation for consensus building and validation

Case Studies Analysis **(Phase 2)** **« Qualitative and Quantitative Research, Consultation Process »**

27 Jan. 2016 – 28 February 2017
EBC project Kick Off Meeting and 1st Discussion Paper released. Start regular case study working groups meetings and data analysis. Consultation around 2nd Discussion Paper and final reports on combined economic evaluation&patient care pathway analysis

Consolidated Study (EBC White Paper) **(Phase 3)** **« Policy recommendations »**

March 2017 – Launch 22 June 2017
Consolidated results case studies and evidence-based policy recommendations

Case studies analysis Working Groups are formed with **experts** within the network of EBC member organizations (e.g. European Academy of Neurology) as well as other industry and patient associations representatives. The setting up of the groups has been a building process to ensure a **high level of expertise** (participation of clinicians, health economists, epidemiologists…) and **an innovative "bottom-up" approach**.

INTRODUCTION

EBC Value of Treatment overall goal: assessing the treatment gap and the cost of non- (or inadequate) treatment, and promoting a holistic healthcare approach (versus fragmentation and results in silo).

IN A WORD [1]

A reality: the brain, source of intellectual capacities and emotional behavior, is essential for people's personal and professional lives, as well as their participation in society. When the brain is damaged, it can affect different functions of the human body and can lead to disorders impacting both the individuals as well as society at large.

Heterogeneity: brain disorders encompass all the conditions and diabilities affecting the brain, caused by illness, genetics or traumatic injuies. It refers to a wide variety of diseases, varying greatly in their symptoms and level of severity. Brain disorders are classified into different categories, including neurogenetic diseases, neurodevelopmental disorders, degenerative diseases, metabolic diseases, traumatic brain injury, brain tumours, addiction to drugs and alcohol, and psychological/mental disorders

For neurological disorders: examples of symptoms include paralysis, muscle weakness, poor coordination, loss of sensation, seizures, confusion, pain, and altered levels of consciousness[2]

For mental disorders: mental health problems can cover a broad range of disorders, but the common characteristic and symptoms is that they all affect the affected person's personality, thought processes or social interactions

- Difficulty to diagnose: variety of forms and symptoms can overlap
- For a same brain disorder: different patient profiles, many care pathways

> In the absence of cure, there is increasing focus on:

1. Risk reduction, early detection and diagnosis, and timely intervention to slow down disease progression rate. It has also proved essential to put scientific evidence into care standards (see fig.2).

   Figure 2: Time matters: treat early and effectively, MS disease-modifying treatments "new treatment paradigm"[3]

2. Some brain disorders can be asymptomatic until it (the first attack or episode) occurs (in the case of **stroke**: ~10% is preceded by a transient ischemic attack). Biomarkers are increasingly researched. When there are no biomarkers, **primary and secondary prevention remain essential** (modifiable lifestyle factors such as physical inactivity, overweight, harmful use of alcohol, smoking cessation, and vascular risk factors, hypertension, diabetes mellitus, atrial fibrillation (anticoagulants). Parkinson's disease is one of the commonest neurodegenerative diseases that often begins with mild symptoms that advance gradually over time. Symptoms can be so subtle in the early stages that they go unnoticed, as there are **no PD-related biomarkers.**

Diagnostic tools available

Diagnostic tests and procedures are vital tools that help physicians confirm or rule out the presence of a neurological disorder, other medical condition or injury. There are **accurate tools to diagnose disease and to test how well a particular therapy may be working.**

> Laboratory screening tests (biological and genetic biomarkers)
Several different biological indicators (biomarkers) in body fluids such as **the brain and spine fluid (cerebrospinal fluid; CSF)** as well as the **blood** and **urine**, are proposed for use in the diagnostic of neurological disorders. In addition to **biological biomarkers**, recent research into genetic biomarkers for early PD for instance has also shown promising results[4].

> Neuroimaging techniques

Several neuroimaging approaches (various techniques to either directly or indirectly image the structure, function/pharmacology of the nervous system) are used as an additional tool in the examination of the brain in order to make a diagnosis of brain diseases[5]. For instance, **Computed Tomography (CT scan)** being used for detecting blood clots or bleeding in patients with stroke, **Magnetic Resonance Imaging (MRI)** to diagnose nervous system disorder such as multiple sclerosis, **Positron Emission Tomography (PET)** Scan being a nuclear diagnostic test, **Single Photon Emission Computed Tomography (SPECT)** Scan is a nuclear test used in patients with epilepsy for instance to help pinpoint the area of the brain involved in producing seizures[6].

Routine mental health screening

Routine mental health screening in primary care can detect possible symptoms of depression and other mental illness, much like a blood pressure test can identify AVC risk factors. Use of MMSE (Mini Mental State Examination) as a validated cognitive screening tool to identify adults with cognitive impairment.
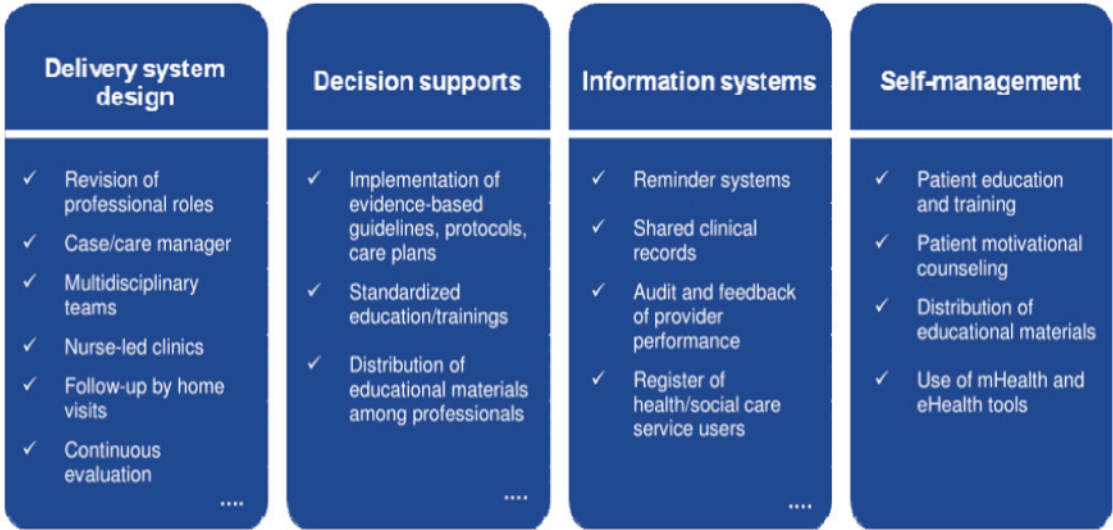
> Recent studies demonstrate that making mental health checkups routine is key to early identification and critical to prognosis for those who suffer from mental illness[7].
> MMSE is used by healthcare professionals to quickly assess cognitive functioning (e.g. for patients presenting dementia-like symptoms of mild cognitive impairment or patients with cognitive impairment associated with a cerebrovascular accident or traumatic brain injury) [8].

3. **Increasing research is needed to understand the progression of brain disorders and to develop new treatments that may modify their course, progression.**
> There have been huge advances in treatment in the last few years, particularly in Multiple Sclerosis with the development of disease-modifying therapies since early 2000s.
> In **epilepsy**, newer drugs have brought more treatment options. However, they do not reduce the prevalence of drug resistant epilepsy or prevent the development of epilepsy in patients at high risk, such as those with a traumatic brain injury.
> **Research** is **actively** looking at **potential disease-modifying treatments (e.g. anti-amyloid drugs), which were previously tested only in patients with AD dementia** with a view to stopping or slowing the course of the disease, are now being tested in selected asymptomatic populations who are at high risk of AD because of an established biomarker burden or a specific genetic profile[9].

4. Optimizing healthcare and removing treatment gaps by implementing initiatives around seamless, integrated care model: transformation of health care from fragmented care towards patient-centred and seamless care (see fig. 3).

Figure 3: **Achieveing quality, continuity of care and more efficiency:** proposed tools for better processes and outcomes

Delivery system design	Decision supports	Information systems	Self-management
✓ Revision of professional roles	✓ Implementation of evidence-based guidelines, protocols, care plans	✓ Reminder systems	✓ Patient education and training
✓ Case/care manager	✓ Standardized education/trainings	✓ Shared clinical records	✓ Patient motivational counseling
✓ Multidisciplinary teams	✓ Distribution of educational materials among professionals	✓ Audit and feedback of provider performance	✓ Distribution of educational materials
✓ Nurse-led clinics		✓ Register of health/social care service users	✓ Use of mHealth and eHealth tools
✓ Follow-up by home visits			
✓ Continuous evaluation			
....	....	....	

Source: Adapted from Nolte & McKee 2014

Many examples were highlighted during the 18th January meeting: **various forms of effective provider networks and interventions** have been set up at country level across Europe. The aim is for instance **to close the gap between primary and hospital services combining information and communication technology (eHealth) as facilitator** (in-hospital patient journeys, intra-extra muros care pathways, multidisciplinary care models based on the bio-psychosocial approach…) with **promising health outcomes and indication of worthwhile investment:** evidence on cost-effectiveness and sustainability is increasingly researched.

There are **effective interventions to be shared**. As illustrations, initiatives such as the "RAI" (Resident Assessment Instruments) for home care, RAI for mental health (RAI MH), the "hospitalization at home", … can be referred to as current initiatives which are being implemented in Europe.

- **RAI MH** is a comprehensive, multidisciplinary mental health assessment system for use with adults in facilities providing acute, long-stay, forensic, and geriatric services. The Resident Assessment Instrument-Mental Health (RAI-MH) comprehensively assesses psychiatric, social, environmental, and medical issues at intake, emphasizing patient functioning. Data from the RAI-MH are intended to support care planning, quality improvement, outcome measurement, and case mix-based payment systems.

- **RAI** for home care is the same instrument but used particularly for patients ranging from medically complex patients needing close attention to relatively well older adults who receive and require less formal support.

- **Hospitalization at home** is defined as a service that provides active treatment by health care professionals, in the patient's home, of a condition that otherwise would require acute hospital in-patient care, always for a limited period.

5. Addressing the marginalization and stigmatization of many disorders of the brain.

> **Case study preliminary results and literature review so far highlight that** an adequate implementation of evidence-based guidelines[10], cost-effective healthcare interventions and more research evidence **to develop better prevention and treatment options** definitely appear to be necessary (see fig. 4: Hospital intra-extra muros care pathways and seamless care), such as:

- **The availability of biological markers (biomarkers) for early disease diagnosis will impact the management of Alzheimer's Disease in several dimensions.** It will 1) help to capture high-risk individuals before symptoms develop, a stage where prevention efforts might be expected to have their greatest impact; 2) provide a measure of disease progression that can be evaluated objectively[11] ;

- **There is solid evidence on stroke unit care and integrated, multidisciplinary care team**, early use of intravenous thrombolysis with alteplase, and more recently, mechanical endovascular thrombectomy in acute ischemic stroke due to occlusion of the large arteries of anterior circulation[12] ;

- **Treat early and effectively new treatment paradigm**: precocious diagnosis and disease-modifying treatments (DMTs) at the early stage of the disease to slow down the progression rate are available to manage relapsing-remitting multiple sclerosis (RRMS)[13]. Since recently, based on the available evidence, clinically isolated syndrome (CIS) patients with visible abnormalities on MRI scans should receive DMTs prior to diagnosis[14].

- In the case of **schizophrenia**, one of the most severe and disabling mental illnesses, the treatment success rate with antipsychotic medications and psycho-social therapies can be high. Still, early identification and intervention at the prodromal phase is paramount[15].

