



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

EARLY DETECTION AND CONTINUITY OF CARE A JOINT VALUE OF TREATMENT STUDY ON ANOREXIA NERVOSA, AUTISM AND DEPRESSION IN EUROPE

#Together4MentalHealth

Case Study Results and Infographics | Brain Awareness Week 2022



VALUE OF TREATMENT (VOT) PROJECT



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



VOT PROJECT COORDINATOR

The **European Brain Council** (EBC), which coordinates the **VOT** project, is a non-profit organisation and network bringing together key partners in the brain ecosystem: scientific societies, patient organisations, professional societies and industry partners. Its main mission is to promote brain research with the ultimate goal of improving the lives of the estimated 179 million Europeans living with brain conditions, mental and neurological alike.

EBC MEMBERS



OBJECTIVES OF THE VOT PROJECT



Identify treatment gaps (or barriers to care) and causing factors along the care pathway and propose solutions to address them.



Assess health gains and socio-economic impacts resulting from best practice healthcare interventions, in comparison with current care or inadequate treatment.



Converge data evidence to policy recommendations on how to improve the care pathways.

There are three VOT project rounds developed as part of the health economics and outcomes research framework:



The VOT 2 project (2019-2021), focusing on Anorexia Nervosa, Autism and Major Depressive Disorder, is coming to an end. 2022 will be an important milestone in terms of case study results dissemination. The study looked at early intervention and explored the benefits of improved detection, continuity of care and treatment, and collaborative care patterns (also addressing mental health problems with comorbid medical conditions) on outcomes to patients and costs. Results provide insight on the value of early intervention to improve children and young people's mental health and the causes of mental ill-health. Case studies which combine a care pathway analysis followed by an economic evaluation were conducted with the support of Academic Partners, applying empirical evidence from different European countries.

RESEARCH COLLABORATION: ACADEMIC PARTNERS IN VOT2

► Mental disorders case studies



Anorexia Nervosa care pathway analysis & health economics study



Major Depressive Disorder care pathway analysis & health economics study



Autism Spectrum Disorder care pathway analysis & health economics study

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“Mental disorders cannot be ignored, nor can their devastating impact on families, communities, and lives. The cost of not acting is tremendous, therefore demonstrating the value of early intervention is essential. There is a need to improve the efficiency of brain health and care pathways, prevent avoidable deaths and implement cost-effective solutions.”

Professor Wolfgang Oertel,
President, European Brain Council.

Foreword

Youth are our future. However, recent studies underscore the severity of the mental health challenges children and adolescents face that can lead to disability, disease, and death.

There are numerous unmet needs along the care pathways, although effective early detection and interventions exist. Navigating the mental health services system is often complex for families, due to fragmented or disrupted services. Mental health issues cost the European economy more than €600 billion a year, which is more than 4% of the GDP of the European Union (EU), with depression being the leading cause of ill health and disability, according to the Organisation for Economic Co-operation and Development (OECD). And the burden is increasing. The COVID-19 pandemic exacerbated the situation with rising healthcare inequalities. Policies and programmes to prevent and mitigate the negative impacts on schooling, employment, mental health, and risky behaviors are therefore paramount. The accumulation of human and social capital must start at a young age, as the brain develops rapidly during early childhood and adolescence. Moreover, early cognitive, and non-cognitive skills and health capabilities lead to enhanced effectiveness of later investment. As a result, by building a strong foundation, investing in optimal interventions tailored to the young generation advances socio-economic development.

Value-based healthcare is gaining traction in Europe as the desired solution or path forward in improving health systems. The approach towards more comprehensive mental health care models critically intertwines wider patient and societal outcomes with efficient spending of resources. Reinforcing this should lead to both a more sustainable framework for payers and better care for patients. Yet, COVID-19 presents an opportunity to reset fragmented healthcare systems so that they are integrated, driven by people and communities and resilient in the face of future systemic shock.

The European Brain Council (EBC) initiated in 2019 a research project on the Value of Treatment (VOT), Early Detection and Continuity of Care for Persons Living with Mental Disorders.

The research project – which prioritizes brain health and efficient care pathways for people living with mental health conditions – includes 3 case studies related to anorexia nervosa, autism spectrum disorder and major depressive disorder. This project aims to uncover the many facets of the policy challenges facing Anorexia Nervosa, Autism and Depression. Analysing these diseases jointly makes it more impactful for public health. Case studies were analyzed in collaboration with EBC's scientific societies and patient organizations in line with the research framework. The project assesses the treatment gaps and the costs of inadequate treatment. Our findings recommend prevention, early intervention, and the implementation of a comprehensive healthcare approach (as opposed to fragmentation in separate medical “silos”). Combined research and public health policy gaps and opportunities at the EU level are addressed, and the findings are translated into policy recommendations.

With this new study, EBC is not only looking at the socio-economic impact and value of optimal healthcare interventions but is also emphasizing how timely care pathways are likely to need greater integration and how collaborative care between primary care and specialist care – inexistant in many countries – can be achieved in the future for the benefit of those living with a mental disorder. We address patients' biopsychosocial needs and concern and pinpoint common denominators linking studies of Anorexia Nervosa, Autism and Depression. We highlight the value of continuity of care as a solution to improve patient quality of life and as beneficial to society and health systems in the long term. Research links early intervention to measurable health gains, reduced complications and disability, improved recovery and better use of resources. However, effective

implementation of early detection and treatment varies widely across health systems and many European countries are still lagging, with wide clinical practice variations even within countries. Mental disorders can be life-threatening, and disproportionately affect children and youth with serious implications for families dealing with prolonged impairment. Patients and their families continue to have difficulties getting a diagnosis and accessing appropriate health services. This is particularly blatant for psychiatric disorders. VOT is addressing the obstacles to optimal care pathways while providing innovative solutions.

The release of the study results is timely. The EU is set to address the pandemic's most serious and enduring consequences: the staggering rise in mental ill-health and the major challenges to reach 2030 targets. Mental health and young people are part of France's Presidency of the Council of the European Union priority agenda during the first semester 2022. This will enable the Commission to examine all possibilities to tackle this, including the urgent development of an EU Mental Health Strategy.

The reality of mental health conditions is increasingly situated at the network level. In May 2022, the World Health Assembly (WHA) – supported by the World Health Organisation – should prioritise mental health and address upfront the mental health crisis. Meeting the added demand for mental health services will be challenging but taking no action should not be an option. Many new innovations and new approaches will be needed to deliver those services and to accelerate action both at European and country level. This is the core of the technical consultation on the implementation of the European Framework for Action of Mental Health as a flagship initiative in the WHO European Region that was kicked off through the Pan-European Mental Health Coalition in mid-February.

Together we are stronger. We don't have all the solutions at once, but these are promising, and the research will be pursued based on a common approach. Through building up evidence, EBC is providing the necessary policy recommendations and a call for action to address the treatment gap and its consequences. We would like to take the opportunity to thank all EBC members and partners for being part of this challenging journey.

by **Hilkka Kärkkäinen** (President, GAMIAN-Europe) and **Peter Falkai** (President, European Psychiatric Association)



Acknowledgements

Due to the often-complex care pathways, mental disorders continue to present policy and health systems challenges globally. Given the related gaps in understanding around best practice to address challenges related to mental health issues, EBC conducted research to highlight the burden, unmet needs and opportunities related to these mental disorders. Key mental health experts and stakeholders were engaged to illuminate challenges, and to stimulate discussion on opportunities for addressing mental disorders. Our sincere thanks go to several people for both their time and contributions to this work.

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Financial support was also provided by EBC member, the European Psychiatric Association (EPA).

Case study results

In this section, we present a summary of each case study, briefly setting out the context, the treatment gaps identified and the proposed recommendations to tackle them, while highlighting the potential socio-economic impact of their implementation. The results of the case studies will be submitted to a peer review journal (The European Psychiatry). All the documents related to the project and to the individual case studies are available online:

[Value of Treatment: 2nd Round – European Brain Council \(EBC\)](#)

VOT

**The Value of
Treatment for
Anorexia
Nervosa**

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Treatment for
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**The Value of
Treatment for
Major Depressive
Disorder**



Anorexia nervosa care pathway in Europe

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Background

Anorexia nervosa (AN) is a severe and enduring illness affecting not just the individual but those caring for them. With onset typically during adolescence, long average duration of 10 years (adolescent onset) and severe consequences of the illness, pull the role of the family into focus (Treasure, Parker, et al., 2021). Timely treatment may avoid the illness becoming protracted (Andrés-Pepiñá et al., 2020), but the duration of untreated illness is long (Austin et al., 2021), as is the length of costly inpatient admissions (Kan et al., 2021). While the intended care pathway for AN is often reflected in national guidelines (e.g. Resmark et al., 2019, NICE 2017), there is a lack of empirical data assessing performance of the care pathway against this model. Optimisation of care pathways is needed to reflect the needs of patients and carers, improve treatment outcomes and reduce the financial and personal burden of disease. We identify treatment gaps and unmet needs from a patient, carer and clinician perspective.

Methods

The AN working group conducted a mapping survey, drawing on a convenience sample of experts on ED in 12 European countries (Austria, England, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Spain, Sweden and Turkey). Topics covered: A - Details of care system and treatment contexts; B - Treatment approaches; C - Outcomes for ED; D - Costs of treatment and evidence of cost-effectiveness; F - Problems to highlight. In addition, experts provided information on key studies and data relating to the care pathway in their respective countries. Three case study countries were selected, based on data availability (England, Germany, Spain). These countries represent three different predominant types of health systems in Europe (Ferreira et al., 2018). We analysed availability of data across all 12 countries. A schematic care pathway for AN in Europe (*Figure 1*) was developed. Then, data on the three case study countries were extracted and specific care pathways were constructed. A rapid survey of the literature on the needs of patients and carers was conducted to identify the main issues with regard to the care pathway.

Treatment Gaps/Unmet Needs

Gaps were analysed from both a patient and a clinician perspective. Our survey identified many gaps in the availability of data about treatment for AN in Europe. While most countries have guidelines for treatment in place (8/12), surveillance systems are immature, with only about half having data on incidence and prevalence available, and two having information on outcomes – although the latter is not routinely collected.

