Unleashing the potential of seizure dogs

an evaluation of their clinical, economic, and broader impacts in the management of epilepsy

Valérie van Hezik-Wester

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Colophon

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Unleashing the Potential of Seizure Dogs

An evaluation of their clinical, economic, and broader impacts in the management of epilepsy

Het potentieel van epilepsiehonden onthuld

Een evaluatie van hun klinische economische en bredere impact in het management van epilepsie

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Chapter 1

General introduction

People with epilepsy experience a substantial disease burden that extends beyond physical health. The disorder affects various aspects of the quality of life of the individuals affected, as well as that of their family members. Despite a wide range of treatment options, some individuals continue to experience frequent seizures. These persons with severe refractory epilepsy (PSREs) face ongoing challenges in managing the disorder's impact in their daily lives. Seizure dogs, trained to recognise and respond to seizures, offer a promising solution to alleviate the burden for PSREs. This thesis presents the design, implementation, and results of a clinical trial evaluating the clinical, economic, and broader impacts of seizure dogs in adult PSREs in the Netherlands. In this introduction, an overview of epilepsy is provided, from its definition to the epidemiology, and a description of the clinical journey. Subsequently, seizure dogs are introduced and their potential benefits in epilepsy management are explained. Then, the basis of Health Technology Assessment (HTA) and its use in policymaking is discussed. Finally, the political rationale behind the trial is presented, followed by an outline of this thesis, its aim, and its structure.

Epilepsy

Definition and classification of epilepsy

Epilepsy is a complex neurological disorder characterised by recurrent seizures, which result from abnormal electrical activity in the brain. The most recent definition, proposed by the International League Against Epilepsy (ILAE), defines epilepsy as a disease of the brain defined by any of the following conditions [1]:

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart;
2. one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
3. diagnosis of an epilepsy syndrome.

Seizures vary in severity and presentation, ranging from brief lapses in awareness to intense convulsions. ILAE divides them into two main categories: generalised seizures, which affect both sides of the brain, and focal seizures, which start in one part of the brain [1]. Generalised seizures come in various forms such as absence seizures, characterised by a short loss of awareness, myoclonic seizures that involve muscle spasms, and tonic-clonic seizures marked by a combination of muscle stiffening and shaking. Focal seizures are either simple (without loss of consciousness) or complex (with impaired consciousness). Epilepsy types are named based on where seizures start in the brain: focal, generalised or a mix of both. In some cases, the onset of seizures and the epilepsy type remain unknown. Rather than a single disease; epilepsy

is a group of disorders with various causes [1]. These include, amongst others, genetic predispositions, brain injuries, infections, developmental issues and metabolic problems. In some people, the cause of epilepsy remains unidentified.

Prevalence, incidence, morbidity, and mortality

Epilepsy stands out as one of the most common serious neurological conditions. Considering the entire spectrum of epilepsy types and causes, approximately 50 million people worldwide are affected by active epilepsy (i.e., persistent seizures, needing treatment, or both) [2]. In the Netherlands alone, an estimated 98,000 individuals experience active epilepsy [3], with every year about 11,000 people receiving the diagnosis [4].

The health impact of epilepsy encompasses both the immediate consequences of seizure activity (e.g., loss of consciousness, muscle aches, exhaustion, incontinence) as well as indirect impacts such as medication side effects and the constant tension of not knowing when the next seizure will occur [5-7]. Moreover, seizures pose a risk of injuries, such as fractures and head traumas, resulting from falls or accidents [8-11]. The broad impact of the condition is further evidenced by psychiatric comorbidities, lower employment rates and impaired self-esteem [12-14]. While those who achieved seizure freedom have a mortality risk similar to the general population, persons with persistent seizures face a mortality risk three times higher [15,16]. The primary contributors to this heightened mortality risk include sudden unexpected death in epilepsy (SUDEP, a condition in which someone with epilepsy dies suddenly without any other apparent cause), status epilepticus (i.e., a prolonged seizure), accidents, drowning, and suicide [15-19].