- **Parkinson's disease** is challenging to diagnose, since there are no well-established biomarkers to determine if the disease is present. There is much research focused on trying to prevent cell loss and therefore to be neuroprotective, but as yet no neuro-protective agents exist and treatment remains symptomatic only. Medical (as well non pharmacological – physiotherapy) treatment is highly successful early on for PD[16].

- **Normal Pressure Hydrocephalus** is a treatable neurologic disorder (Ventrilo-peritoneal-shunt). Treatment by diversion of CSF to the peritoneal cavity or heart is successful in reversing symptoms of dementia, incontinence and gait disturbance in more than 80% of the patients. Idiopathic NPH is thus one of the few causes of reversible dementia, but it is still underdiagnosed.

- Early diagnosis of Restless Legs Syndrome is a major problem in the diagnosis of RLS. Patients often wait for many years before a diagnosis is made. Secondary prevention (proper case history) may lead to improvement of this situation. Assessing the severity of RLS can be done by using the RLS validated international rating scale[17].

- Medicalization overuse (/underuse) headache. This is significantly under-diagnosed[18]. The role of primary care and pharmacists is key. Implementation of structured headache services (usually 3 tier model, but always based in primary care) assumed to achieve higher coverage. Such intervention supported by educational initiatives aimed at both consumers and healthcare providers assumed to achieve better adherence.

- Up to 70% of people with **epilepsy** could become seizure free with anti-epileptic drugs (AEDs) treatment. In 25–30% of people with epilepsy the seizures cannot be controlled with drugs[19]. Epilepsy surgery is a safe and effective alternative treatment in selected cases. Investment in epilepsy surgery centres, could greatly reduce the economic and human burden of epilepsy. There is a marked treatment gap with respect to epilepsy surgery[20].

Figure 4: Hospital intra-extra muros care pathways and seamless care[21]

Health systems reforms in Europe are calling for **more efficiency savings with high societal value and re-organisation of care: new models of care** including a societal benefits approach are being examined for a better coordination, integration of care to overcome treatment gaps. **A key policy driver,** therefore, is to look at the outcomes or health benefits and to optimize healthcare sevices delivery (with high quality standards, better use of resources and interaction). **As referred by the WHO[22], a people-centred approach** promises to raise care quality, improve outcomes and enable better resource allocation, but most health systems are yet to fully embrace it. **Health spending is rising again in the EU** but not for more efficiency and performance, at the contrary. The **OECD Health Ministers forum**, in Paris in January 2017 put **waste reduction** in healthcare front and centre of the agenda[23].

As highlighted during **the Experts roundtable on 18th January,** the debate on value of treatment **is very timely.** Healthcare policy has been **dominated by cost containment**, and yet **need** is growing. This is the right time for policy recommendations reaching policy makers. A lot of money is spent on **low value care, rather than bringing optimal value for patient and society. Pinpointing the value of treatment and the cost of non-treatment** is therefore essential. **Measuring outcomes** will offer data on patient health outcomes, paramount to measure effective treatments. Such a goal requires a **combination of good clinical data with patient reported outcomes**. It's a common theme for **brain disorders:** patient and caregivers reporting is needed **to really assess value of treatment.** The OECD has common mandate to measure these outcomes. Ordinarily, **integrated or seamless care** is about **clinical integration, multidisciplinary teams, data… Health care systems** also need **integration of payment models and budgets**. Inconsistently, **budget is segmented**: prevention budget, primary care budget, drugs budget, etc. There should be one budget aimed at achieving certain health outcomes for the patients. Moreover, contradictorily to **early intervention, prevention budgets** have been **slashed**. And lot of the **cost savings will affect social care budgets.**

There is a **strong social gradient** (WHO social determinants of health) within **mental illness co-morbidity** in terms of cause, incidence, prevalence and consequence – most of them **are more common in economically disadvantaged groups.** This **inequality pattern** will be prominently discussed in **the EBC Policy White Paper.**

RESEARCH METHODOLOGY

EBC scope and vision: promoting a holistic healthcare approach (versus fragmentation and results in silo)

A large body of research links **early intervention** to **measurable health gains** such as improved survival rates, reduced complications and disability, **and lower treatment costs**. However, effective implementation of early diagnosis and treatment varies widely across health systems and many European countries are still lagging severely behind (with clinical practice variations even within countries).

The Value of Treatment case studies will address this.

The vision is clear: mental and neurological disorders, or **"disorders of the brain"** [24] **are complex and interlinked with hundreds of specific diagnosis, codified in diagnostic classifications systems** (WHO International Classification of Diseases, ICD-10[25] and American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, DSM-V[26]). Until recently, brain disorders were associated with disciplinary fragmentation in research and practice using different concepts and approaches. **There is today greater awareness on their burden and challenges to manage them,** and even **to prevent** some of them (modifiable risk factors reduction).

All this emphasizes the need for:

> **At healthcare level**, improving **the patient flow** in the whole process of care (care pathway)[27] for **better outcomes**;

> **At research level**, addressing **1) prevention and research gap (causes of many of brain disorders are uncertain) 2) prevention and the use of biomarkers for risk assessment - when available (e.g. Alzheimer's disease)** to identify patients with a brain disorder as **early** as possible in the disease stage; **3) policy implementation research** at healthcare level – when it has an impact demonstrated, to replicate in similar settings.

> **At macro health system governance level,** developing an **EU-wide research and public health combined Plan to address brain health in a comprehensive (biopsychosocial approach), transversal (across diseases) and collaborative way** [28].

Case studies research objectives, process and tools

The **Value of Treatment (VoT) research project** draws from the EBC Report "The Economic Cost of Brain Disorders in Europe" published in 2005 (Balak and Elmaci 2007) and updated in 2010 (Gustavsson et al. 2011) that **provided a solid estimation on the costs of brain disorders in Europe and enlightened necessary public health policy implications**.

'Patient-centeredness' for 'shared clinical decision making'

In the continuity of these findings and as highlighted in EBC Discussion Paper[29], **VoT** aims to propose the best return on investment solutions as well as provide evidence-based and cost-effective policy recommendations for a more patient-centred and seamless care model for brain disorders. Outcomes are assessed using clinical indicators and patient outcome indicators for defined patient groups.

Based on **research methodology** defined by two Academic Partners (the London School of Economics for the "economic evaluation" and the Rotterdam Institute of Health Policy and Management for the "patient journey analysis"), VoT is developing **case studies analysing (i) health gains and (ii) socio-economic impacts resulting from best practice health** (pharmacological, nonpharmacological and psychosocial) **interventions** (see fig. 5: EBC Value of Treatment research framework and data analysis).

The benefits of best clinical practice interventions will be compared with the current standard of care or, where appropriate, non-treatment. The comparisons will take account of **cost burdens** (including socio-economic costs) to **assess value**.

Case studies analysis are being conducted for **the following disorders:** *schizophrenia, Alzheimer's disease, idiopathic normal-pressure hydrocephalus, stroke, Parkinson's disease, epilepsy, headache, multiple sclerosis and restless legs syndrome.*

Figure 5: EBC Value of Treatment research framework and data[30] analysis
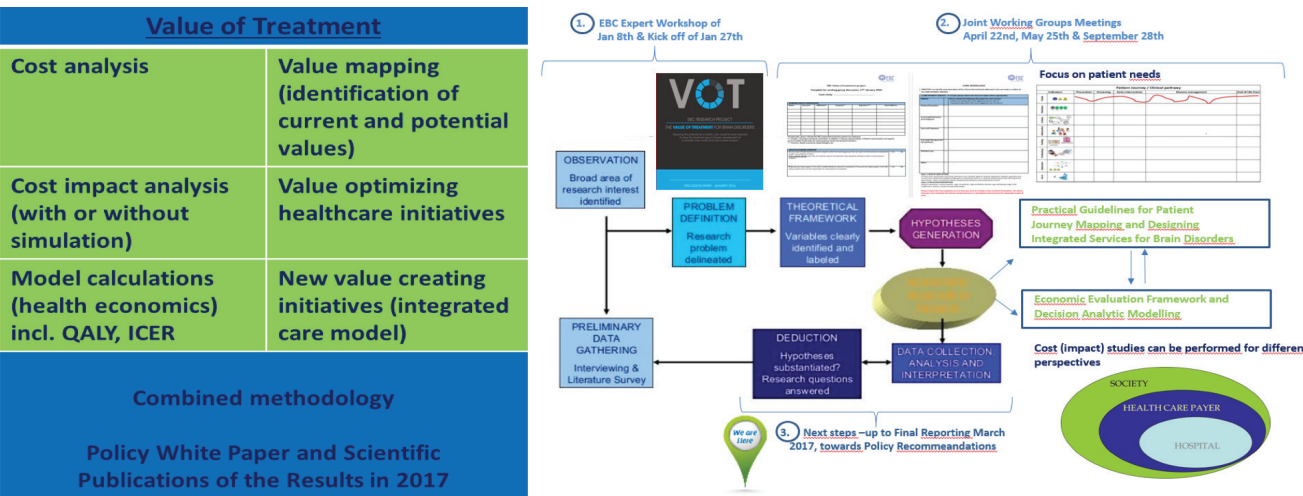
Objectives of the combined case studies methodology are twofold:

- **Patient's care pathway analysis** is to assess needs and identify gaps and opportunities for improvements in the current care pathway
- **Economic modelling** assessing the socio economic impact of specific clinical interventions targeted to close some of the gaps identified in the patient journey analysis

Analyzing the "**treatment gap**" or unmet needs **is central in the study**. A definition of the treatment gap "is the number of people with an illness, disease or disorder who need treatment but who do not get it"[31, 32] (see fig. 6). It is used **as an outcome measure in health care**.

Figure 6: Possible causes of the treatment gap[25]

ILLUSTRATION 1: ECONOMIC EVALUATION FRAMEWORK AND CASE STUDY ANALYSIS

Cost effectiveness analysis is performed (quantitative research) on prevention and care interventions in specific patient groups with aim to identify best buys for key contributors to disease burden. Type of study (decision analytic methods, population-based disease modelling) is defined based on the scope of the case study. Countries of focus for the case study are determined with the availability of data/evidence including epidemiology analysis. The treatment gap is assessed between current practice/non-treatment and best practice, looking at economic consequences to closing the gap (« how much we lose when we are not treating »). As far as possible, a consistent approach can be used in the coverage and measurement of economic impacts, in order to put the various interventions on a common ground and to allow comparisons between them and comparison of the same intervention when delivered in different country settings. With regard to the time frame and analytic horizon (the period over which costs/benefits of the health outcomes resulting from the intervention are measured) should be long enough as QALY, QoL, EQ5D are measured.

The economic model can look at whether investments in defined interventions can be cost saving in terms of use of health care services, social services, productivity at work (outcomes of rehabilitation programmes could be a better quality of life, improved general social functioning and better functioning in, for instance, performance at work and improved social contacts). For each intervention, economic modelling (using simple decision analytic modelling) will allow to produce a detailed breakdown of costs and consequences, year by year and by individual sector and budget type (long-term evaluation and long-term consequences).

DATA TOWARDS BUILDING ROBUST EVIDENCE

ILLUSTRATION 2: GUIDELINES - PATIENT CARE PATHWAY ANALYSIS FROM BOTH PATIENT AND CLINICIAN PERSPECTIVES

Patient care pathway analysis from both patient and clinician perspectives (qualitative approach) aims to highlight 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. Gap(s) is assessed along a set of indicators defined (such as access, adherence, satisfaction, QoL, EQ5D) and recommendations are proposed on how these can be improved.