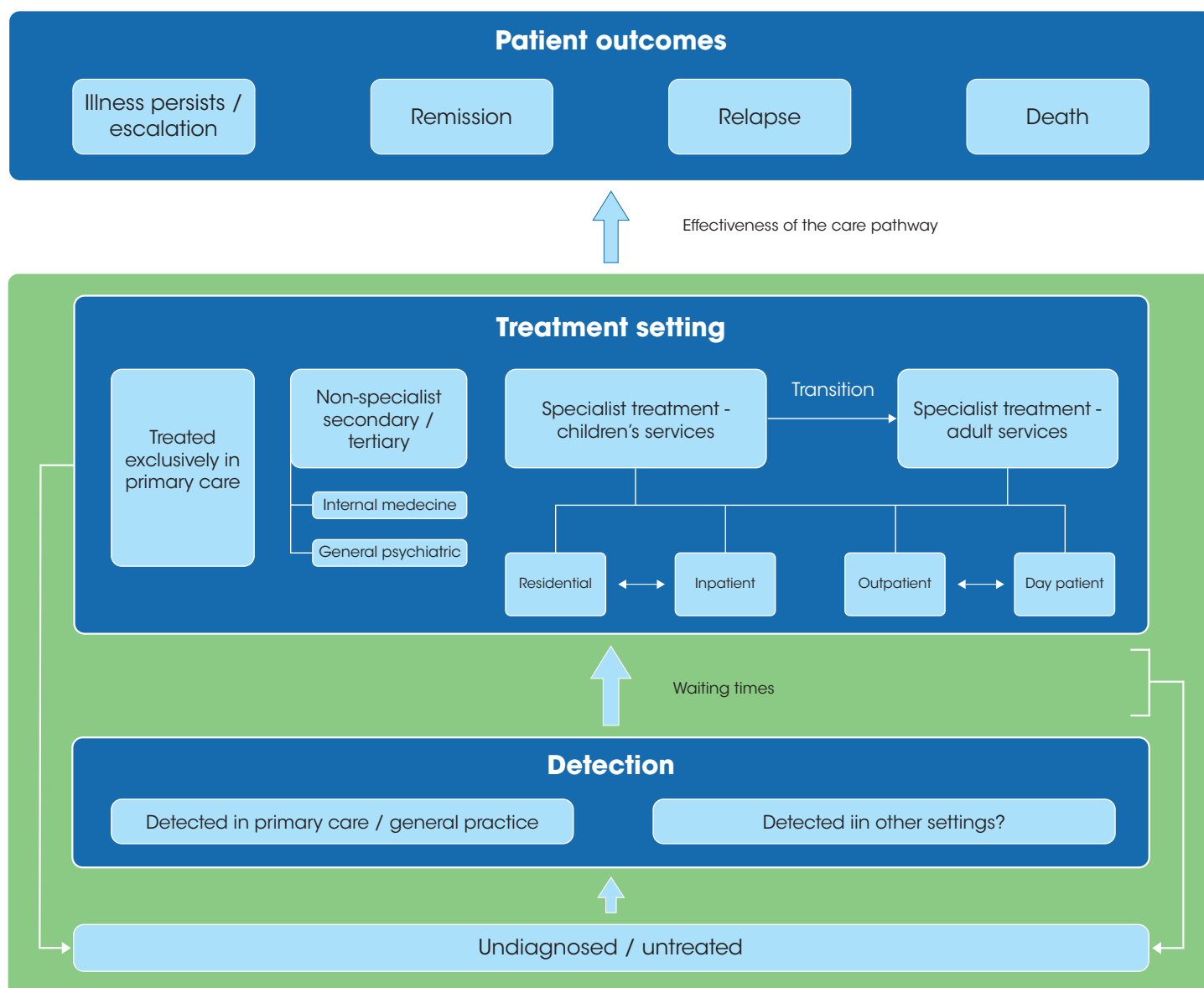
In addition, our survey identified systemic issues hampering timely and effective care for AN, such as a lack of availability of inpatient beds or specialist services, organizational gaps in the transfer between child and adolescent and adult services, and regional differences in the availability of specialist care, which reflects previous research (Royal College of Psychiatrists, 2012, Herpertz-Dahlman et al 2021). Other potential contributors to delayed or inadequate treatment are GPs lacking confidence and skills in treating AN (Currin, Waller and Schmidt, 2009). The duration of untreated illness is high as a result, at 14.6 months (Austin et al., 2021), and is associated with poorer prognosis (Fernandez-Aranda et al, 2021).

Carers experience greater distress than carers of people with psychosis (Treasure et al., 2001; Whitney et al., 2005), and many meet criteria for anxiety and depression (Kyriacou, Treasure and Schmidt, 2008). The disorder can lead to social isolation and put financial strain of the family (Hillege, Beale and McMaster, 2006).

A recent study by Beat is representative of broader findings and highlights the fact carers often do not feel supported or adequately informed, as communication between services and carers can be poor (Rothwell, 2019). The same study found carers had to fight for the provision of appropriate and evidence-based treatment.

While the configuration of services with regard to transition from child and adolescent ED services to adult services varies across Europe (Herpertz-Dahlmann 2022), around 15% to 30% of patients may face this transition, while 2/3 may not have any contact with adult services (McClelland et al 2020). This points to a need for transition support, as well as a possibly large treatment gap for those ageing out of CEADs.

Figure 1. Schematic care pathway for AN in Europe



Recommendations

High quality ED services should entail “well-coordinated care delivered by a knowledgeable and specialist treatment team centered around the patient and their social support” (Treasure, Oyeleye, et al., 2021, p.308). Research informed by patient priorities is more likely to focus on early intervention and recovery (Wade et al., 2021), and supporting carers can enhance and improve treatment for AN (Treasure, Parker, et al., 2021).

Recommendations to close the current treatment gaps therefore include addressing the following “pinch points” along the care pathway for adults (Treasure, Oyeleye, et al., 2021):

- Improving detection in primary care to improve access to treatment;
- Reduction in waiting times to enter specialist treatment and avoiding delay;
- Increasing the effectiveness of routine treatment through a) a triage system and b) augmentation;
- Bridging the transition from inpatient treatment and increasing support in the community;
- Rehabilitation services and new treatments for those not responding to available treatments.

In addition, families would priorities an increase in specialist ED services for children and young people as well as adults, an increase in available inpatient beds, improvements in GP training and supporting transitions across services (Beat, 2017), including special treatment offers for the transitional age group (Herpertz-Dahlmann 2022). Improving the availability and quality of data relating to treatment and outcome of AN across Europe is an additional priority that can support evaluation and better decision making.

Conclusions

There is a dearth of data on ED services in many European countries, making it difficult to establish a clear picture of the overall care pathway. However, the experience of patients and carers along the care pathway is well documented. Improvements are needed to increase capacity for treatment, reduce waiting times and the duration of untreated illness, support transitions across services and involve carers and families while supporting them appropriately. In addition to improving treatment outcomes, there is a potential that this optimisation is cost-saving.

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Potential savings from improving transitions along the care pathway for **anorexia nervosa** in three European countries

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Background

The health care costs associated with Anorexia nervosa (AN) are high (van Hoeken and Hoek, 2020; Streatfeild et al., 2021), but there is often a lack of specific treatment for the eating disorder (Striegel Weissman and Rosselli, 2017). The costs of failing to treat effectively and early are numerous: The average length of admission in Europe is 106 days (Kan et al., 2021), and readmission rates may be increasing (Holland et al., 2016). While the evidence on education attainment for young people with AN is mixed (Keski-Rahkonen et al., 2007), the impact of current AN on productivity is severe (Hjern, Lindberg and Lindblad, 2006) and many are reliant on benefits (Su and Birmingham, 2003). A recent meta-analysis (Ágh et al., 2016) found that ED were associated with reduced quality of life, and AN was associated with reduced mobility compared to BN and healthy controls. Improvements to the care pathway are thought to reduce treatment costs as well as longer-term individual and societal costs associated with AN.

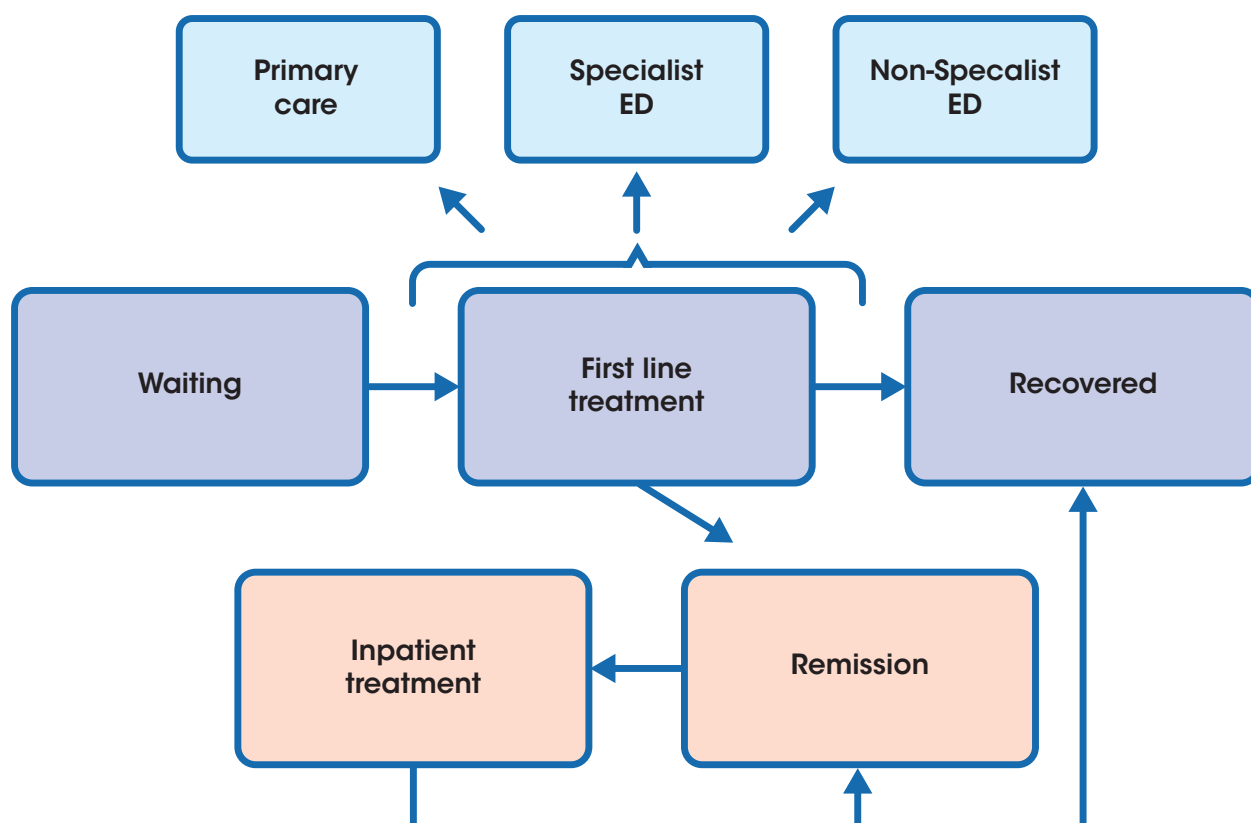
Methods

Figure 1 shows the state transition diagram underpinning the model presented here, representing treatment seeking adult patients following a diagnosis of AN.