Clinical pathway

The clinical pathway for individuals with epilepsy can be complex and lengthy. It generally involves a comprehensive evaluation including electroencephalogram (EEG) to confirm the diagnosis and identify the type and location of seizures. Following diagnosis, individuals are typically prescribed anti-seizure medications with the aim of achieving seizure freedom [20].

About one-fourth of persons with epilepsy continues experiencing seizures even after trying multiple anti-seizure medications [21-24]. These individuals, categorised as having refractory epilepsy, may be referred to a tertiary epilepsy centre for further assessment and treatment. This could involve additional diagnostic procedures to assess eligibility for resective surgery, depending on the location and extent of the epileptic focus.

When surgery is either not an option or fails to provide seizure freedom, alternative treatments like neurostimulation (e.g., vagus nerve stimulation and deep brain

stimulation) and dietary therapies (e.g., ketogenic diet) can be considered [20]. Nevertheless, there is a distinct subgroup known as persons with severe refractory epilepsy (PSREs). These individuals continue to experience frequent seizures despite all available treatment options, including both pharmacological and non-pharmacological approaches.

Persons with severe refractory epilepsy are challenged with adapting to the prospect of lifelong seizures, which often requires changes in lifestyle, behaviours, and expectations

PSREs are challenged with adapting to the prospect of lifelong seizures, which often requires changes in lifestyle, behaviours, and expectations. A range of assistive care services is available to support them, designed to enhance safety and improve disease management. These services include seizure monitoring and alarm systems, home safety modifications, self-management tools and counselling [20]. Despite these aids, living with frequent seizures necessitates careful planning and caution, often leading to restrictions in mobility, learning and career opportunities, hobbies and independent living. These restrictions in day-to-day activities, along with the unpredictable nature of seizures and the complexity of managing treatment, frequently lead these individuals to rely heavily on informal care, that is, family members and friends providing the support they need.

In other words, despite the treatments and assistive care services available, PSREs and their informal caregivers continue to face a significant disease burden. Innovative solutions are constantly explored to address these unmet care needs and improve the quality of life of PSREs and their informal caregivers. Among these, seizure dogs have gained attention as a unique approach to address both the seizure-related risks and emotional aspects of living with severe refractory epilepsy [25]. Exploratory studies suggested increased quality of life and even reductions in seizure frequency [17-19,26-29], the latter possibly linked to reduced stress, a known trigger for seizures [30-32].

Seizure dogs

Within the domain of seizure dogs, two distinct functions can be distinguished: responding and alerting. This distinction is important in understanding the way these dogs can assist PSREs.

To develop response behaviour, dogs undergo formal, specialised training to deliver immediate and tailored assistance when a seizure occurs. The training equips them with the skills necessary to enhance the safety and comfort of PSREs during and after a seizure. These skills are tuned to align with the unique needs and specific seizure characteristics of their human companion. These skills may, for instance, be oriented

towards facilitating medical intervention by activating an alarm system to notify family members or health care professionals, or retrieving a phone or bringing medication. Seizure dogs can also be trained to provide physical support by placing the PSRE in the recovery position or intervening to limit their movement when seizures lead to impaired awareness.

Alert behaviour, in contrast, may occur spontaneously. It consists of presenting distinct behaviour — such as increased eye contact, circling, or pawing — prior to a seizure in their human companion. When such a pattern is identified, the behaviour can serve as a warning for the PSRE, allowing them to prepare or seek assistance. Both formally trained dogs and regular companion dogs have been reported to show these alert capabilities [17,28,33-35]. Research indicates that these dogs may respond to specific scents produced before a seizure [34,36-38]. While some assistance dog organisations claim this behaviour can be acquired through training as well for certain PSREs [26,39-41], the medical community remains sceptical about the reliability and trainability of alerting behaviour [28,42-45].