Case studies research questions

The following questions were addressed to the Working Groups in order to **prepare reporting and were discussed during the 18th January plenary meeting to examine the best options towards three goals:** a public health policy impact, improve patients' quality of life and reduce the socio-economic burden.

• What is the amplitude of **current unmet needs** in health care in Europe? What is the width and breadth of so-called **"treatment gaps"**, not only within the provision of medicines and medical devices, but also within health care systems and services? **Obstacles** such as:

> misdiagnosis,
> delayed treatment, non-adequate treatment,
> non-adherence,
> unaffordable access to care and pricing incl. innovative therapies, reimbursement and social safety net cutbacks[33]…),

What is the **socio-economic impact** of targeting these gaps (e.g. avoidable costs…)?
What have we learned from the **"Patient Journey"** (clinical patient care pathway) analysis?

• What are the **new research developments** with regards to timely intervention to improve **[primary and secondary] prevention and treatment**, knowing that, as of today, there is no cure? What about the **potential benefits for integrated, coordinated care** combining effective team care and care planning? What are the **priorities for policy making** in the current context of health systems reforms (articulating their impact investment social return) and **legislation implementation**?

These questions are addressed in the following next sections:

1. BRAIN DISORDERS AND INCREASING BURDEN OF DISEASES
2. EBC CASE STUDIES
3. ADDRESSING THE NEEDS AND EARLY INTERVENTION AS A COMMON DENOMINATOR

ILLUSTRATION 3: TREATMENT GAP FOR NEUROLOGICAL DISORDERS SUCH AS DRUG-RESISTANT EPILEPSY.

The surgical treatment gap describes people with an illness who do not get the needed surgical treatment they need. For epilepsy this gap is very wide, even in well-developed countries. Misdiagnosis and no referral for epilepsy surgery rise up to 80% in some European countries. More should be done to address the high number of people who live with ongoing seizures[34]. **Seizures are not benign events.** They can lead to accompanying conditions such as anxiety, depression and increased risk of premature mortality. People experience seizure related injuries, impaired ability to establish families, inability to drive and with hospital admissions there are increased healthcare costs.
Optimizing healthcare - For patients with drug resistant epilepsy, their seizure control can be optimized, side effects minimized and quality of life maximized. Treatment options such as neurostimulation could help to close the treatment gap.
EBC case study is addressing these questions: what is the cost of non-treatment of epilepsy and how would access to new medical treatment/surgery change the socio-economic impact of drug-resistant epilepsy?

> **See EBC Case study page** 33

ILLUSTRATION 4: HEALTH ECONOMICS OF DEMENTIA PREVENTION

Increasing evidence that the disease process can start many years before the onset of cognitive impairment and dementia in people with AD has driven a shift in focus from advanced disease to earlier stages (healthcare services are less needed and costs are lower in the early stages of cognitive impairment than in the later stages of the disease), with trials for prevention (delaying or preventing disease onset) and treatment (targeting disease mechanisms to modify disease course) now targeting very similar groups of people in the preclinical stages of AD.
Assessing the benefits of delaying or preventing the onset of dementia from an economic perspective is complex. Approaches such as economic evaluations using a Markov decision-analytical model (multifactorial approach with a filter to select at-risk participants and sufficient statistical power in terms of sample size and intervention duration) can be beneficial for the estimation of prevention programmes cost-effectiveness.

> **See EBC case study on developing a simulation model** and estimating the impact of a hypothetical disease-modifying intervention page 26

Reporting requirements

Report Economic Evaluation (healthcare provider, societal perspective)	Report Patient Care Pathway Narrative (seamless care perspective)

Report Economic Evaluation
(healthcare provider, societal perspective)

1. **Discussion:** overall. The discussion section should be more limited than that typically found in a peer-reviewed manuscript.

2. **Discussion:** limitations. Study limitations must be discussed. Limitations shall include accuracy of any epidemiologic model and input data. Any implicit assumptions, such as an adequate supply of vaccine, should be mentioned.

3. **Discussion:** relation to other relevant studies. Results must be discussed in relation to other similar studies if such studies are available.

4. **Discussion:** how results may change. There must be an explicit discussion, typically drawing from the results of the sensitivity analyses, of how results would change if key assumptions or values were to change.

5. **Discussion:** policy implications. The report should include a discussion of the policy implications of the results and limitations. It will be responsibility of EBC to revise the overall text and make policy interpretations for final discussion with the WG leaders.

Report Patient Care Pathway Narrative
(seamless care perspective)

1. **Background and epidemiology analysis**

2. **Description of patient needs along the care process**

3. **Treatment gaps** (select two or three to be focused): In this section, the main factors underlying the treatment gaps identified along the journey are discussed from both a clinician and patient perspective. Moreover the factors of these treatment gap should be highlighted and the current clinical practice in comparison to the proposed improved scenario, evidence based practice or guidelines

 > deeper analysis confronting findings with lit. review (published evidence, EB diagnostic and treatment guidelines,…), experts and patients opinions

4. **Discussion:** policy implications. The report should include a discussion of the policy implications of the results and limitations. It will be responsibility of EBC to revise the overall text and make policy interpretations for final discussion with the WG leaders.

Overview case studies from a health care perspective to a societal perspective: work in progress (as per February 2017)

Mental disorder	Study objectives and settings
1. Schizophrenia	**Study objective:** to provide evidence-based information on what is available and needed to overcome the treatment gap in schizophrenia in a cost-effective manner (intervention strategies in the early illness course of schizophrenia). Areas of focus: 1) indicated prevention (when there are prodromal signs of an attenuated psychotic syndrome), 2) reducing the duration of untreated psychosis (DUP), 3) relapse prevention and risk reduction (recovery approach) **Setting:** specialist care with primary care, community care
Neurological disorder	**Study objectives and settings**
2. Alzheimer's Disease (AD)	**Study objective:** to develop a simulation model and estimate the impact of a hypothetical treatment for AD in terms of wellbeing and resource use costs in a population of people with memory complaints from a societal perspective **Settings:** memory clinics and various care provider settings during the progression of dementia (home setting, day care, hospital care and institutionalization)
3. Headache	**Study objective:** to develop an interventional model for headache management and to value the socio-economic impact and health gains of best practice in early detection (early intervention) compared with current care (/no treatment) in adult population **Settings:** structured headache services primary care, specialist care, pharmacists
4. Stroke	**Study objective:** to perform a systematic analysis of cost-effectiveness of the core acute and secondary treatment modalities in acute ischemic stroke: focus on Stroke Unit and capture LT benefits of secondary prevention **Setting:** secondary care (in-patient stroke unit) and primary care

5. Parkinson's Disease	**Study objective:** to identify issues and gaps (such as non-adherence) in the treatment of Parkinson's Disease (PD) in Europe, to work on the gaps at least for the most relevant issues and assess qualitative but also economic value of treatment for the identified gaps **Setting:** specialists care including primary care and rehabilitation specialists
6. Epilepsy	**Study objective:** « new » antiepileptic drugs have had little impact on the proportion with refractory epilepsy. A minority is suitable for surgery. Best option to improve QoL and efficiency is to ensure services are resourced and configured to meet patients needs. The study will aim to 1) assess the health and economic outcomes of ideal versus existing services and 2) propose a care model starting with diagnosed epilepsy **Setting:** specialists care
7. Multiple Sclerosis (MS)	**Study objective:** to value the socio-economic impact and health gains of primary prevention, early diagnosis (to slow down the progression rate) and treatment - Clinically Isolated Syndrome (CIS) and Relapsing-Remitting MS **Setting:** primary care, secondary care including rehabilitation specialists
8. Restless Legs Syndrome (RLS)	**Study objective:** to assess the current burden of RLS (as whole) to healthcare and society in Europe and address specific patient journey gaps pending on data availability (early intervention, etc…) **Setting:** primary care and specialists care
9. Normal Pressure Hydrocephalus (NPH)	**Study objective:** to assess the cost effectiveness of NPH treatment and to assess the socio-economic impact of NPH non-treatment (burden) and address unmet needs in order to:1) increase awareness; 2) improve the possibilities for diagnosis and treatment of NPH **Setting:** primary care and specialist care

1. BRAIN DISORDERS AND INCREASING BURDEN OF DISEASES

Alzheimer's disease and other dementias, schizophrenia, depression, stroke, migraines, epilepsies, Parkinson's disease, multiple sclerosis, sleep disorders, chronic pain, autism, addiction to drugs and alcohol and brain tumors will affect **at least one in three European citizens will be affected during their lifetime - currently 165 million people in Europe** (estimated **38.2%** of the EU population annually)[35].

Brain disorders[36] **are highly prevalent medical conditions, being the seat of many chronic disabling diseases**[37].

Brain disorders prevalence is increasing due to the **increase in life expectancy but also because of a number of socio-economic, environmental and behavioral health determinants that are still poorly understood. Their causes are heterogeneous** ranging from degeneration or immune processes to developmental and functional abnormalities, and frequently implicate a complex interplay between genetic and environmental factors. A better understanding of these causes is a necessity **to improve treatment and primary or secondary prevention.**

Today, mental disorders and other brain disorders **across the lifespan** represent **35% of the burden of all diseases in Europe**[38]**. And the burden of diseases is increasing.**

Direct costs of brain disorders make up for **60%**[39] **of the total costs** (40% attributable to lost productivity) – which EBC estimated at **800 bln€/year in Europe**[40]. At European level, this health budget far exceeds that of cardiovascular diseases, cancer and diabetes together[41]. **To compound this public health major issue and beside brain disorders escalating costs**, out of 10 individuals with a brain disorder, **from 3 to 8 remain inadequately treated although effective treatments exist** (except in the case of dementia where no effective, substantial symptom relieving treatment is available)[42]. **All types of cost increases** with the **severity** of the disease[43].

This is particularly **challenging for brain disorders** considering the **management of long-term conditions including co-morbidities, loss of independence, occurrence of acute, relapsing episodes and rehabilitation phases (motor, cognitive, social).**

Major depression together with stroke, dementias and alcohol use are among **the top four causes** in the **burden of disability** (in terms of DALY[44]) in the European region[45]. **The consequences extend well beyond the healthcare system**: loss of healthy life years and quality of life, **burdens** on health and social welfare systems, implications for labour markets (loss of productivity).

More than **half of people** **with chronic illness** have multiple conditions with **complex health needs, the so-called "high needs, high costs", a multiplier effect on the burden of disease**[46]**. Prevalence of co-morbidity increases with age** but is not just an issue for older adults[47]. The actual number of people with multimorbidity is **higher at younger age and is more common among those living in deprived areas (health inequalities)** (see fig. 7 and 8).