Three broad categories of interventions were modelled over a 6-year period (Markov cycles: 312 weeks), compared to a base case scenario (1) using the NICE care pathway for AN as a counterfactual for improvements:

- (2) Reducing waiting times: Average time from first contact with services to treatment reduces by 50% from the status quo, leading to treatment being provided sooner and a decrease in the proportion experiencing a protracted course of illness (fewer re-hospitalisations).
- (3) Expanding the availability of specialist treatment: Specialist treatment is offered to all who are referred beyond primary care, reducing the overall hospitalisation rate.
- (4) Improving specialist treatment by offering transition support for patients and carers: Assuming the effectiveness of specialist treatment (SSCM and MANTRA) in terms of (re-) admissions is increased by 50% compared to current data.

Finally, a scenario combining all three improvements was modelled (5). The analysis was repeated for three European countries (England, Germany, Spain), incorporating local parameters where these were available. Note that in the Spanish model, a relatively short inpatient spell is followed by 3.5 months of day hospital treatment. Costs associated with each scenario are presented as present value (discount rate 3.5%) in 2018/19 prices and show in EUR. Unit costs were drawn from publicly available sources and research papers. Disability weights for AN (0.224, WHO 2020) were assigned to all treatment and waiting states to estimate the burden of disease associated with each scenario in addition to direct treatment costs.

Figure 1. State-transition diagram**Table 1. Model parameters, by scenario (generic model)**

Scenario Parameter	(1) Base Case	(2) Waiting Time	(3) Specialist Treatment	(4) Transition Support	(5) Combined
Average waiting time (months)*	14.6 ¹	7.3 ²	14.6	14.6	7.3
Treated in primary care ³	30%	30%	30%	30%	30%
Receiving specialist treatment ⁴	49%	49%	70%	49%	70%
Receiving non-specialist treatm.	21%	21%	0%	21%	0%
Hospitalisation ff primary care ⁵	40%	40%	40%	40%	40%
Hospitalisation ff non-specialist ⁶	40%	40%	40%	40%	40%
Hospitalisation ff specialist ⁷	17%	17%	17%	9%	9%
Re-hospitalisation (all pathways)	34% ⁸	17% ⁹	34%	17%	17%
Av. length inpatient stay (days)*, ¹⁰	106	106	106	106	106

* State transitions are normally distributed.

¹Austin et al. (2021); ²Andrés-Pepiñá et al. (2020); ³ e.g. Hoek and van Hoeken (2003); ⁴House et al (2012), Byford et al (2021); ⁵As hospitalisation following non-specialist care; ⁶House et al (2012); ⁷Schmidt et al. (2015), Schmidt et al. (2016); ⁸Hibbs et al (2015); ⁹Andrés-Pepiñá et al. (2020); ¹⁰Kan et al (2020)

Results

Figure 2 shows total costs (present value) and total disability weighting for the five scenarios over the 6-year period. Total treatment costs are highest in the base case, followed by the waiting times scenario (2), improving access to specialist services (3), offering transition support (4) and the combined scenario (5). This ranking is the same for all countries. The relative reduction for scenario 2 is between 3 and 11%, while for scenario 5, it is between 36 and 38% for all countries.

Burden of disease patterns across countries are again similar, but the order of scenarios is different: The burden is generally lowest in the waiting times (2) and combined (5) scenarios. The exception here is Spain, where waiting times are relatively low, and the burden is lowest in scenario 3 (access to specialist services).

The duration of the waiting period affects the timing of costs but has a small overall impact only through the downstream reduction in hospitalisations. Comparing scenarios (2) and (5), which both involve a reduction in waiting times, with the base case shows that scenario (2) provides little potential savings. However, disability weights are reduced by up to 30% (Germany),

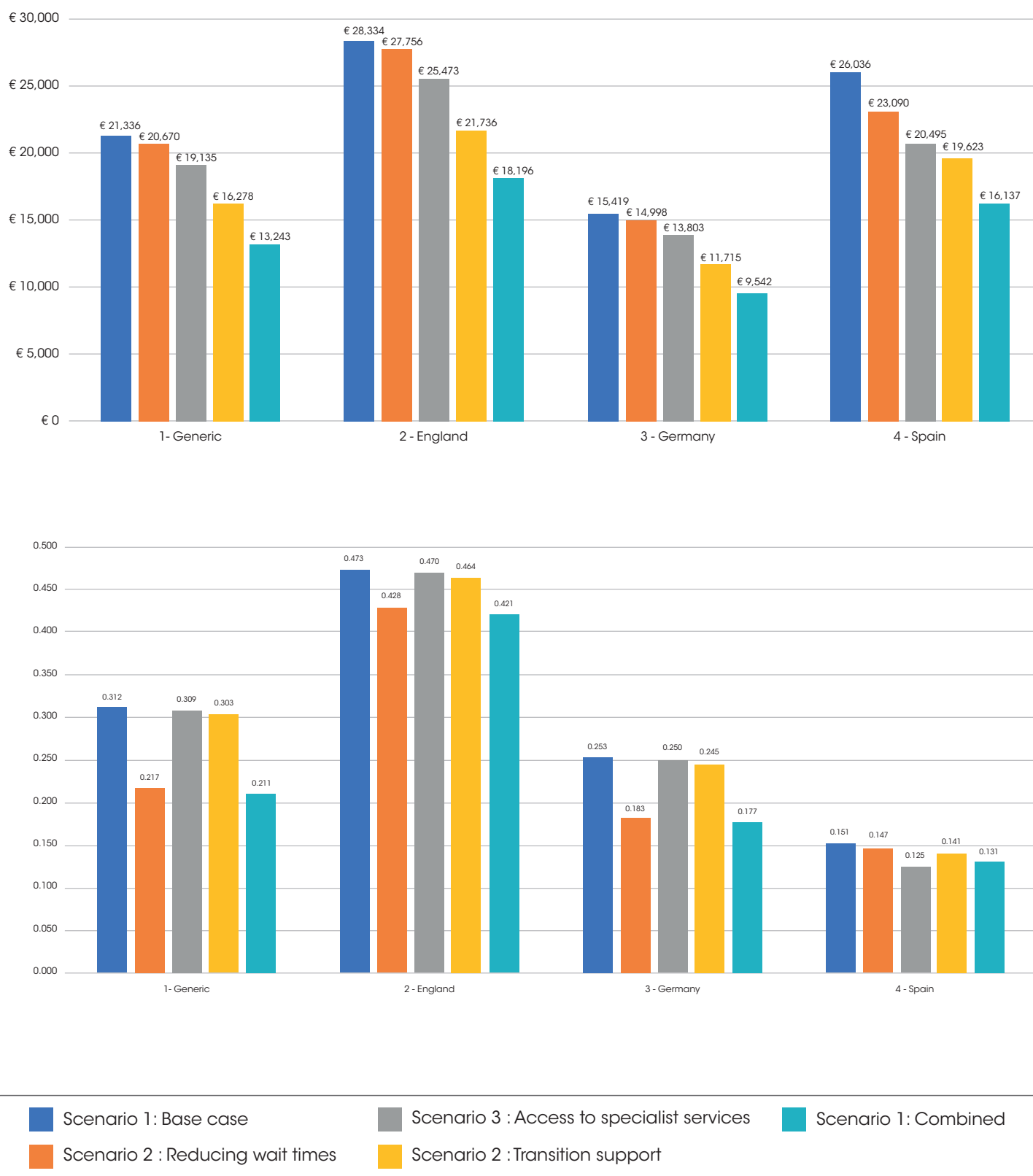
As can be seen from the variability in findings across countries, model estimates are sensitive to assumptions about the length of inpatient treatment, duration of the waiting period, assumptions about the population treated exclusively in primary care and on an outpatient basis, and about further treatment beyond inpatient spells – as well as the choice of unit cost parameters.

The model does not capture impacts of service improvements on wider service use, time of caregivers, productivity losses, out of pocket expenditure, nor does it capture potential reductions in mortality. These limitations are mitigated to some extent by the inclusion of a measure of disability weighting associated with poor health.

Conclusions

In this model, implementing all three improvements to the care pathway result in a cost reduction of 38% and a reduction in disability weighted time of up to 33%. The largest cost reduction can be achieved by implementing all optimizing strategies, driven by reductions in hospitalisation rates. The most significant reductions in the burden of disease can be achieved by reducing waiting times. Additional savings from reduced wider service use and service use of caregivers, as well as the value associated with potential improvements in productivity and reductions in excess mortality are likely to exceed this figure. This is predicated on the assumption that early and effective treatment can change the trajectory of the illness and prevent it from becoming protracted. More information on transitions between treatments and individual patterns of treatment over the life course is needed to create a more accurate model. An optimized care pathway needs to be implemented, supported by effective interventions, to reap these potential benefits.

Figure 2. Cost and burden of disease, by scenario and country



Acknowledgements:

Financial support was provided by EBC member, the European Psychiatric Association (EPA).

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Autism care pathway in Europe

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Background

Autism is a lifelong complex neurodevelopmental condition of early onset that affects brain development and behaviour, characterized by difficulties in social communication, restricted and repetitive patterns of behaviour, interests or activities, and sensory issues which have significant consequences in daily life¹.

Early intervention can play a crucial role in the earlier social-communicative and emotional development which will act as a bridge for other more complex abilities². The primary goal of early intervention is to maximize functional independence and quality of life³. Despite its great societal and personal impact, Europe-wide consensus and support for early detection, diagnosis, and intervention of autism are lacking⁴.

The objectives of this study were:

1. To analyse autistic children care pathway and early journey in three European countries: Italy, Spain and the United Kingdom.
2. Propose policy recommendations on how to improve the care pathway (i.e. minimise treatment gaps).

Methods

The care pathway of autistic children was analysed from a carer, autism community and professional perspective to identify major barriers (treatment gaps) preventing carers of autistic children from receiving information, support, timely screening/diagnosis and treatment/intervention.

We conducted a very rapid literature review of the existing care pathway in Europe. We also conducted a survey aimed at carers of autistic children ages 0 to 18 living in Italy, Spain and the UK. Additionally, members of the working group met in Brussels and remotely (due to the COVID-19 pandemic) between 2019 and 2021 to identify the main treatment gaps and their causing factors, prepare a survey to evaluate service users unmet needs, discuss results, and propose policy recommendations.