Beyond their immediate response behaviours surrounding seizures, seizure dogs may provide emotional support in navigating the challenges of epilepsy in daily life

Additionally, beyond their immediate response behaviours surrounding seizures, these dogs may provide emotional support to PSREs as they navigate the challenges brought by epilepsy in their daily lives. The multifaceted potential of seizure dogs is difficult to replicate with existing technologies alone, positioning them as a promising complementary source of assistance and reassurance.

Seizure dogs in the Netherlands

In the Netherlands, there are currently three accredited organisations that train seizure dogs in compliance with the international standards for assistance dogs [46]. The training program of the two organisations that supply the majority of seizure dogs is dedicated to developing response behaviours in the dogs. Due to limited understanding of the underlying mechanisms, alerting behaviours are not part of their training program, but trainers actively monitor for spontaneous occurrence. The costs of seizure dogs are substantial and are currently not covered through the basic health insurance package. Hence, financing a seizure dog currently relies on family resources, charitable contributions, crowdfunding, or, in some cases, municipal funding under the Social Support Act. The costs may be a hurdle for PSREs to obtain a seizure dog and, consequently, only few PSREs in the Netherlands currently have a seizure dog.

In this thesis, aligning with its prominent current use in the Netherlands, the term 'seizure dog' will be used to refer to a dog formally trained in response behaviours, regardless of whether it also has the natural ability of alerting to seizures.

The costs of seizure dogs are substantial and are currently not covered by basic health insurance

Health Technology Assessment

In publicly funded health care systems, like in the Netherlands, the adoption of new medical interventions into clinical practice depends heavily on their eligibility for reimbursement, particularly for high-cost interventions. Health systems aim for an efficient and fair allocation of their limited funds. As medical technology rapidly advances and health care demands increase, deciding which interventions should be covered by basic health insurance becomes progressively challenging. HTA emerged as a key tool in guiding these decisions. HTA is a comprehensive process to systematically assess the properties, impacts and value of health technologies. Its goal is to guide decision-making processes to foster an equitable, efficient and high-quality health system [47]. The primary focus often is on clinical benefits and efficiency expressed through cost-effectiveness, hereby promoting that funds are directed towards the interventions that prove most beneficia [48]. A full HTA process may, however, also consider broader societal impacts such as ethical, legal, practical and distributional consequences of implementing health care services [49]. In this respect, the field of HTA has increasingly recognised the value of including qualitative research to highlight aspects that quantitative methods might overlook, especially when evaluating complex interventions [50-55]. Integration of qualitative methods, such as interviews and focus groups, can result in a more informed and nuanced understanding of the intervention's impacts by capturing patient experiences, social contexts and ethical considerations. Policy makers can then consider these factors alongside the quantitative assessment in their decision on the reimbursement of the intervention.

HTA in the context of Dutch reimbursement decision-making

In the Netherlands, the National Health Care Institute (Zorginstituut Nederland, ZIN) has an important role in safeguarding the quality, accessibility and sustainability of the health care system. ZIN uses HTA to advise the Minister of Health, Welfare and Sport on reimbursement decisions. At the moment, ZIN does so only in certain cases, such as for outpatient pharmaceuticals, expensive inpatient pharmaceuticals, or in situations where there are disputes among stakeholders about the reimbursement of health care interventions [56,57]. However, ZIN aspires to systematically apply HTA to a wider range of health care services [58]. The first step in ZIN's assessment is evaluating

an intervention's clinical effectiveness against usual care [56]. This acts as a gateway criterion; adequately demonstrating meaningful health benefits (relative to usual care) is a legal requirement for inclusion in the basic health insurance package, as regulated by the Health Insurance Act (Zorgverzekeringswet) [59]. Alongside effectiveness, ZIN may consider broader societal criteria encompassing necessity, cost-effectiveness and feasibility, collectively known as the package criteria [57]. For the consideration of cost-effectiveness, ZIN requires an economic evaluation to determine whether the societal value of the health gains outweigh the costs of the intervention [57,60]. In practice, given that conducting economic evaluations is resource- and cost-intensive, this criterion is only evaluated for pharmacological interventions that bring significant costs per patient or have considerable cumulative impact on the health care budget [57]. However, the growing recognition of the relevance of cost-effectiveness in decision-making is fuelling discussions about possibly giving this criterion a formal legal status, which would expand the application of economic evaluations to a more diverse range of interventions [57].