Fig. 7: Physical health risks for people with severe mental health problems & **Fig. 8**: Multimorbidity more common in deprived areas[48]
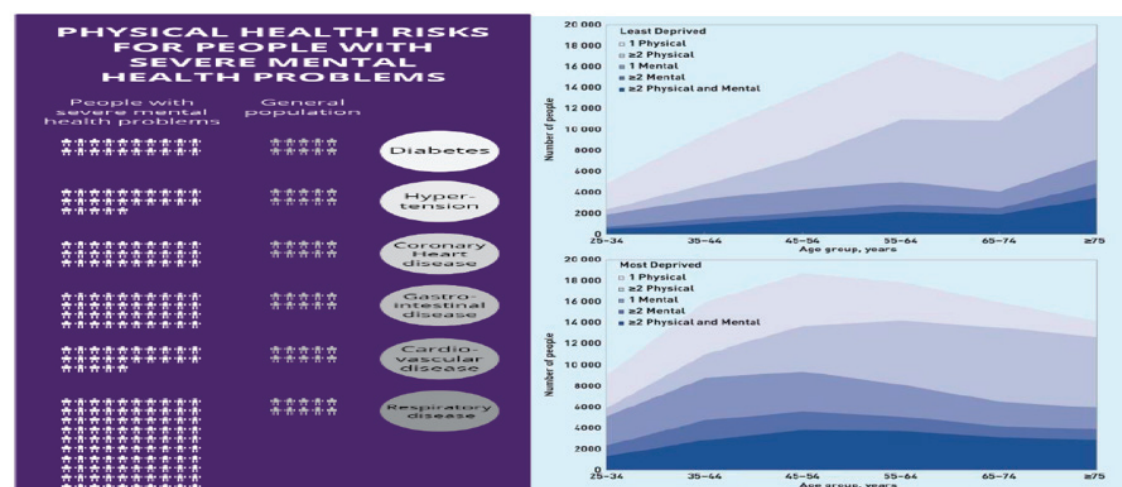
ILLUSTRATION 5

People with severe mental health problems such as schizophrenia and bipolar disorder face increased risk of physical health problems, including diabetes, hypertension, coronary heart disease and cardiovascular disease. Weight gain, metabolic change and smoking mean that most patients with severe mental illness by the time they reach 40 are already on a path which includes CVD, diabetes and premature death[49].

Co-morbid mental illness generates significant additional costs in and beyond the health-care system: co-morbid mental health problems raise total health care costs by at least 45% for each person with a long-term condition and co-morbid mental health problem[50]. **There is a strong economic case to be made for investment in interventions that promote/preserve the physical health of people with mental illness: screening and early intervention are essential with a key role identified in primary care.**

2. EBC CASE STUDIES

> Note: below information is gathered from Working Groups presentations at the Plenary Meeting of 18 January 2017 and LSE completed templates, as well as background additional literature research – Content in progress.

2.1. Scope of EBC case studies analysis - Mental disorders

Schizophrenia[51, 52]

Schizophrenia is **the most common form of psychotic disorder.** It affects **7 in 100 adults**, onset typically between the age of 15 and 35.

Schizophrenia remains the most common cause of major psychosis and can have devastating consequences

It is usually associated with a prodromal period brief of 1-3 years, and in very high risk patients 20-40% "transition" to schizophrenia within a year. **During the prodromal period, brief intermittent psychotic symptoms may appear.**

Psychosis and schizophrenia are commonly associated with anxiety, depression, post-traumatic stress disorder (PTSD), personality disorder and substance misuse.

Poor physical health is strongly associated with schizophrenia, with men dying 20 years and women 15 years earlier than the general population.

Although many people with acute psychosis respond to drugs, 80% relapse within 5 years.

Approximately 50% have a moderately good long term outcome. In the last decade, there has been **much more emphasis on early detection and intervention**, with a more positive approach to long-term recovery (back to work).

EBC case study scope from a healthcare and societal perspective

To value the socio-economic impact and health gains of 3 identified main scenarios (care interventions): 1) indicated prevention (when there are prodromal signs of an attenuated psychotic syndrome); 2) reducing the Duration of Untreated Psychosis (DUP) and 3) relapse prevention and risk reduction (recovery approach)

> Care pathway "patient journey" analysis highlighting treatment gaps - based on defined patient profiles (and needs) and description of disease symptoms and progression:

- individuals at risk of developing schizophrenia
- patients after first relapse of schizophrenia
- patients with episodic course of illness

Care pathway services addressed: early detection/prevention, early treatment to reduce DUP, preventing relapse

Major gaps highlighted:
- **lack of general awareness and stigma associated with mental illness**
- **non-availability of preventive and early intervention guidelines and sevices**
- **inadequate education of patients and families**

> Economic evaluation: ONGOING - development of economic model to explore the economic impact of indicated prevention, reducing the duration of untreated psychosis (DUP) and relapse prevention on outcomes and costs for young people **Country settings used:** UK, Czech Republic, possibly also Netherlands (Early detection model)

2.2. Scope of EBC case studies analysis - Neurological disorders

Alzheimer's disease – Dementia[53, 54, 55, 56, 57, 58]

Dementia affects **5% over 65, and 20% over 80**. Alzheimer's disease is thought to account for 60% of dementia cases followed by vascular dementia, mixed dementia, and dementia with Lewy bodies.
The prevalence (8.7 million) in the EU is expected to double by 2040. It is estimated that only 50% of people are diagnosed so the actual number of cases is likely to be much higher than the figures suggest.
The total cost of illness of dementia disorders in EU27 in 2010 was estimated to 160 billion € (€22 000 per demented per year), of which 56% were costs of informal care. Costs increase with dementia progression.

Dementia contributes to 1 in 4 hospital admissions and of all the chronic diseases is one of the most important contributors to dependence and disability.

As many as 80% of people with Parkinson's disease develop dementia.

Early diagnosis improves the quality of life of people with dementia and their families. The principal goals for dementia care are:

- Diagnosing early
- Optimizing physical health, cognition activity and well-being
- Detecting and treating behavioral and psychological symptoms
- Providing information and long-term support to caregivers

Diagnosis is difficult because of the insidious onset and difficulty in differentiating this from "normal ageing". Family concern is of particular importance. **A key role of primary care** is to exclude a potentially treatable reversible cause of the dementia. The potentially reversible causes of memory loss are depression, thyroid disturbance, vitamin B12 deficiency.

In the absence of cure [no interventions that cure or alter the LT progression of dementia], a belief that nothing can be done has contributed to delays in diagnosis.

However, increasing evidence showing that dementia may be preventable has led to an international focus on earlier diagnosis and intervention[59, 60].

- Earlier diagnosis of dementia is being encouraged by national dementia strategies in some EU countries. Population based screening is not recommended and there is evidence that screening for Alzheimer's disease is not beneficial. There is now greater emphasis on prevention and risk reduction with a proactive process of memory assessment of at risk groups (case finding of mild cognitive impairment MCI).
- Arguments for case finding is based on the premise that early diagnosis allows:
  For advanced care planning at a stage when the patient is able to contribute to planning - Exclude other reversible causes of memory loss e.g. depression - Allow for treatment of other risk factors e.g. vascular, which may affect progression - Initiate support at an early stage and, if appropriate, treatment

More research is needed on the cost-effectiveness of case finding. Amyloid aggregation can now be detected early (25 years before onset) - asymptomatic. This is a theoretical model as new treatments are coming up. New drugs are being tested early. Simulation modelling will assess if a disease-modifying therapy, that could keep patients from progressing to the costly dementia phase, could have a profound effect on societal burden.

EBC case study scope from a healthcare and societal perspective

To estimate the socio-economic impact of early diagnosis and early hypothetical treatment (disease-modifying intervention) initialized in the pre-dementia state of AD (normal cognition NC stage or mild cognitive impairment/MCI stage).

> Care pathway "patient journey" analysis highlighting treatment gaps - based on defined patient profiles (and needs) and description of disease symptoms and progression:
Patients and caregivers in early symptomatic stages of AD.
Interviews conducted to collect information (N=6, VUmc Alzheimer Center) in addition to Alzheirmer's Europe data

> Economic evaluation: to develop decision analytic modelling and estimate the impact of a hypothetical disease-modifying intervention (that will slow the progression of AD) in terms of well-being and resource use costs in a population of people with memory complaints from a societal viewpoint.

Country setting used: Netherlands

Parkinson's disease[61, 62, 63]

Parkinson's disease (PD) **is the second most common chronic, progressive neuro-degenerative disease** (Alzheimer's being the first) and whilst treatments are still lacking to delay disease progression, there is a wide range of evidence-based therapies for motor and non-motor complications.

In industrialized countries, the prevalence of Parkinson's disease is about 1% for people over 60, with estimates of up to 4% for people in the highest age groups. It is rising in prevalence with the ageing population, and is expected to double by 2030. Socioeconomic impact of PD is important. In Europe, Gustavsson et al (2011) estimated the 2010 cost of Parkinson's disease to be €13.9 billion.

All suspected cases should be **referred** by GPs for specialist confirmation before starting treatment. This is partly to exclude common mimics e.g. cerebrovascular disease, Alzheimer's, cerebellar ataxia etc.

Early diagnosis improves the quality of life of people with Parkinson's disease and their families.

Diagnosis depends on the presence of bradykinesia plus one of rigidity, rest tremor or postural instability (in elderly person with bradykinesia and postural instability, PD is a possible cause). **>** Unilateral onset with persisting asymmetry and slow progressive course are characteristic

The symptoms of PD are caused by two processes: cellular degeneration within the substantia nigra and a resulting deficiency of dopamine.

There are **drug treatment of motor symptoms** of PD and **drug treatment options for non-motor symptoms** of PD. All drugs are for symptomatic benefit and none influence LT progression. **>** Non-motor symptoms maybe present from the outset, especially depression, fatigue and sleep disorders. Dementia, autonomic dysfunction and psychosis are common later in the disease.

There is much research focuses on trying to prevent cell loss and therefore to be neuro-protective, but as yet **no neuro-protective agents exist and treatment remains symptomatic only.** **>** **Trials are on-going for neuroprotection**, including anti-oxidants (there is much interest in glutathione), nicotine patches (the incidence of PD is lower in smokers) and surgical 'deep brain stimulation'.

Non-pharmacological interventions exist. Before considering drug treatment, evidence indicates that all patients should be strongly encouraged to exercise. Exercise for patients with PD is important and also difficult. Ideally all patients should be referred for supervised exercise programmes and/or physiotherapy.

EBC case study scope from a healthcare payer perspective

To value the socio-economic impact and health gains of early diagnosis and treatment. More specifically to identify issues and gaps in the treatment of Parkinson Disease (PD) in Europe, to work on the gaps for the most relevant issues and assess qualitative but also economic value of treatment for the identified gaps

> Care pathway "patient journey" analysis highlighting treatment gaps - based on defined patient profiles (and needs) and description of disease symptoms and progression:
Information based on survey "What matters most" conducted by Parkinson's UK in 2016 with 1,047 persons (mainly patients and family members)

> Economic evaluation: to assess the economic impact of non-adherence to treatment; 2) cost effectiveness of advanced treatment in PD and 3) economic impact of early diagnosis&treatment; non-motor symptoms

Country settings used: Germany and UK

Multiple Sclerosis[64, 65, 66, 67]

Multiple sclerosis is **an inflammatory demyelinating and degenerative disease of the central nervous system** and the most common cause of serious physical disability in working age adults.

- Prevalence estimate in Europe 1 per 1.000 and incidence increasing
- Twice as common in women, typically presenting aged 20 to 40

Considerable social impact and economic consequences. Non-medical costs and informal care dominate the costs of MS. Disease modifying treatments (DMTs) are also costly but can have an impact in slowing disease progression. All types of costs increase with increasing severity of the disease. Also, similar drop in quality of life with increased disability.

The cause remains unknown. It is an acquired immune-mediated inflammatory disease believed to be due to an abnormal immune response to environmental triggers in people who are genetically predisposed.

The initial inflammatory phase is followed by a progressive degenerative phase due to neuronal damage. The most common pattern is relapsing-remitting MS (RRMS)

- 85% have RRMS at onset
  > disease modifying therapy (DMT) reduces relapse rate
- 66% with RRMS go onto develop secondary progressive MS (SPMS)
  > DMT however does not reduce secondary progression
- 15% have primary progressive MS (PPMS) at onset, where symptoms do not remit but gradually progress and worsen from onset
- A sub-set of RRMS is 'rapidly evolving severe RRMS' (RES) defined by 2 or more disabling relapses in one year

There is increasing evidence that early diagnosis and treatment may delay or prevent the previously inevitable disability, DMT is mainly reserved for RRMS and since recently for Clinically Isolated Syndrome (CIS) patients. However, despite the considerable success with **new disease-modifying therapies that reduce relapse frequency**:

- over half of people develop non-relapsing secondary progressive MS 10 to 20 years after the onset of RRMS.