Survey was approved by local ethics committees in Italy, Spain and the UK.

The following critical points of the care pathway were addressed:

1. Screening/diagnosis after carers raise first concerns to health professionals.
2. Intervention/treatment once diagnosis is confirmed.
3. Information about access to services and support for families and carers of autistic children.

Sample characteristics

Autistic child's age at time of survey, mean (SD)	10.17 (4.39)
Sex of autistic child (% male, % female)	76,8%, 23,2%

Country	Male	Female	Total
Italy	129	29	158
Spain	222	65	287
UK	158	60	218
Total sample	509	154	663

Quotations from survey respondents (parents or carers):

"No one from health services mentioned a possibility of autism until my child was 11 years old."

"Health professionals are not trained in autism."

"There are not enough diagnostic clinics/services."

"Never received any early intervention programme."

"Early intervention is crucial."

"I was given minimal information after diagnosis."

Treatment Gaps/Unmet Needs

Current care pathways (split by treatment gap) averaged across data sources and countries. For specific country data, please see figures on the right.

1. Delayed screening and diagnosis:

- 70% of family members raised first worries about their child's development and/or behaviour, 19% were raised by school/nurseries staff while only a concerning 6% were raised by health staff.
- 28% of respondents stated it took them over a year after first worries were raised to be offered a screening visit.
- 44% of respondents reported it took them over one year after the screening visit to have a diagnosis assessment.

2. Delayed or no access to intervention once diagnosis has been confirmed:

- 36% of respondents stated that the autistic children did not receive any intervention after diagnosis. Despite the high percentage of people in Spain and Italy receiving intervention after diagnosis, a good proportion of these relied on private funding or a combination of both private and public funding.

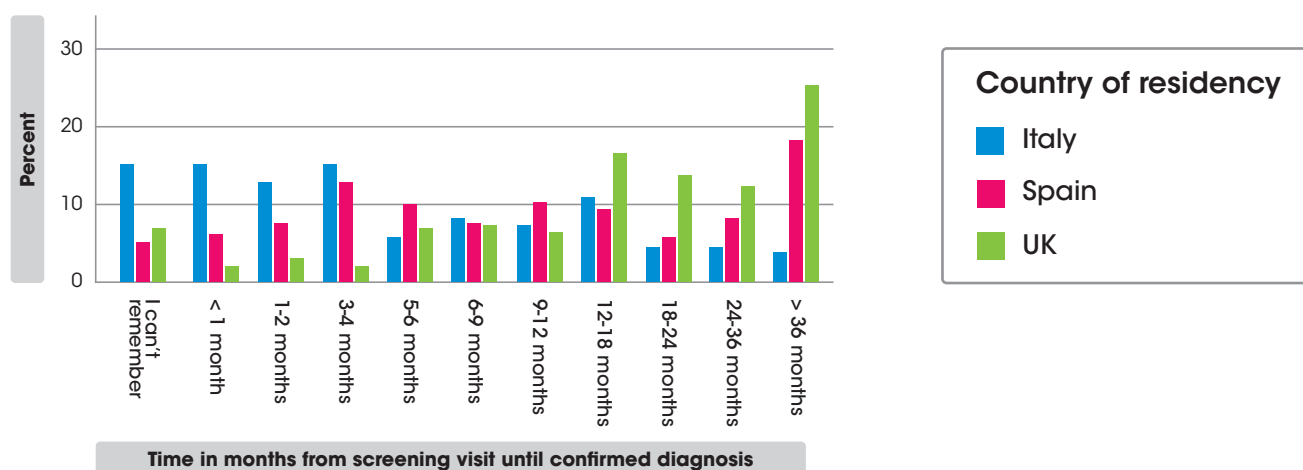
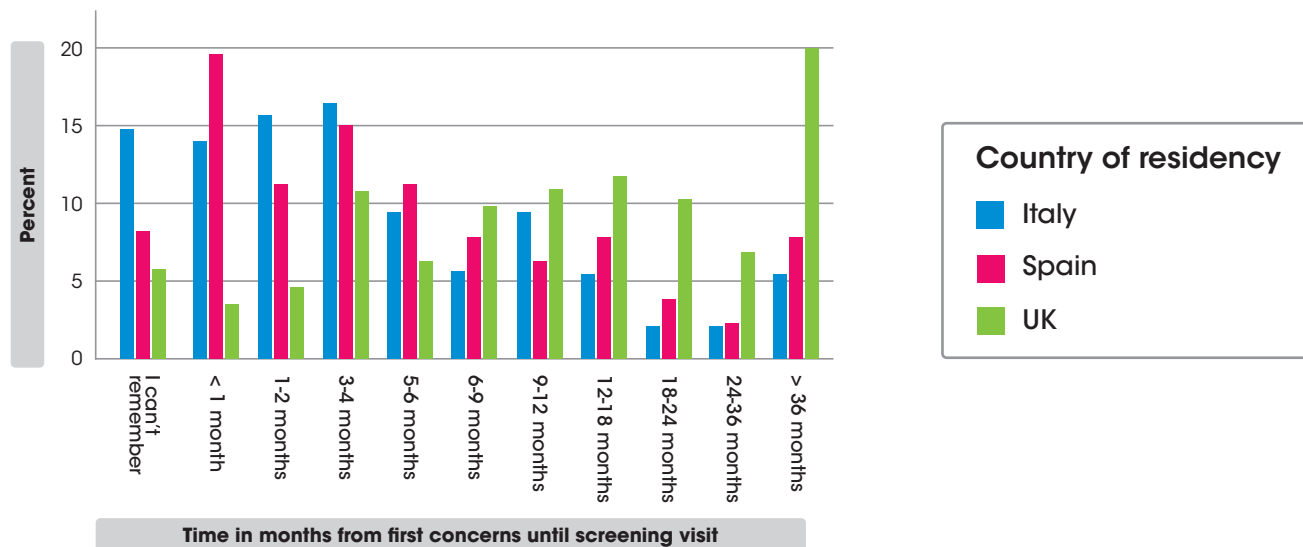
3. Limited information about autism and how to access early detection services:

- 62% of respondents reported that it was not easy to access information about early detection services.

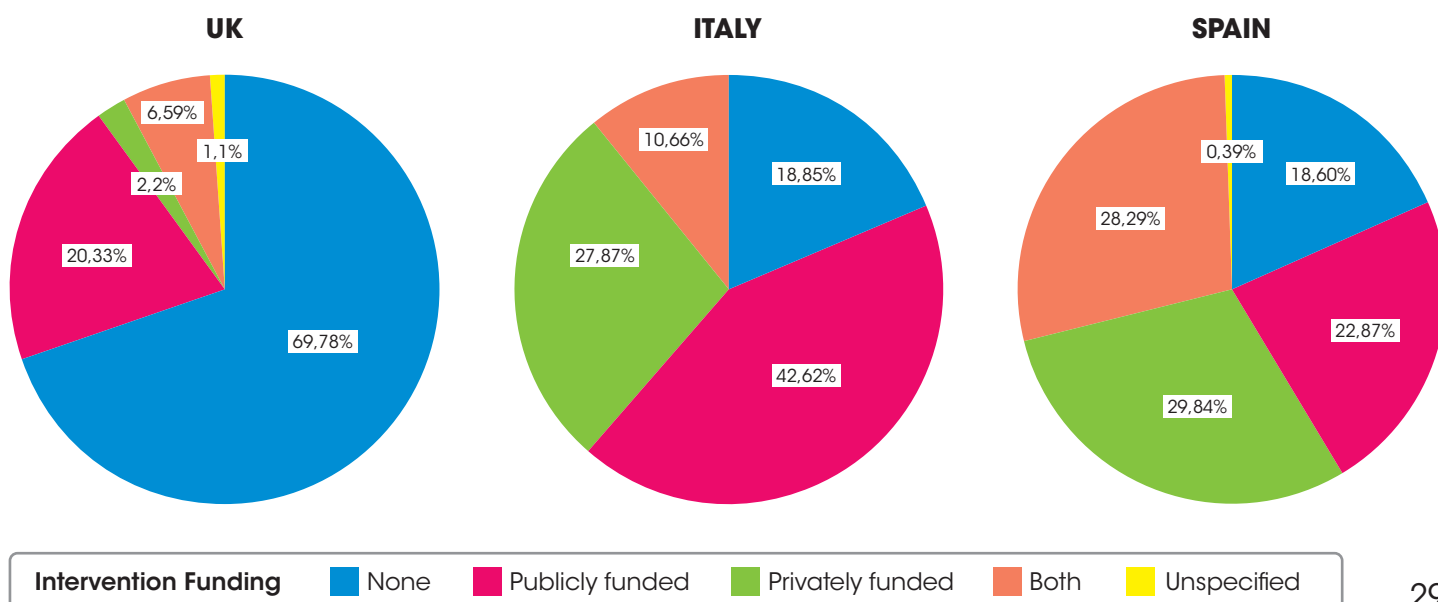
4. Lack of support to parents/carers of autistic children:

- 41% of respondents reported receiving no guidance or support after raising their first concerns to their assigned professional.
- 30% of respondents said they received very little or no support after the diagnosis was confirmed.
- 58% of carers that took part in our survey, said they had not received any training, coaching, or counselling to help them cope with their child's difficulties.

Screening/diagnosis times in each country:



Early intervention funding:



Recommendations

- **Raise awareness** among parents, family members, the community and primary care providers about developmental milestones, the early signs of autism and the importance of early detection and early intervention.
- **Encourage professionals to listen** to family concerns **and address** them immediately.
- **Increase autism-specific triage programmes** at well baby clinics.
- **Provide autism training** to first-line health professionals.
- **Reduce the delay in screening and diagnosis**, thus enabling children **to begin intervention programmes earlier**.
- **Increase support** to families of children diagnosed with autism.
- **The development of evidence-based interventions** for autistic people and their families must be considered a key research and clinical priority.
- **Perform further assessment** in order to identify and learn from countries/areas with better patient journey experiences.
- **Reduce economic inequality**.

Acknowledgements:

This work has received support from the EU/EFPIA/SFARI/Autistica/AUTISM SPEAKS, Innovative Medicines Initiative 2 Joint Undertaking (AIMS-2-TRIALS grant n° 777394), Servier and Roche.

References:

¹World Health Organization 2018; ²Myers et al 2021; ³Magan-Maganto et al 2017; ⁴Berajamo-Martin et al 2019.