At the end of the spectrum of care, there is an increasing range of treatment options for those with disability. NICE Guideline 2014 recognize the crucial role of the GP in the long-term management of MS relapses, exacerbations and fluctuations, and associated disabilities. Overall, a multi-disciplinary approach is needed to manage MS symptoms.

Diagnosis remains **a specialist clinical diagnosis** (MRI) based on the dissemination of clinical attacks and lesions in time and space using the McDonald criteria.

- Importance of early treatment: the progression of MS will increase significantly if left untreated or treatment is delayed. Beginning treatment early shows lower amounts of progression, which supports beginning treatment at the time of diagnosis.

There are currently **no biomarkers** that are pathognomonic for a diagnosis of Clinically Isolated Syndrome (CIS) or MS.

EBC case study scope from a healthcare and societal perspective
To value the socio-economic impact and health gains of prevention, early diagnosis (to slow down the progression rate) and treatment.

> Care pathway "patient journey" analysis highlighting treatment gaps - based on defined profiles (and needs) and description of disease symptoms and progression.
Information based on semi-structured interviews (N=2, one patient with RRMS and one patient with progressive MS, conducted by the European Multiple Sclerosis Platform (EMSP), Aug. 2016)

> Economic evaluation: averting MS LT societal /health care costs.
1) Assessment of the socio-economic impact of early treatment to reduce conversion from Clinically Isolated Syndrome (CIS) to definite MS. Although the economic impact of early use of DMTs has been addressed in a limited number of studies only, these have indicated that initiation of a DMT in the early stages of disease (after diagnosis of RRMS or even at the stage of Clinically Isolated Syndrome CIS) may be cost-effective in the long term. The outcome of reduced relapses, hospitalization and indirect costs and QALYs gained seemed to outweigh the long-term costs of DMTs, although more research is needed to gather evidence of long term benefit.

2) Prevention of MS through lifestyle modifications in the general population (challenging) with a focus on removing/reducing exposure to smoking and promoting sun exposure/ vitamin D supplementation.

Country settings used: Italy, Sweden and Spain

Stroke[68, 69, 70, 71]

Stroke is **one of the top three causes of death in Europe**. Despite improvements in care, around one third of the 1.3 million people who have a stroke in Europe each year will not survive. One third will make a good recovery, but one third will live with long-term disability.

Stroke remains the leading cause of severe adult disability, so further understanding of stroke, implementation of preventive measures, and improvements in rehabilitation is vital.

Stroke is more likely to occur with ageing, with 75% of strokes happening to people aged 65+. Women have a higher risk for stroke.

- Overall incidence of stroke in Western countries is approximately 2.400 per year per million inhabitants.
- Stroke is costing Europe over 64 € billion a year
- About 80% of stroke is ischemic in nature. A lot has become known about the pathophysiology of ischemic stroke in the past decades. Several treatments have been proven effective, in acute treatment as well as in secondary prevention of new strokes.

It is mainly asymptomatic until stroke occurs (~10% preceded by TIA). It is a largely preventable condition by attention to and treatment of vascular risk factors including hypertension, diabetes mellitus, physical inactivity, dyslipidaemia, smoking, atrial fibrillation (anticoagulation)

In the acute phase, there is solid evidence on the stroke chain of survival (time is brain) and stroke unit care, for early use of aspirin, intravenous thrombolysis with alteplase, salvage hemicraniectomy, and more recently, also mechanical endovascular thrombectomy in acute ischemic stroke due to occlusion of the large arteries of anterior circulation. **Multidisciplinary teamwork is a key characteristic.**

For secondary prevention (prevention of new strokes), there is also solid evidence on antiplatelet therapy, statins, blood pressure lowering, carotid endarterectomy (in patients with symptomatic carotid stenosis), and oral anticoagulants (in patients with atrial fibrillation). It has been estimated that combined adequate use of all secondary preventive strategies could reduce new ischemic strokes by 80% or more.

Primary preventive efforts of high blood pressure control and modifications of life style factors apply also to patients who already have had a stroke event.

> Several studies have shown that there still exists a large gap between this evidence and the effective implementation of these interventions in the field. Addressing the treatment gap should reduce the number of avoidable ischemic strokes and costs.

EBC Case study scope from a healthcare payer perspective
To perform a systematic analysis of cost-effectiveness of the core acute and secondary treatment modalities in acute ischemic stroke, collect data on the use and non-use of these treatment modalities and estimate the cost burden of non-treatment of Stroke in selected EU countries and the cost saving by implementing high quality stroke units.

> Care pathway "patient journey" analysis highlighting treatment gaps - based on defined patient profiles (and needs) and description of disease symptoms and progression Information based on lit. review, experts input and SAFE shared data.

> **Economic evaluation: to assess the cost of not treating stroke although effective therapies exist**

Country setting used: UK NHS based data

Epilepsy[72, 73, 74]

Epilepsy is a condition characterized **by recurring seizures caused by abnormal and excessive electrical activity in the brain. Head injuries, brain infections and strokes may cause epilepsy.**

The World Health Assembly (May 2015) approved the WHO Resolution on the Global Burden of Epilepsy.

Epilepsy has considerable social impact and economic consequences.
Avoiding premature death in epilepsy:

- An estimated 1.16 per 1,000 people with epilepsy die suddenly and prematurely each year
- Sudden death in epilepsy peaks in young adults, especially men
- A 20 year old man with epilepsy has a 1% chance of dying before the age of 30
- Epilepsy is second only to stroke in years of life lost to neurological disease
- 30% of deaths are accidents, mostly from drowning or burns

Many of these deaths are unavoidable, but there is evidence to suggest that improved care may result in fewer untimely sudden deaths.

Specific risk factors for death in epilepsy have been discovered, these include: alcohol problems; failure to collect anticonvulsant prescriptions in the preceding 3 to 6 months; a history of injury in the previous year; depression (due to poorer seizure control, often through non-adherence to treatment); tonic-clonic seizures that have increased in the frequency in the last 6 months.

Early and accurate diagnosis can be an issue **from first seizure to appropriate epilepsy diagnosis (delayed diagnosis)**. A risk assessment tool needs to be developed to automatic-ally identify these **high risk patients**. In the meantime, GPs need to take a pro-active approach in looking for and managing these risk factors to try to reduce sudden death in epilepsy.

Referrals to specialists first seizure clinic and treatment with antiepileptic drugs (AEDs) adequately controlled.

- **Symptoms** can be successfully treated in most patients with one or more antiepileptic drug. About two in three adults with new onset epilepsy will achieve lasting seizure remission on or off these drugs, although around half will experience mild to moderately severe adverse effects.

- **Patients with epilepsy, especially the 20-30% whose seizures are not fully controlled with available drugs (drug resistant epilepsy)**, have a significantly increased risk of death, as well as psychiatric and somatic comorbidities, and adverse effects from antiepileptic drugs (referral for surgery).

Newer drugs have brought more treatment options, and some such as levetiracetam cause fewer drug interactions and less hypersensitivity than older ones. However, they do not reduce the prevalence of drug resistant epilepsy or prevent the development of epilepsy in patients at high risk, such as those with a traumatic brain injury.

- The development of antiepileptic drugs urgently needs to be revitalized so that more effective antiseizure drugs can be discovered for the treatment of drug resistant epilepsy, including catastrophic forms. **Antiepileptogenic agents to prevent epilepsy before the first seizure in at risk patients and disease modifying agents to control ongoing severe epilepsy associated with progressive underlying disease** are also needed.

Attention to the psychosocial, cognitive, educational and vocational aspects is an important part of comprehensive epilepsy care.

EBC Case study scope from a healthcare and societal perspective
To perform a systematic analysis of cost-effectiveness of the core acute and secondary treatment modalities in acute ischemic stroke, collect data on the use and non-use of these treatment modalities and estimate the cost burden of non-treatment of Stroke in selected EU countries and the cost saving by implementing high quality stroke units.

> Care pathway "patient journey" analysis highlighting treatment gaps - based on defined patient profiles (and needs) and description of disease symptoms and progression
Focus on high risk patients with a patient pathway description taking into account first seizure, new epilepsy, early refractory and highly refractory

> Economic evaluation: to model the benefits of an ideal neurology service versus a less good service

Country setting used: UK data

Restless Legs Syndrome[75, 76, 77, 78]

Restless legs syndrome/Willis-Ekbom disease (RLS/WED) refers **to an overwhelming urge to move the legs**, usually associated with unpleasant sensations. The urge to move the legs is worse at rest and at night and relieved by movement.

RLS/WED is commonly associated with sleep disturbance and with involuntary, jerking movements of the legs during sleep, known as periodic leg movements of sleep (PLMS).

- Reported RLS general prevalence rates ranged from 4% to 29% of adults in North America and Western Europe
- RLS severity can be assessed with international rating scale.
- RLS may lead to socio economic problems where the patient is no longer able to work. Chronic sleep deprivation due to nocturnal RLS symptoms is one major reason for disability.

Primary prevention: risk groups for Restless Legs Syndrome (RLS) are e.g. the genetically predisposed, pregnant women, patients using antidepressants, patients on renal dialysis, patients with iron deficiency with or without anemia, patients with polyneuropathy, or diabetes, patients with a positive family history of RLS.

Early diagnosis: this is a major problem in the diagnosis of RLS. Patients often wait for many years before a diagnosis is made. Secondary prevention (proper case history) may lead to improvement of this situation.

Care and treatment: worsening of the RLS symptoms over time, eventually leading to comorbidity, or vice versa (comorbidities will worsen with additional RLS symptoms such as chronic sleep deprivation) is an important element of the disease.

Not only is the disease itself **chronic progressive**, a major point of attention is the phenomenon called **"augmentation"**: the drugs available as first choice treatment (dopamine agonists) have severe side effects and cause deterioration of the symptoms, if used at higher dosages or in a chronic manner over years.

EBC Case study scope from a healthcare and societal perspective
To compare the socioeconomic burden of RLS with that of other chronic diseases (eg coronary diseases, diabetes, depression, osteoarthritis, Parkinson's disease); 2) to assess the economic burden of untreated RLS and therefore model the added value of shifting the portion of patients currently not diagnosed/untreated to diagnosis/treatment.

> Care pathway "patient journey" analysis highlighting treatment gaps – based on defined patient profiles (and needs) and description of disease symptoms and progression
  3 patient profiles 1) patient with missed diagnosis; 2) patient with insufficient response to treatment; 3) patient with augmentation as a result of dopamine agonist therapy in high dosage

> Economic evaluation: despite very limited data, aim will be to showcase the burden of RLS in Europe and to address the following treatment gaps identified in the patient journey: missed diagnosis, augmentation and insufficient response

Country settings used: France, Germany, Italy

Headache disorders[79, 80]

The first and highest barrier to effective health care for **headache (including tension-type headache, migraine, and medication-overuse headache)** is failure to seek treatment. There is **evidence that interventions (part of the interventional model) are highly cost effective** using the WHO-CHOICE model (and Russian data expanding to Italy with an economic impact analysis of migraine).