Autism with co-occurring epilepsy care pathway in Europe

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Background

Autism and epilepsy are frequently associated¹. Electroencephalography (EEG) has been used to investigate epilepsy in autism². However, there is not a consensus regarding the time and frequency it should be conducted and routine EEGs are not recommended as a screening tool for epileptic activity in autistic children in current clinical autism guidelines. EEGs are only recommended if there is suspicion of epilepsy³ but the clinical identification of seizures in autism may be difficult as its presentation can be complicated by the presence of atypical body movements and behavioural patterns⁴.

Associated conditions in autism such as epilepsy have a substantial impact on the well being of autistic people and their families, contribute to reduced quality of life and may increase premature mortality⁵. Despite this, there is a current lack of studies assessing the journey experienced by autistic children with co-occurring epilepsy and their families in Europe.

The objectives of this study were:

1. To analyse autistic children with associated epilepsy's care pathway in three European countries: Italy, Spain and the United Kingdom (UK).
2. To propose policy recommendations on how to improve this care pathway (i.e. minimise treatment gaps).

Methods

The care pathway was analysed in order to identify major barriers preventing parents or carers of autistic children from receiving timely screening, diagnosis and treatment of possible co-occurring epilepsy.

We developed a survey aimed at parents or carers of autistic children ages 0 to 18 living in Italy, Spain or the U.K. The purpose of this survey was to collect information about carers' experience with local services from the moment they noticed difficulties with their children behaviour and/or neurodevelopment (first concerns), the time an autism diagnosis was confirmed, if an EEG was collected, time EEG was conducted, if autistic children were diagnosed with associated epilepsy and if epilepsy was treated.

Survey was approved by local ethics committees in the three countries.

Current pathway

552 of respondents (n=663) completed the questions about an associated epilepsy diagnosis (*Table 1*).

The majority of respondents (95%) who stated their autistic children were diagnosed with associated epilepsy said their children had an EEG done. The majority of the respondents (77%) stated EEGs were publicly funded.

The average age (in years) when epilepsy was diagnosed was 5.4 (SD 3.7) in Spain, 7.17 (SD 4.3) in Italy and 10.44 (SD 4.54) in the U.K.

The average age antiepileptic medication was initiated was 6.3 (SD 3.98) in Spain, 6.5 (SD 3.9) in Italy and 10.4 (SD 4.1) in the U.K.

Table 1.

Sample characteristics						
Autistic child’s age at time of survey, mean (SD)					10.17 (4.39)	
Sex of autistic child (% male, % female)					76,8%, 23,2%	

Co-occurring diagnosis of epilepsy						
			Italy	Spain	UK	Total
Diagnosis of epilepsy	No	Count	112	221	164	497
		%	94.1%	88.0%	90.1%	90.0%
	Yes	Count	7	30	18	55
		%	5.9%	12.0%	9.9%	10.0%
Total		Count	119	251	182	552

Treatment Gaps/Unmet Needs

1. Lack of screening of epilepsy in all autistic children:

44% of total respondents said their children were not screened for epilepsy using an EEG after autism diagnosis (*Graph 1*).

2. Delayed screening/diagnosis of epilepsy:

The average time from a confirmed autism diagnosis until EEGs were performed was 6 months in Spain and 2 years in the UK. However, they were done 4 months before in Italy.

The average time from EEGs until epilepsy diagnosis was on average 1 year in Spain and in the UK and over 3 years in Italy.

3. Delayed treatment of epilepsy in autistic children after diagnosis of epilepsy:

The average time from epilepsy diagnosis until medication was initiated was on average 15 months in Spain. However, medication in Italy started 8 months before epilepsy was diagnosed and 3 months before in the UK.

4. Lack of treatment of co-occurring epilepsy:

43% of autistic children with epilepsy in Spain and 33% in the UK were not taking any antiepileptic drugs while in Italy 100% of them were on antiepileptic drugs.

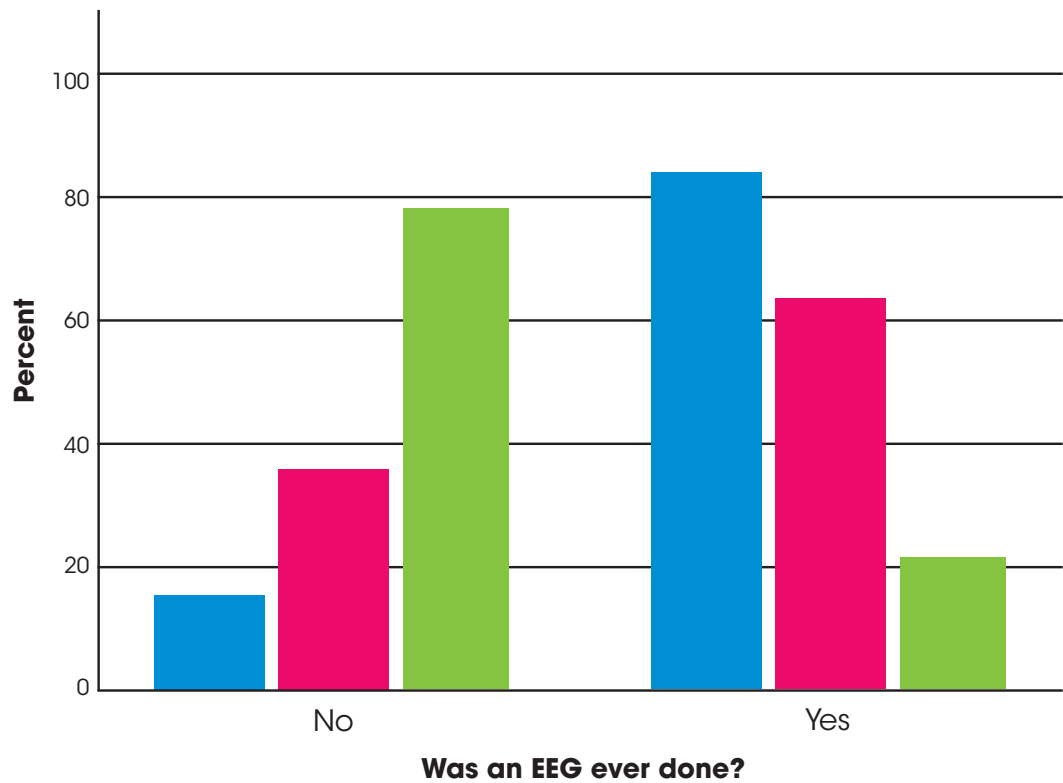
5. Use of multiple antiepileptic drugs:

43% of respondents in Spain stated their children were prescribed multiple antiepileptic drugs (*Graph 2*).

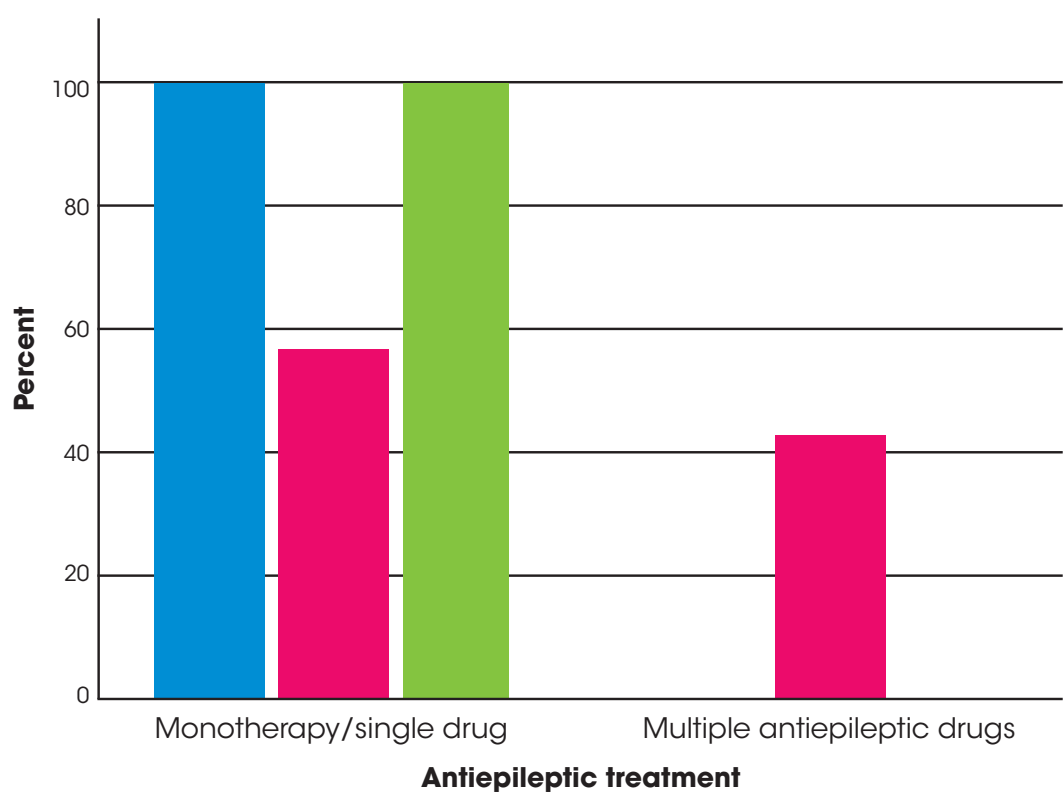
Recommendations

- **Screen every autistic child** for epilepsy using EEG soon after autism is confirmed.
- **Refer** the autistic child to an epilepsy specialist for **timely diagnosis and treatment of associated epilepsy**.
- **Provide information** on seizures characteristics, crisis management and basic life support to carers of autistic children.
- **The development of clinical guidelines specific** for epilepsy in autism must be considered a clinical priority.
- **Follow up** any children with an EEG showing epileptiform abnormalities without clinically evident seizures with an EEG recording once a year to assess evolution.
- **Avoid** use of multiple antiepileptic drugs in autistic children; however, the choice of treatment should be made by the specialist (in agreement with carers) and based on seizure type and/or epilepsy syndrome.
- **Clinical monitoring** of autistic children with diagnosed epilepsy at least twice a year.

Graph 1.



Graph 2.





Acknowledgements:

This work has received support from the EU/EFPIA/SFARI/Autistica/AUTISM SPEAKS, Innovative Medicines Initiative 2 Joint Undertaking (AIMS-2-TRIALS grant n° 777394), Servier and Roche

References:

¹Lukmanji et al 2019; ²Holler et al 2018; ³NICE 2021; ⁴Minshew et al 1997; ⁵Mason et al 2018.