For migraine, the specific interventions are the timely use of appropriate effective and cost-effective medications used in stepped-care paradigm (simplest and cheapest first, moving on to the more costly treatments for those proved to need them)

- Headache disorders are the **third highest cause of disability measured in years of life lost to disability (YLDs)** according to GBD 2010.
- "Chronicisation" is a real issue, it creates the severity in migraine
- Co-morbidities: depression, obesity
- Chronic disease with acute, episodic episodes
- Biopsychosocial approach

Lifting the burden has estimated the financial cost of headache disorders to Europe at well over 100 billion eur per year, >90% of this in lost productivity. About half of this cost is attributed to migraine.

EBC Case study scope from a healthcare and societal perspective
To develop a headache interventional cost saving model for structured headache service including primary care and specialists care and pharmacists. Interventional model has been developed

> Care pathway "patient journey" analysis highlighting treatment gaps – based on defined patient profiles (and needs) and description of disease symptoms and progression
  Implementation of structured headache services (usually 3 tiered, but always based in primary care) assumed to achieve higher coverage. Such intervention supported by educational initiatives aimed at both consumers and healthcare providers assumed to achieve better adherence

> Economic evaluation: to estimate cost-effectiveness of treatments with known efficacy (RCTs) and delivered through structured headache services supported by education

Country setting used: Russia, Lombardi model

Normal Pressure Hydrocephalus[81]

Normal pressure hydrocephalus (NPH), also termed symptomatic hydrocephalus, is **a type of brain malfunction caused by expansion of the lateral cerebral ventricles and distortion of the fibers in the corona radiata. The term «normal pressure» is somewhat misleading.**

Hydrocephalus is a common condition in which there is too much cerebrospinal fluid (CSF) in the ventricles. This occurs when the natural system for draining and absorbing extra CSF is dysfonctioning. The ventricles enlarge to accommodate the extra fluid and then press on different parts of the brain, causing a number of different symptoms.

Its typical symptoms are urinary incontinence, dementia (similar to those of Alzheimer's disease), and gait disturbance (difficulty walking).

The usual treatment is **surgical installation (neurosurgery) of a ventriculoperitoneal shunt to drain excess CSF into the lining of the abdomen where the CSF will eventually be absorbed.**

- NPH epidemiology: 65+ (up to 5%). Patients with dementia who are confined to a nursing home and may have undiagnosed NPH can possibly become independent again once treated. So far there are few data, one study in Norway evaluated the prevalence of NPH, both diagnosed and undiagnosed, among residents of assisted-living facilities, showing a prevalence in 9 to 14% of the residents.

NPH is a treatable neurologic disorder (Ventrilo-peritoneal-shunt). Treatment by diversion of CSF to the peritoneal cavity or heart is successful in reversing symptoms of dementia, incontinence and gait disturbance in more than 80% of the patients. Idiopathic NPH is thus one of the few causes of reversible dementia, but it is still underdiagnosed.

- NPH is a very common progressive, severe but underdiagnosed and undertreated disease.
- Diagnosis of NPH is usually first led by brain imaging, either CT or MRI, to rule out any mass lesions in the brain. This is then followed by lumbar puncture and evaluation of clinical response to removal of CSF. Persons with the diagnosis of NPH and limited comorbidity could be treated with shunt but NPH is not known (wrong interpretation of imaging).

Neurosurgery research highlights that medical expenditures for patients with NPH treated with shunt surgery are significantly lower than expenditure for untreated patients.

- Cost of non-treatment is an important aspect. Early surgery show the best results: early treatment (surgery) expected outcomes are improved quality of life and independence. Findings indicate that the shunt operation can reduce the caregiver burden.

There is a need for more research on NPH to foster multidisciplinary care.

EBC Case study scope from a healthcare and societal perspective
To assess the cost effectiveness of NPH treatment and to assess the socio-economic impact of NPH non-treatment (burden) and address unmet needs in order to 1) increase awareness and 2) improve the possibilities for diagnosis and treatment of NPH.

> Care pathway "patient journey" analysis highlighting treatment gaps – based on defined patient profiles (and needs) and description of disease symptoms and progression
Treatment gaps identified are related to 1) uncertainties (clinical deterioration, diagnosis not clear, late and/or wrong diagnosis), 2) limited access to specialized care and inadequate monitoring and support

> Economic evaluation: to assess the cost-effectiveness of addressing the treatment gap in NPH population

Country setting used: Germany

3. ADRESSING THE NEEDS AND EARLY INTERVENTION AS A COMMON DENOMINATOR

3.1 Health services challenges to bridge the treatment gap

Primary care is increasingly taking on a greater role in both the assessment and the long-term care of people.

Mental health services

According to the WHO, **treatment is hindered by several factors**:
- attitudinal barriers, including stigma associated with receiving treatment
- inadequate resources devoted to mental health sector
- spread of the low wage non-standard employment, accentuating financial barriers to treatment
- inadequate emphasis on early treatment and psychiatric diagnosis for children and adolescents
- lack of integration of mental health into primary care facilities; disproportionate emphasis on psychiatric institutions compared to cost-effective community-based services
- information-related barriers, including non-existent population-based surveys and poor surveillance systems in many countries[82].

There are also **no consistent indications of improvements** with regard to **delayed diagnosis and treatment provisions, with considerable differences in the treatment gap within and between countries** (health inequalities)[83]. Many mild to moderate mental disorders are under-diagnosed and untreated[84].

Overcome barriers and model shift
Across Europe, much effort has been made over recent decades to overcome these barriers and to ensure high-quality longer-term care.

These efforts started with new pharmacological treatments for psychoses which radically changed the prognosis of severe mental disorders, and the emergence of new psychosocial interventions and new concepts of mental health care organization in several European countries. Sector psychiatry in France, social psychiatry and mental health in primary care in the UK, psychiatric reform and deinstitutionalization in Italy[85] as well in Belgium ("Psy107")[86] became significant landmarks.

These initiatives have been followed by a multitude of developments **to advance mental health care in many European countries**: improvements in the living conditions in psychiatric hospitals, development of community services, integration of mental health care within primary care, development of psychosocial care (housing, vocational training), protection of the human rights of people with mental disorders and increasing participation of patients and families in the improvement of policies and services[87]. Research into many of these developments has provided an increasing evidence base to guide investment into appropriate mental health care systems.

Nowadays there is a **broad consensus on the need to shift from the model of care based on the traditional large psychiatric institutions to modern comprehensive community-based models of care, including acute patient units at general hospitals[88]**.

Accessibility to mental health care for people with longer-term mental disorders is much better with community-based services than with the traditional psychiatric hospitals: **greater user satisfaction and increased met needs, better continuity of care, more flexibility**, making possible to identify and treat more often early relapses, and to increase adherence to treatment. **These services better protect human rights** of people with mental disorders and prevent stigmatization.

Studies:
- show significant better outcomes on adherence to treatment, clinical symptoms, quality of life, housing stability, and vocational rehabilitation.
- suggest that care in the community for acute psychoses is generally more cost effective than care in a hospital, although these results cannot be generalized to all patients requiring admission to psychiatric beds.
- also show that, for patients who require prolonged stays in the hospital, hostel wards provide a cost-effective alternative preferred by the patients themselves. Other studies show that, when deinstitutionalization is correctly developed, the majority of patients who moved from hospital to the community have less negative symptoms, better social life and more satisfaction.

However, institutions such as the WHO[89, 90, 91] indicates that **much more has to be done to provide accessible, effective and high quality longer-term mental health care to all people with severe mental disorders in Europe.**

EBC case studies analysis demonstrates the benefits of early intervention.
In disorders management, "time is brain". Early intervention in primary care and community care is paramount, meaning also early referral from the GPs to specialists care (psychiatrists).

ILLUSTRATION 7- EARLY INTERVENTION TO PREVENT PSYCHOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS[92]

It is usually associated with a prodromal period of 1-3 years, and a very high risk patients 20-40% 'transition' to schizophrenia within a year. The prodromal period is characterized by:

- **Non-specific psychological and physical symptoms** with functional deterioration
- **Brief limited intermittent** psychotic symptoms

This meta-analysis included 11 RCTs n=1246 looked at psychological and pharmaceutical interventions which may have an impact. They found:

- **Individual CBT** with or without family therapy could reduce transition rates to schizophrenia by almost half at 12 months (RR 0.54, 95% CI 0.34 to 0.86)

In absolute terms, very high risk patients risk of transition was reduced from 30% to 16% and high risk patients from 10% to 5.4%

Overall 5 trials of CBT had a moderate effect on transition to psychosis at 12 months

- **Psychological interventions** also reduce the severity of symptoms
- **There was no significant evidence** that pharmaceutical interventions delay or prevent transition

Conclusion

Individual CBT with or without family psychotherapy can help prevent transition to schizophrenia. CBT, no antipsychotic drug therapy, is the most sensible first line treatment for people at high risk to prevent progression to schizophrenia. This research has strongly influenced the recent NICE guidelines[93].

> See also EBC case study on schizophrenia p25

Routine mental health screening in primary care can detect symptoms of depression and other mental illness, much like a blood pressure test identify possible AVC risk factors. Recent studies demonstrate that making mental health checkups routine is key to early identification and critical to prognosis for those who suffer from mental illness[94]. **Primary care settings are ideal for implementing mental health checkups to ask adolescents about their emotional and behavioral health**, given the regularity with which patients can see their GPs and the existing screening practices already in place there for other health issues. **Validated screening questionnaires** proven to accurately assess potential mental health disorders are widely available at little or no cost[95]. Reimbursement and adequate referral resources remain the two most significant challenges to mental health checkups in primary care.

Neurological health services

Insufficient diagnostic services remain a major barrier to the provision of appropriate care for patients with neurological disorders. Timely and correct diagnosis is a prerequisite for access to support services.

Only 20-50% of patients living with dementia have a documented diagnosis in primary care in Europe[96]. In many countries (Germany), a large proportion of patients with AD is seen only by general practitioners (GPs), and a diagnostic is often not firmly established. The same for PD. Some patients are referred to neurologists or psychiatrists or geriatrists in private practice, but a very small proportion of patients is diagnosed in specialised centres such as memory clinics, usually linked to large hospitals and universities. No specific reimbursement structure exists for guideline-based diagnosis[97].

The organization of services for delivery of neurological care has an important bearing on their effectiveness. Countries have various forms of service organization and delivery strategies. The differing availability of financial and human resources also affects the organization of services. Depending upon the health system in the country, there is a variable mix of private and public provision of neurological care.

Primary, secondary, tertiary

The three traditional levels of service delivery are primary, secondary and tertiary care. Primary care includes treatment and preventive and promotional interventions conducted by primary care professionals (GP, nurses, other health-care staff and nonmedical staff) to primary care workers based in rural areas. **Primary care represents the point of entry for most people seeking care and is the logical setting where neurological disorders should begin to be addressed.** Users of primary care are more likely to seek early help because of the wide availability of facilities, easy accessibility, cultural acceptability and reduced cost, thus leading to early detection of neurological disorders and better clinical outcome.

Integration of neurological services into the primary care system needs to be a significant policy objective in countries[98]. Providing neurological care through primary care requires significant investment in **training primary care professionals to detect and treat neurological disorders. Ongoing training** should meet the needs of primary care professionals such as doctors, nurses and community health workers.

Primary care centres are limited in their ability to adequately diagnose and treat certain neurological disorders. For the management of severe cases and patients requiring access to diagnostic and technological expertise, a **secondary level of care is necessary**.

Tertiary care is the most specialized form of neurological diagnosis, treatment and rehabilitation, and is often delivered in teaching hospitals. They also serve as facilities for clinical research, collection of epidemiological data, and the creation and distribution of health educational materials.

Neurological specialist services require a large complement of trained specialist staff. Very few countries have an optimal mix of primary, secondary and tertiary care. Even within countries, significant geographical disparities usually exist between regions. In some countries, neurological conditions are at the forefront of national initiatives to improve health services for particular patient groups or conditions[99].

Integrated and coordinated systems of service delivery need to be developed where services based in primary, secondary and tertiary care complement each other.

A clear referral

In order to address the needs of persons with mental and neurological disorders for health care and social support (e.g. help with living, employment arrangements), a clear referral and linkage system needs to be in place.

The complex basis of these conditions requires **constantly assessing the situation** and the **patient's level of risk (risk stratification and case identification,** see <u>fig. 9</u>)[100], which may vary according to the **severity** of the pathology, and **redefining the care plan**[101].

Figure 9: Kaiser Permanent risk stratification pyramid
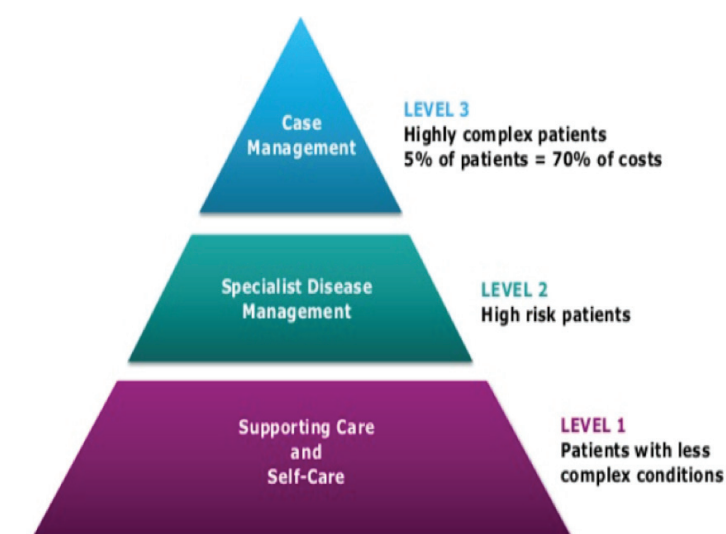
Case management[102] by a healthcare provider being responsible for the assessment of needs and implementation of care plans can be an additional support to coordinate medical, paramedical care and well-being and **to avoid unplanned hospital admissions** (due to increased frailty, falls, adverse drug event) and **to monitor polypharmacy** (medicines optimization). It is usually required for individuals who have a serious and persistent mental illness or severe neurodegenerative diseases.

3.2 Other challenges

Non-adherence

Poor treatment adherence is also a significant challenge to optimizing health outcomes.

Any therapeutic strategy must take into consideration factors impacting treatment adherence - such as polypharmacy, depression, deficits in the management of cognitive processes, poor quality of life and symptoms control, lack of social support/partner, cost of medications[103].

Medication non-adherence is prevalent in brain diseases and associated with an increase in costs of inpatient care (>20% of hospitalizations in elderly patients are attributable to non-adherence)[104]. Non-adherence among patients suffering from chronic conditions represents 50% on average[105] and for instance, is particularly high for patients with Parkinson's disease, resulting in substantial motor dysfunction. Estimates of non-adherence prevalence in PD range widely, from 15-20% by self-report, to 67% and higher in studies using pharmacy refill data and pill counts[106]. Non-adherent individuals are more

likely to report being untreated, rather than recognizing that their sub optimally controlled symptoms may be caused by their non-adherence to treatment. Similarly, the healthcare provider may react by changing the medicine regimens or questioning the diagnosis, leading to additional diagnostic testing, patient stress, and further non-adherence[107].

Efforts to empower patients to be engaged in responding to their health needs may improve adherence to treatment and help them to make informed decisions related to their health[108].

Unaffordable access to care

There is a direct correlation between out-of-pocket medication costs and use of medication and health care services and stopping treatment[109]. Ensuring that patients have access to essential and affordable medicines is one of the core objectives of the EU[110] and the WHO[111].

The increasingly high cost of medicines and shrinking public health budgets jeopardize access to essential medicines. The recent economic crisis has only exacerbated the problem.

There are **considerable variation in access to treatment for MS patients:** the proportion of all MS patients including patients with Relapsing-remitting MS (RRMS) receiving Disease-Modifying Treatments (DMTs) vary from Poland (13%), UK (21%) and other Eastern Europe countries as poor performers to Germany (69%)[112].

Insufficient access to essential medical products poses a serious threat to the well-being of a large section of the population in Europe. Difference in access can be explained by a series of factors including healthcare infrastructure.

Access to a neurologist can be problematic in some member states. **The role of GPs and nurses** have been highlighted in assisting in the management of the diseases and the use of treatments), **restrictive reimbursement** (being amongst Eastern European countries with the lowest access to MS DMDs resulting in a high number of untreated patients) and **affordability** (it remains a barrier in some Eastern European countries). New results (2016 observational involving EU countries from G. Kobelt et al.) will be released soon: it will look beyond the access statistics and seek to characterize more precisely what barriers prevent access to good clinical care.

Proper access means that medicines, even those for rare illnesses, should be made readily available and affordable in addition to being safe, effective, and of high quality. Various factors influence their availability: selection of medicines on the market, the focus areas of pharmaceutical research, the supply systems, financing mechanisms, pricing,

reimbursement and cost-containment policies of individual countries, as well as rigid patenting rules. **The high prices of new treatments for diseases such as Hepatitis C for instance recently prompted member states to call for EU-wide measures to enable patients to access affordable and innovative therapies[113]**.

Many initiatives at EU level have been taken in that direction. **PRIority MEdicines (PRIME)** is a scheme launched in March 2016 by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need[114]. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. Through PRIME, the Agency offers early and proactive support to pharmaceutical industries to optimize the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications. This will help patients to benefit as early as possible from therapies significantly improving their quality of life.

The Council of the European Union has also adopted in June 2016 conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States[115].

3.3. A "Paradigm Shift": Early Intervention - Transformation of health care from fragmented care towards patient-centered care and seamless care

The whole spectrum of care, from prodromal, early diagnosis to disease management

From the patient perspective, timely detection and diagnosis can prevent unnecessary pain and suffering. **Early diagnosis and treatment make not only clinical but also economic sense.** Diagnostic testing is an integral part of the healthcare system, providing **essential information to enable providers and patients** to make the right clinical decisions. Indeed, some **75% of clinical decisions** are based on a **diagnostic test**[116].

Computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized the study of the brain by allowing healthcare practitioners and researchers to **look at the brain noninvasively**. These diagnostic imaging techniques evaluate the brain structure, allowing healthcare providers to infer causes of abnormal function due to different diseases.

Demand for access to quicker, more accurate diagnosis is rising. Making detection more efficient, timely and accurate will contribute to generate savings required by health systems. For instance in order to address this, integration of specialists neurological services into the primary care system needs to be a significant policy objective in countries. Moreover, the gate keeping "referral" function of community nurse/GP practice in pro-active screening is to be fully effective[117].

Value in health care: measuring health outcomes

Achieving high value for patients is the overarching goal of health care delivery, with value defined as the health outcomes achieved by money spent[118].

Each age group according to disease stage has specific needs to be addressed along the care process (biological, psychological, health care services, social needs)[119]. Care for brain disorders usually involves multiple specialties and numerous interventions, with final outcomes determined by interventions across the full cycle of care.

Measuring, reporting, and comparing outcomes is crucial to improve outcomes and make informed choices about how to optimize healthcare and rationalize costs (see fig. 10: patient-centred, measuring value in health care and the patient pathway)[120]. Efforts to empower patients to be engaged in responding to their health needs may improve health outcomes, adherence to treatment, and has the potential for patients to make more informed decisions with regards to their health[121]. Research shows that adherence among patients suffering from chronic conditions is only 50% on average[122]. To ensure that health care is centred on patients, the patient journey approach aims at giving patients a "voice" through enhancing collaborative multidisciplinary teamwork, shared ownership and decision-making, providing evidence to substantiate change, and achieving results[123].

Figure 10: Measuring Value in Health Care by achieved outcomes, starting with defining the patient's needs
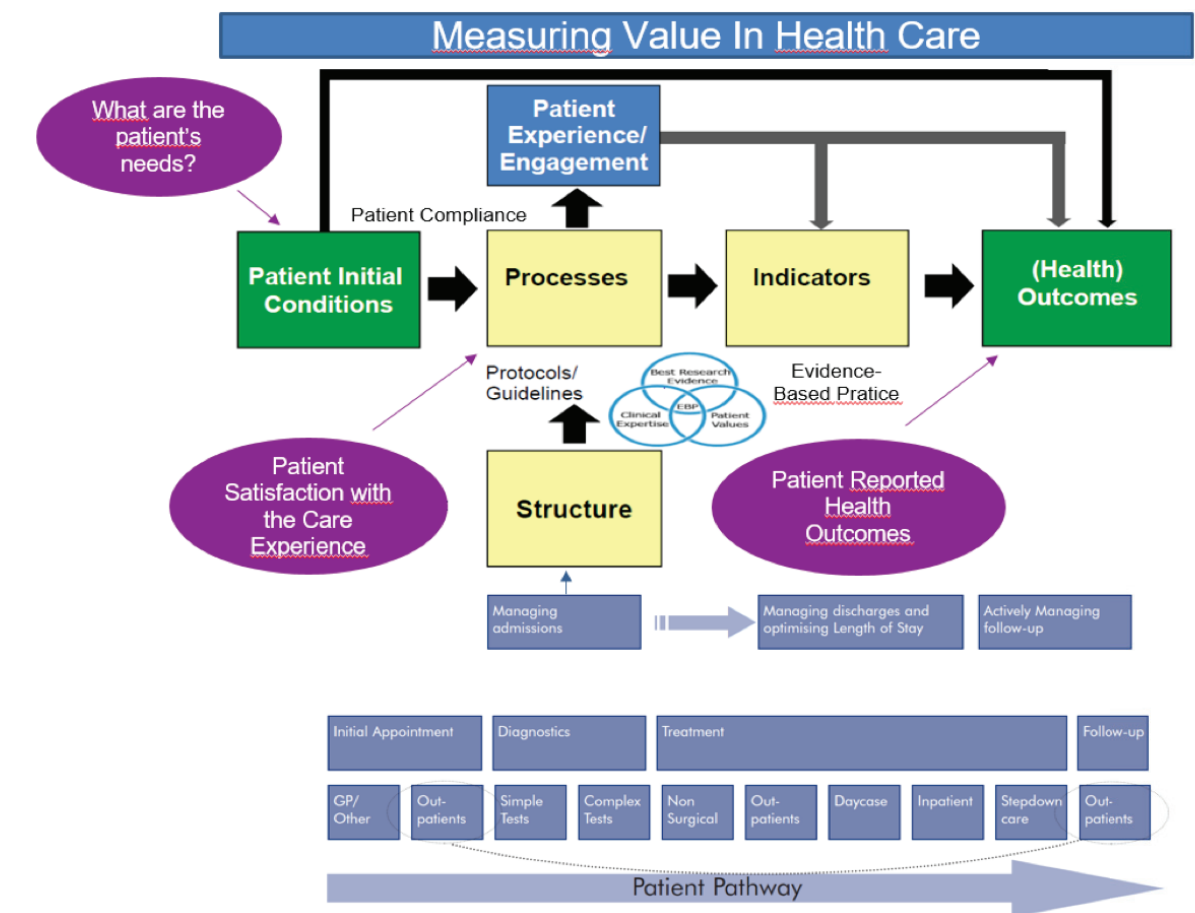
Value is the combination of reducing symptoms, guaranteeing safety, cost-effectiveness, improving quality of live and respect of patients' rights. It cannot be only related to economic, financial aspects.