Economic evaluation of anti-epileptic medicines for **autistic children with epilepsy:** healthcare provider and family perspectives

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Background

- Autism spectrum conditions (ASC) generate high costs, associated with use of long-term healthcare resources and have long-term negative impact on educational level, employment status and earned income.
- Aim of the **Value of Treatment (VOT) ASC case study**: to evaluate costs and consequences of two major treatment gaps: (a) appropriate early interventions; and (b) treatment for epilepsy in children with autism. Included countries are England, Ireland, Italy and Spain.
- **This poster reports preliminary results for economic analysis of treating epilepsy in autistic children, looking at the impact on healthcare providers (in England, Ireland, Italy and Spain) and children's families (in Ireland).**

Methods

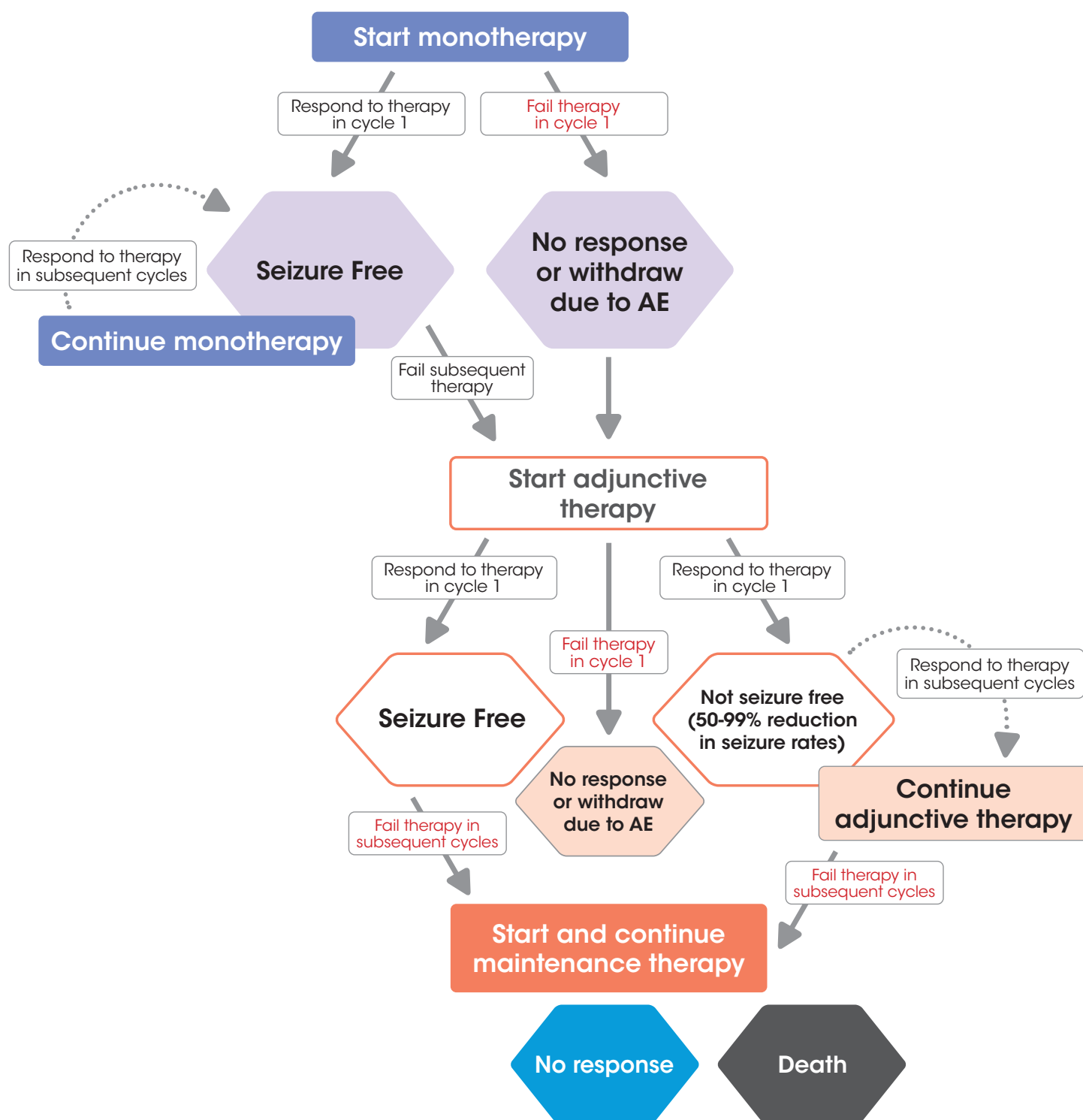
Impact on healthcare providers:

- We started with the economic model of pharmacological treatments for children with focal epilepsy published by NICE (*Figure 1*) and assumed that it would be applicable to autistic children with focal epilepsy.
- Costs (euro, 2020 prices) are associated with included hospitalisations, accident and emergency (A&E) visits, healthcare specialist visits and general practitioner (GP) visits.
- Effectiveness: response to monotherapy or adjunctive therapy (proportion who are seizure-free) and no response to therapy or withdrawal (due to adverse events); Quality Adjusted Life Years (QALYs).
- Comparison of alternatives: cost-consequence approach in alignment with other VOT case studies; plus incremental cost-effectiveness ratios (ICER per QALY) as in NICE guideline.
- Time horizon and sample: 15 years for a hypothetical cohort of 6-year-old children with newly diagnosed focal seizures.
- 3.5% discount rate was applied in order to adjust to the time expenses occurred.
- The robustness of the model was tested with deterministic and probabilistic sensitivity analyses.

Impacts on families:

- Costs (euros): out-of-pocket expenditure, lost earnings and informal (unpaid) care costs per child. Data collected in Ireland in 2015, adjusted to 2020 costs.
- Sample: families with a 6-year-old autistic child on epilepsy medication vs autistic children without epilepsy.
- Analysis and time horizon: separate scenario analyses for 7-year, 10-year and 15-year time-frames.
- Scenario analysis based on annual costs using 6 to 10 years cost data up to year 4. Cost data for year 5 onwards were based on the age category 11-13 years. We applied a 3.5% discount rate.

Figure 1. Impact on healthcare providers: Decision-analytic model of treatment with different antiepileptic medicines. (Note AE = adverse event)



Results

Impact on health care providers:

- **Monotherapy (Table 1):** Analysis for **the four countries** demonstrates the effectiveness and cost-effectiveness of carbamazepine as the optimal medicine to try first in children with newly diagnosed focal seizures.
- **Adjunctive therapy (Table 2), England:** Oxcarbazepine is potentially the most cost-effective adjunctive AED given a €20,000 per QALY threshold and preferred option for **Spain. In Ireland and Italy:** Gabapentin is the preferred option.

Impacts on families:

Difference in yearly family costs per child for autistic children on epilepsy medication vs those without epilepsy:

- €30,437 vs €20,867 (Age group: 6 to 13 years);
- €37,724 vs €21,149 (Age group: 6 to 10 years);
- €33,796 vs €16,966 (Age group: 11 to 13 years).

Results from the scenario analysis (7 to 15-year timeframes) are given in *Table 3*.

In Ireland, long-term family costs for autistic children treated for their epilepsy (€441,505 **for 15 years** (*Table 3*) **are likely to be 46 times more than costs for healthcare providers** when treating a similar cohort with focal epilepsy for the same period of time (€9,658 for children on monotherapy with carbamazepine, see preferred option in *Table 1*, vs. €7,128 for those on adjunctive therapy with gabapentine, see preferred option in *Table 2*).

Conclusions

Treating autistic children with epilepsy with medication is cost-effective, although different strategies may be needed in different countries. Including family costs is important because of the impact that extra caring demands place on family time and resources.

Acknowledgements:

The work was supported by the European Brain Council as part of the Value of Treatment 2.

References:

- 1 <https://www.nice.org.uk/guidance/cg137/>

Table 1. Impact on healthcare providers: summary results per child receiving monotherapy (15 years)

		England	Ireland	Italy	Spain	
	Total QALYs	Total Costs	Total Costs	Total Costs	Total Costs	ICER
Carbamazepine	10.18	27,627	9,658	6,690	7,377	Preferred*
Lamotrigine	10.09	27,686	14,552	12,385	11,013	Dominated
Oxcarbazepine	10.02	30,694	12,750	8,045	9,358	Dominated

*More effective and cost-saving than other alternatives.

Table 2. Impact on healthcare providers: summary results per child receiving adjunctive therapy (15 years)

		England	Spain		Ireland	Italy	
	Total QALYs	Total Costs	Total Costs	ICER	Total Costs	Total Costs	ICER
(Continued monotherapy)\$	9.41	23,495	10,208	(comparator)	9,647	8,057	(comparator)
Gabapentin	9.46	24,100	9,599	Dominated	7,128	5,381	Preferred*
Lamotrigine	9.47	24,290	9,944	Dominated	13,694	10,692	Dominated
Topiramate	9.51	25,376	8,456	Dominated	12,838	7,757	Dominated
Levetiracetam	9.52	26,169	7,886	Dominated	8,426	10,496	Dominated
Oxcarbazepine	9.52	25,218	6,721	Preferred*	8,806	6,084	Dominated

^ More cost-effective than comparator; *More effective and cost-saving than comparator.

Table 3. Impact on the family: Total costs (for the entire period featured in the scenario) per child for family out-of-pocket expenditure, lost earnings and informal care costs.

Ireland	with Epilepsy on Medication N=7	without Epilepsy N=214
Scenario 1: 7 years	€258,800	€140,254
Scenario 2: 10 years	€333,220	€177,613
Scenario 3: 15 years	€441,505	€231,917



Cost-effectiveness of early intervention for **autistic children**: findings from four case studies in England, Ireland, Italy and Spain

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Murphy D⁴, Oakley B⁴, Canitano R⁵, Quidbach V⁶.

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Background

- Autism spectrum conditions (ASC) can generate high costs, associated with use of healthcare and impacts on education, employment and income.
- Many interventions have been evaluated to support autistic people and families, but few show positive results.
- There is limited evidence on: improvements in cognitive ability and adaptive behavior for autistic children; improvements in quality of life and other important outcomes for children or families; cost-effectiveness; family impacts and societal consequences.
- The aim of the **Value of Treatment (VOT) ASC case study** was to evaluate costs and consequences of two major treatment gaps: appropriate early interventions and treatment for epilepsy in children with autism.
- **This poster reports preliminary results of the economic analysis of early intervention for autistic children in the four countries.**

Methods

Selection of intervention:

- Five criteria: effectiveness, cost-effectiveness, affordability, availability of staff skills and acceptability, and reach.
- Preferred intervention: Preschool Autism Communication Trial (PACT)¹⁻⁶.
- Effectiveness¹⁻⁵: Primary outcome: Effective reduction in symptom severity (trial and follow-up period). Secondary outcomes are listed below.
- Cost-effectiveness⁶: Not cost-effective. Improvements in outcome generated by PACT come at a cost.
- Affordability: £15.57 mean intervention costs per participant during the 13-month follow-up period (UK 2015; ⁶).
- Staff skills availability: More likely to be available across country settings (Therapists drawn from a variety of professions).
- Acceptability and reach: Accepted by professionals and reach across nations.

Analysis plan:

- **Model:** cost-consequences analysis
- **Measure of effectiveness:** primary outcome was severity of the symptoms of autism.
 - Secondary outcomes
 - > PACT trial: child language, parent-child dyadic communication, restricted and repetitive behaviours, difficulties with social interaction and communication and co-occurring mental conditions.
 - > Long-term follow-up study: parent-child interaction, child language and social communication, outcome assessments that were rated by the teacher.
- **Measure of costs:** intervention delivery plus use of resources and productivity loss.
- **Comparators:** treatment as usual (TAU) vs early intensive intervention (PACT+TAU).
- **Time horizon and perspectives:** 13 months and 6 years; public sector and societal perspectives (family employment impacts).
- Settings: Ireland, Italy, Spain and UK.
- **Deterministic sensitivity analyses** to test robustness of the model.

Results

Effectiveness, from the PACT trial and follow-up study:

- **After 13 months:** reduced symptom severity; increased parental communication synchrony with the child; and increased child communication initiations with the parent¹.
- **After 6 years:** significant overall reduction in symptom severity².
- PACT intervention was not associated with changes in parental mental health outcome or mental wellbeing levels when the children were in middle childhood³.
- Positive effect on family life experience measured with the Autism Family Experience Questionnaire (AFEQ⁴).
- Overall, parents reported positive changes in their interaction and relationship with their child and improvements to their child's communication and interaction⁵.

Costs:

- **At 13 months:** Service costs were significantly higher for PACT+TAU (for example England: mean difference euros 5,839, $p < 0.01$), but the differences in total societal costs were smaller and non-significant (*Table 1*).
- **At 6 years:** For England, the education and childcare costs were significantly lower for PACT+TAU (difference: -6,385; $p = 0.02$), but the difference between groups was non-significant (-40,835; $p = 0.43$; *Table 2*).
- For Ireland, Italy and Spain, the hospital-based health services costs were significantly lower for PACT+TAU (Ireland: difference is - 2,811; $p < 0.01$; Italy: difference is -3,629; $p < 0.01$; Spain: difference -2,010; $p < 0.04$), but the difference between groups was non-significant (*Table 2*).

Sensitivity analysis:

If we consider individual categories of costs, and we vary their relative unit costs estimates in the model by a given amount (+/- 20%; +/-30% and +/- 50%), preliminary results showed that:

- > If we increase family impacts by 20% or more, the PACT intervention is likely to be cost-saving. Changes in family impacts have a significant influence on the model results, followed by speech and language therapy (if cut down by 50%).

If we add out-of-pocket expenditure estimates (from Irish data [7]) the PACT intervention was found to be cost-saving (analysis limited to Ireland).

Conclusions

The PACT intervention is effective (at 13 months and longer term) in terms of reduced symptom severity and other secondary outcomes.

In the longer term, there is no statistically significant difference in costs (from both public service and societal perspectives across all four countries).

It is found to be cost-saving in sensitivity analysis which used Irish out-of-pocket expenditure estimates, which were substantially higher than those reported by families participating in the RCT in England.

Table 1. Total costs (euro) at 13 months

	PACT-TAU	TAU	Difference*	
	Mean	Mean	Mean	P Value*
ENGLAND	96,206	99,307	4,847	0.19
IRELAND	100,288	100,915	-627	0.96
ITALY	78,649	79,549	-899	0.92
SPAIN	73,356	70,804	2,552	0.80

*between intervention and control; no statistically significant effect.

Table 2. Total costs (euro) at 6 years

	PACT-TAU	TAU	Difference*	
	Mean	Mean	Mean	P Value*
ENGLAND	465,567	506,40	-40,835	0.43
IRELAND	490,634	527,352	-36,718	0.50
ITALY	366,300	398,463	-32,162	0.43
SPAIN	368,496	389,119	-20,622	0.61

*of intervention minus control; no statistically significant effect.

Acknowledgements

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⁵Leadbitter K, et al. 2020; ⁶Byford S, et al. 2015; ⁷Roddy and O'Neill, 2019.



Care pathways for people with major depressive disorder

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Background

Major depressive disorder (MDD) is now considered the leading cause of disability worldwide (World Health Organization, 2017) in part due to its high prevalence (which exceeds 300 million) and often enduring nature. The high rates of recurrence, chronicity and treatment-resistance indicate that MDD is treated suboptimally despite a multitude of effective interventions and well-regarded best-practice treatment guidelines. MDD's burden also stems from the widespread, common comorbidities with other physical and mental health conditions. Many individuals are not receiving treatment at any one time and it is known that both duration of untreated illness and the number of ineffective treatments trialled are risk factors for poorer long-term outcomes. Together, these phenomena demonstrate a need for improved management of MDD. To achieve this, we need to understand the nature and extent of 'gaps' in care pathways.

This project aimed to:

1. Identify the current 'treatment gaps' and patient needs along the care pathway, and determine the extent of these gaps (i.e. discrepancy between best- and current-practice).
2. Propose policy recommendation on how to improve the care pathway (i.e. minimise treatment gaps).

Methods

1. Care pathway analysis (objective 1):

- The project working group agreed upon a set of relevant treatment gaps, a priori, based on the current gold standard 'stepped care' MDD management guidelines (e.g. NICE).
- Data was gathered from a variety of sources pertaining to each treatment gap in each country - UK, Sweden, Germany, Italy, Portugal and Hungary – and was synthesised.

2. Consensus recommendations to optimise care pathways (objective 2):

- Based on the care pathway analysis, a modified-Delphi approach was undertaken for attaining expert consensus on proposed recommendations (Hidalgo-Mazzei et al. 2019).
- A set of 35 possible recommendations was developed by a core group based on our previous results. A panel of 15 experts across European countries [including mood disorders specialists, GP's, psychiatrists, people with lived experience of depression (non-clinicians)] rated their views across three survey rounds. New items were introduced or modified where suggested by panel members.
- Recommendations accepted where >80% agreement of item being 'essential' or 'important'.

Treatment Gaps/Unmet Needs

Current care pathways (split by treatment gap) averaged across data sources and countries.

- 1: Rate of depression detection: ~ **50% episodes**
- 2: Delays to detection or treatment of depression: ~ **1-5 years**
- 3: Rates of treatment: ~ **25-50% of patients**. Low rates particularly of psychological therapy
- 4: Follow-up after treatment initiation: ~ **30-65% of patients seen < 3 months**
- 5: Access to secondary (psychiatric) services: ~ **5-25% of patients**
- 6: Access to specialist mood disorders services: **Limited/no data**

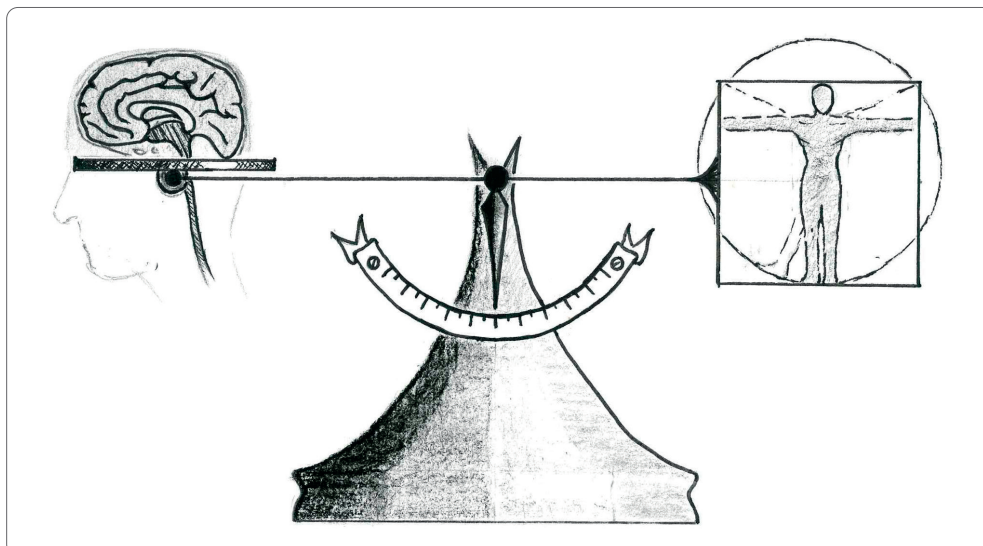
Quotations from project communications

"Primary care should have also employed psychologist, social workers and links with psychosocial rehabilitation units and institutions supporting employment seekers." [Psychiatrist, Sweden]

"We're 10,000 GPs short in England... We need as much help as we can get to deliver a caring, effective service." [GP, UK]

"I feel that physicians MUST be able to allocate the time that is really needed for a thorough evaluation of the patient and careful integrated therapy plan (pharmacological + psychological) prescription."

"Increases in access to secondary care for those who are suffering from depression is very important - rejection to access these services can really be damaging to the patient." [Person with lived experience, UK]



Recommendations

Consensus reached on 28 recommendations to optimise care pathways:

- 1. To enhance depression detection (pathway entry):** improved information provision to patients, increased service availability (GP appointment number, flexibility, duration), integrate self-management e-mental health tools with healthcare practice.
- 2. To improve treatment provision:** The right treatment to each patient (via e.g. decision-support tools, information provision to patients and encourage patient preference), prescribing support tools (integrated with electronic health records & facilitate shared-care provision between types of staff), increased provision of various psychological therapies, help for patients time off from work/education.
- 3. Continuity of follow-up after treatment:** Optimise self-management tools & feedback to clinicians, automatic appointment scheduling & reminders, increased service provision, standardised assessment of symptoms and side effects, screen for risk factors to indicate if more (or less) follow up needed.
- 4. Access to specialist care:** Enhanced training programs for clinicians to obtain specialism, clear and more lenient criteria for accepting psychiatric referrals (for those not responding to initial treatments), increased resources to services, integrating specialists into primary care, systems for transition into and out of specialist services – *applies to both secondary and tertiary care.*

Conclusions

There are substantial and concerning treatment gaps in depression care across Europe, from the proportion of people not entering care pathways to those stagnating in primary care with impairing and persistent illness. A wide range of recommendations can be made to enhance care throughout the pathway.