> Value = treatment based on the demand (the needs of the patient) <-> treatment based on the offer/supply of treatment structures

> Value = optimisation of the networking, easy transfer between different treatment structures (e.g. in mental health care, hospitals – community centres – psychiatrists – psychologists - GP's – self-help groups). The changing nature of the demands made on hospitals means that it is particularly important for them to work closely with the different health and social care services.

ILLUSTRATION: OPTIMIZING HEALTHCARE IN THE CHAIN OF SURVIVAL - THE EXTREME IMPORTANCE OF TIME

Every step of the patient trajectory from symptoms onset to start of treatment should be optimized in order to decrease loss of **time**.

VOT example: identifying the treatment gap and improving care for ischemic stroke patients

An illustration of the EBC approach, and one of the VoT case studies, is acute stroke care.

- Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) is one of very few effective treatments for acute ischemic stroke. In most centers, however, only a small proportion (2%–7%) of patients with ischemic stroke receive this treatment.

- The most important factor limiting IVT administration is **time**: it has to be administered within 4.5 hrs of symptom onset. Even within that window, reducing **'time-to-needle'** (the time between symptom onset and IVT administration) can improve functionality and reduce complications for the patient.

- The clinical benefit from IVT declines rapidly however. **Time is brain, and every minute counts**[124, 125]:

  > If IVT is started within 90 minutes after stroke onset, the number of patients that need to be treated (NNT) in order to achieve an excellent clinical outcome (based on modified Rankin scale – a measure of disability and dependence in daily activities) is 4.

  > Within the 180–270-minute time window, the number of patients that need to be treated to achieve an excellent outcome increases dramatically – to 14.

Put simply, a shorter delay from symptom to IVT (the so-called symptom-to-needle **time**) can make **the difference between being independent and being dependent.**

Policy implications

- **Reducing the symptom-to-needle time is vital.** Most **time** is lost in the prehospital period (patients waiting before they seek medical attention). Unfortunately, awareness campaigns have been found to have limited impact in addressing this.

- **Inside the hospital, the focus should be on decreasing the time** from arrival to IVT administration – the so-called door-to-needle time (DNT). In most countries, national guidelines recommend that the DNT should not exceed 60 minutes. However, 15 years after IVT was proven to be clinically effective, in most institutions, the DNT is still more than 60 minutes for the majority of patients.

- **Reducing DNT** will also increase the proportion of patients eligible for IVT, because more patients can be treated within the 4.5-hour time window.

ILLUSTRATION: IMPORTANCE OF EARLY TREATMENT AND MULTIPLE SCLEROSIS

Treat early in the case of MS and disease-modifying treatments DMTs (see fig.11)[126]. MS has become a treatable disease and the natural course of MS can be changed: early diagnosis and early intervention decrease the rate of progression.

Fig. 11: The new treatment paradigm for MS
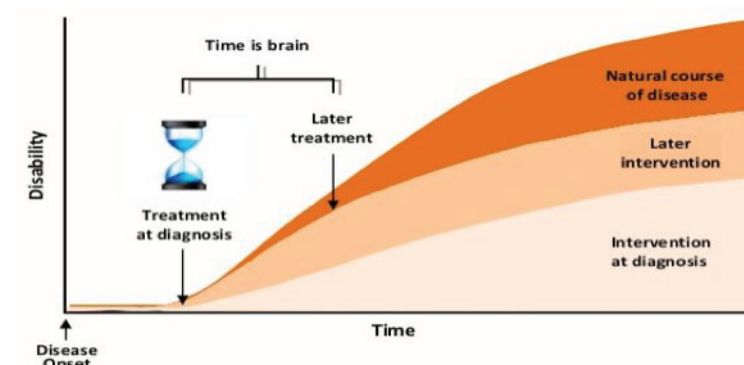
There have been huge advances in treatment in the last few years: 6 different immune-modulating therapies are now recommended. There is increasing evidence that early diagnosis and treatment may delay, or even prevent, the previously inevitable disability (and, at the other end of the spectrum, there is an increasing range of treatment options for those with disability.

ILLUSTRATION 11: MS DISEASE MANAGEMENT IS KEY

MS diagnosis remains a specialist clinical diagnosis based on the dissemination of clinical attacks and MRI lesions in time and space using the McDonald criteria[127]. However, the diagnosis can be made at presentation allowing earlier access to disease-modifying therapies. Once the diagnostic is confirmed, a coordinated multidisciplinary approach is needed, but importantly all patients should have easy access to a single point of contact to help them access care and services.

Patients should have a management plan with clear guidance as to who to contact if there is a significant symptom change. First steps should be: providing information and support, coordinating care & healthy lifestyle advice. The role of the GP is recognized in the long-term management of MS and associated disabilities[128].

> See EBC Case study on MS page 30

NEXT STEPS

After case studies preliminary results presentation at the VoT Plenary Meeting on 18 January, **this working document is providing an overview on the harvest so far.** In this current version, some additional literature review has been conducted to feed the current case studies available Data. **This document will be discussed at the EBC Board on 8-9 February.**

It is important to highlight that as per today **case studies analysis** is still **ongoing**. 5 out of 9 case studies are more advanced based on well defined scope.

This document is a **first step in harmonizing data and analysis. Final reporting** on the economic evaluation and the patient care pathway should be provided by the Working Groups **by the 28th of February. Aim should be to have a standardized approach for all case studies and to start defining research conclusions.**

Further evaluation and literature review for the White Policy Paper should be conducted where necessary. **Suggestion would be** to select [4 to 5] different EU countries and compare their health systems (including regulations, legislations, financing plans and priorities) and conduct additional evaluation of the existing literature and policy best practices. Consultations will also take place with external experts in respect of the timelines and the conference of 22 June 2017 (see fig. 12: EBC project milestones and expected deliverables).

Fig. 12: EBC project milestones and expected deliverables
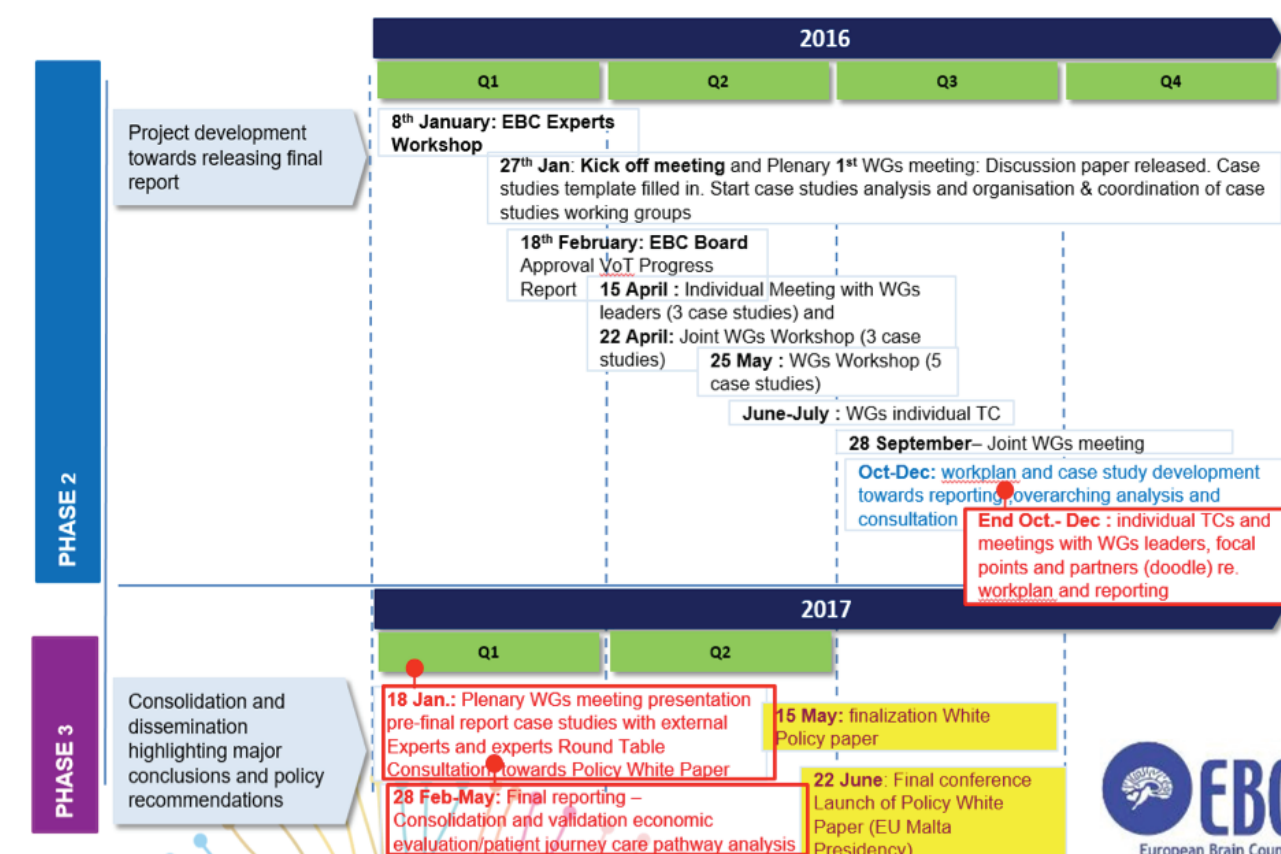
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ANNEX

Expert roundtable participants

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Working Groups participants

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Cyril	Hoschl	EPA	Secretary	Clinician	Schizoprenia
Pavel	Mohr	EPA	Secretary	Clinician	Schizoprenia
Petr	Winkler		Expert		Schizoprenia
Patrice	Boyer	EPA	Expert	Clinician	Schizoprenia
Aagje	leven	EUFAMI	Family Organisation	Informal Care	Schizoprenia
Hilkka	Kärkkäinen	Gamian	Patient representative		Schizoprenia
Paul	Arteel	Gamian	Patient representative		Schizoprenia
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Veronica	Zilli	Janssen	Industry Representative		Schizoprenia
Maria	Cristiana	Janssen	for information		Schizoprenia
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Philip	Scheltens	Vumc	Expert	Clinician	Dementia
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Dianne	Gove	Alzaheimer Europe	Patient representative		Dementia
Ana	Diaz	Alzaheimer Europe	Patient representative		Dementia
Joel	Bobula	Pfizer	Patient representative		Dementia
Charles	Faid	Pfizer	Industry Representative	Public affair	Dementia
Amir	Inamdar	Takeda	Industry Representative		Dementia
Meni	Styliadou	Takeda	industry Delegate		Dementia
Michele	Potashman	Biogen	Industry Representative	Market access	Dementia
Tresja	Bolt	Biogen	Industry Representative	Delegate	Dementia
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Eveline	Sipido	EAN	for information		Dementia
Wolfgang	Oertel	EAN	for information		Dementia
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Koen	Paemeleire	EHF - European Headache Federation	Expert	Clinician	Headache
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Sonia	Gonzalez	EHA - European Headache allaiance	Patient representative		Headache
Pamela	VO	Novartis	Industry Representative	HEOR	Headache
Annik	LAFLAMME	Novartis	Industry Delegate		Headache
Frédéric	de Reydet de Vulpillieres	Novartis	Industry Delegate		Headache
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Andrew	Bolan	TEVA	Industry Representative		Headache
Erick	Tyssier	TEVA	Industry Representative		Headache
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Wolfgang	Oertel	EAN	for information		Epilepsy
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Manfred	Westphal	EANS			NPH
Franziska	Greifzu	Aesculap			NPH
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Jutta	Ahmerkamp Bohme	Young and Parkinson	Patient representative		PD
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