Acknowledgements

We are most grateful to the European Brain Council (EBC) for managing this project and for grants from Boehringer Ingelheim and Johnson & Johnson. This work is also supported by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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Economic impact of reducing treatment gaps in depression

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Background

Major depressive disorder (MDD) is highly prevalent across the world. While recovery over time is experienced for many, for others it represents a recurrent and chronic condition, and it imposes high economic costs in terms of use of services and impact on employment, education, and social participation. As with other mental health problems there is also stigma attached to having MDD. While there is a good evidence base to support the use of medication and different types of psychological therapy in the treatment of MDD, it is well-known that there are gaps in detecting MDD and the provision of effective treatment and continuity of care. If these gaps are reduced, there are likely to be impacts on healthcare and societal costs and patient outcomes. This study explores these issues, and this poster presents preliminary findings.

Methods

A decision analytic model (*Figure 1*) was constructed which follows the form of a care pathway which may be affected by treatment gaps. Patients with MDD are assumed to either have their condition detected or for it to be undetected. Care for detected cases can then be provided either in primary care or secondary care settings and follow-up support may be provided. For detected and undetected cases there will be some who recover and those who do not. To run the model, we use data on the probabilities of different events occurring, the costs of those events, and the quality-adjusted life years (QALYs) accrued over time which depend on treatment outcomes. This allows us to estimate expected costs and QALYs with existing patterns of care and then following the reduction of treatment gaps.

In these analyses we focus on certain aspects of the care process (*Figure 1*). These aspects are the probabilities of cases being detected and different treatments being provided or remaining untreated. Probabilities for the model are obtained from the linked study,¹ using data from Germany, Hungary, Italy, Portugal, Sweden, and the UK as well as from the wider literature on depression care. The costs of care and associated QALYs are based on recognised therapies (medication, cognitive behaviour therapy, or combined treatment).² Assumptions are made about costs and QALYs for undetected cases. Costs are adjusted to reflect prices in each country³ and incremental cost-effectiveness ratios calculated. Uncertainty is addressed through a series of sensitivity analyses around key model parameters.

Results

From the included countries we estimate 69% of cases are undetected. Of detected cases, around 50% receive treatment and of these we estimate 70% receive medication only, 23% receive psychological therapy, and 7% receive both. Expected costs and QALYs over a 27-month period for those receiving care for MDD based on the above estimates are shown in Table 1 for each of the six countries. Uncertainty exists around the costs for cases of undetected and untreated MDD. These were initially assumed to be €750 and €100 respectively in the UK and sensitivity analyses were conducted whereby these were increased or decreased by 25%. Expected QALYs are **0.716** assuming that those undetected or untreated do half as well as those on medication. If they do 75% as well then expected QALYs overall are **0.977**.

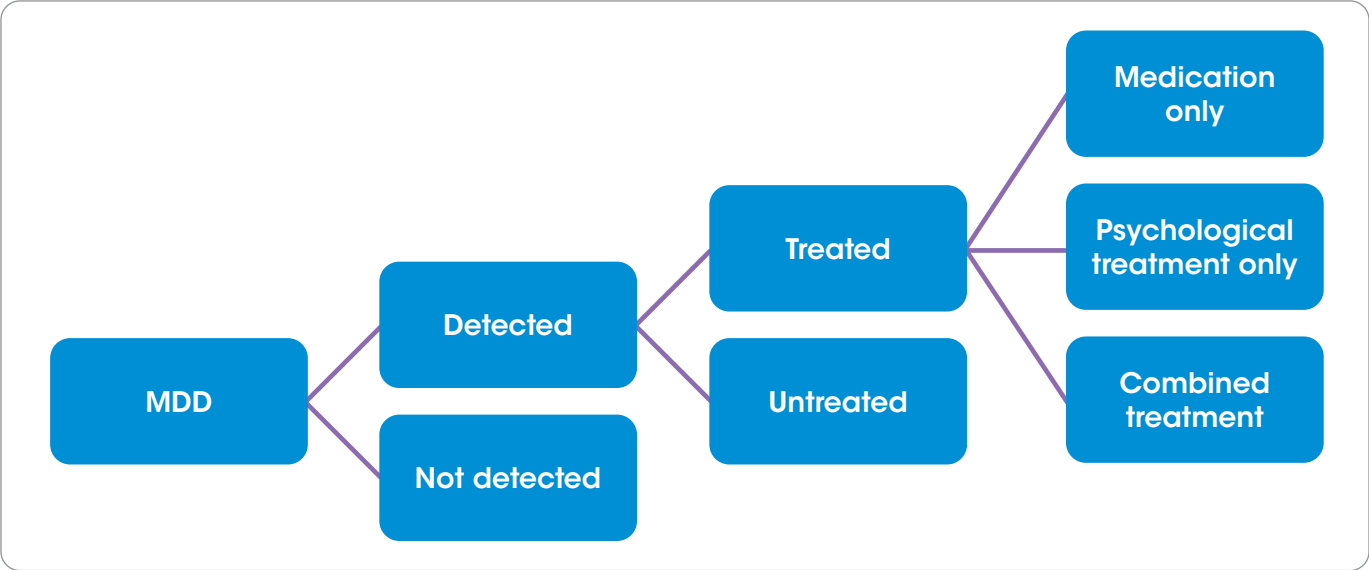


Figure 1: Decision model to access economic impact of reducing treatment gaps

	GERMANY	HUNGARY	ITALY	PORTUGAL	SWEDEN	UK
Expected costs	1236	476	1413	938	2093	1495
Undetected and untreated costs decreased 25%	1097	422	1254	832	1857	1327
Undetected and untreated costs increased 25%	1376	529	1572	1043	2328	1663

Table 1: Expected costs for baseline model by country (2020 €s)

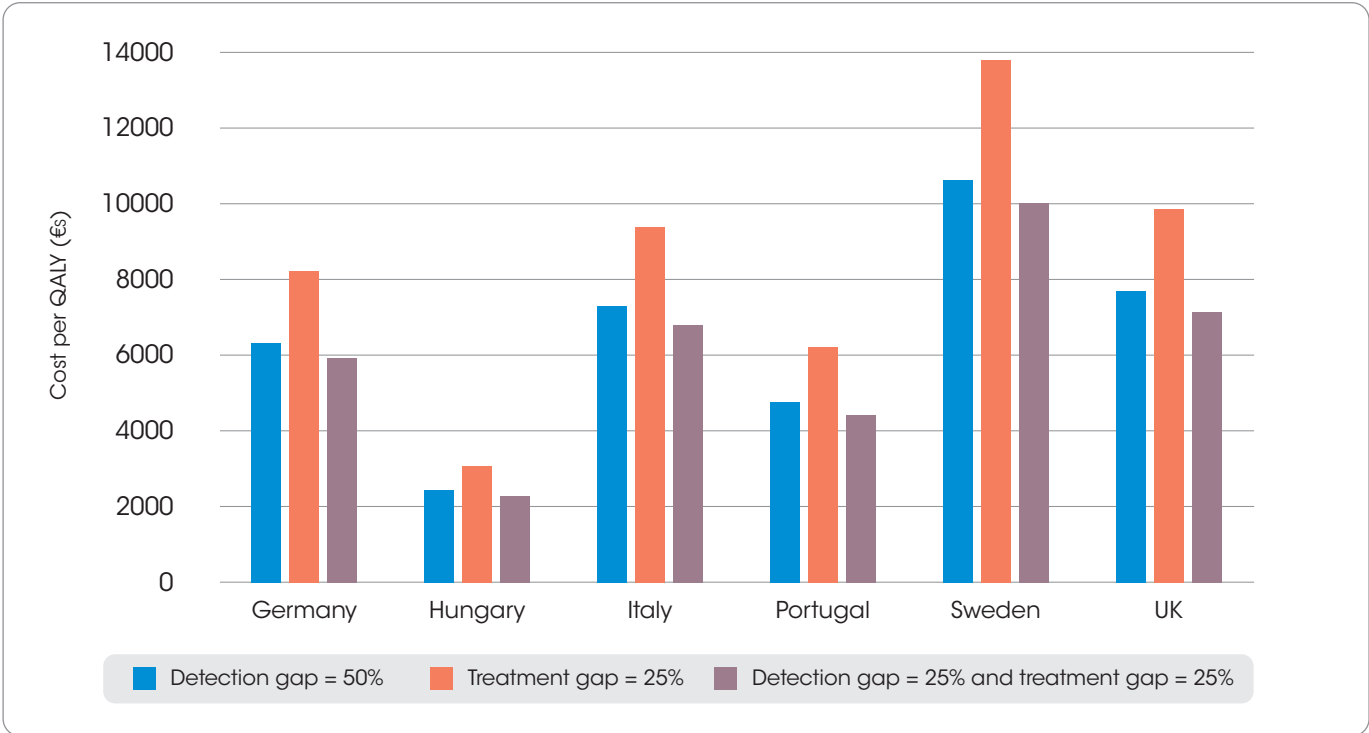


Figure 2: Incremental cost per QALY of reducing detection and treatment gaps

Based on the model, we show that if the detection gap is reduced from 69% to 50% there are increased costs over a 27-month period but also increased QALYs. This is also the case for reduced treatment gaps for cases which are detected. Figure 2 shows the extra costs incurred to achieve one extra QALY. In the UK, the threshold is £20,000 (around €23,000) and it can be seen that each of these scenarios would be cost-effective with current models of care. If extra resources are required to reduce the detection and treatment gaps then we can see how much these could amount to and remain below the threshold. For example, in the UK the incremental cost associated with reducing the detection gap to 50% is €456. This could increase by €919 and cost-effectiveness would still be achieved. Similar findings apply to the other countries.

Conclusions

Reducing gaps in the detection and treatment of MDD is important for the quality of life of those affected. Reducing treatment gaps may actually increase economic costs. This is likely to be particularly the case in the short term. However, increased costs can be entirely justified if outcomes are sufficiently improved. The preliminary findings from our modelling work suggests that QALYs are increased if more cases of MDD can be detected and if more of those who do have MDD detected go on to receive treatment. The incremental cost-effectiveness ratios suggest that interventions to reduce the treatment gaps may represent good value for money. There are limitations to the study. It focuses on healthcare costs and some benefits from increased detection and treatment will arise in other sectors. Also, we do not evaluate the means by which the gaps may be reduced and that is a useful topic for further research.

Acknowledgements

We are most grateful to the European Brain Council (EBC) for managing this project and for grants from Boehringer Ingelheim and Johnson & Johnson. This work is also supported by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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