There is a growing recognition of the relevance of cost-effectiveness in reimbursement decision-making

Economic evaluations often take the form of cost-utility analyses, which relate the costs of the intervention to its health outcomes expressed as quality-adjusted life-years (QALYs) gained. The QALY is a way to measure health outcomes by considering both the quality and the duration of remaining life. This approach assigns a utility value to health states, where 0 is equivalent to the health state 'dead' and 1 reflects the state 'perfect health'. The utility value is usually measured using generic health-related quality of life instruments, allowing for comparisons between various health conditions. EQ-5D is the preferred instrument by ZIN and other HTA bodies [61,60]. The utility value of a health state is multiplied by the duration spent in that health state to calculate QALYs. Therefore, one QALY represents one year lived in perfect health, while two years lived in a health state with a utility score of 0.5 (indicating relatively poor health) would also equate to one QALY.

On the cost side of the cost-utility analysis, what is included depends on the perspective taken for the evaluation. To inform an assessment by ZIN, a societal perspective is preferred [60]. This broader approach considers the medical costs and the expenses that fall outside the health care sector. For instance, this may include valuing the time individuals are absent from work due to their illness (i.e., productivity costs) or the time family members dedicate to providing informal care.

To determine whether an intervention can be considered cost-effective, ZIN compares the ratio of the incremental costs and incremental effects (ICER), that is, the costs per QALY gained of an intervention, to a predefined reference value that reflects the

societal willingness-to-pay for one QALY. These thresholds are scaled according to disease severity at €20,000, €50,000, and €80,000 per QALY, reflecting a greater willingness to invest in interventions for more severe conditions [62].

Challenges in HTA

HTA facilitates a comparison of benefits and costs across different conditions and interventions and thus contributes to a more consistent evaluation of health care services and a fairer and more transparent reimbursement decision-making process. However, several challenges remain to fulfilling this ambition. Although HTA was originally focused on a broad spectrum of health technologies, HTA guidelines and decision-making processes have been primarily developed to align with the characteristics and evidence standards of pharmacological interventions [63,64]. The assessment of other types of health care interventions sometimes requires changes to these methodologies and processes. The application of HTA methodologies is, for example, more challenging when evaluating assistive care services such as lifestyle interventions, digital health solutions, psychotherapy, community-based health programs and medical aids. These interventions differ from pharmaceuticals, which are typically standardised products with clear mechanisms of action. In contrast, these non-pharmacological interventions are dynamic and often involve complex context-sensitive interactions that influence intervention outcomes [65]. One major hurdle in broadening HTA's application is, therefore, its reliance on a single standardised metric like the QALY for capturing the value of the intervention. Non-pharmacological interventions often target a broader spectrum of benefits that extend beyond immediate health outcomes, such as enhancements in autonomy or societal participation, which these conventional metrics may fail to capture adequately. Additionally, the absence of marketing authorization processes and proprietary rights for many assistive care services means that there is often no single entity responsible for investing in the generation of robust evidence through costly clinical trials [63]. This situation presents a substantial barrier to the comprehensive evaluation of these diverse health care interventions, which may explain their underrepresentation within HTA studies and guidelines.

Another challenge arises when HTA is applied to interventions aimed at conditions with an episodic nature, such as epilepsy. The fluctuating impact of such conditions on a patient's quality of life complicates the consistent quantification of the health benefits of interventions [66-68]. This creates a particular difficulty in evaluating interventions like seizure dogs, where both the intervention itself and the condition it addresses exhibit dynamic and unpredictable characteristics.

The rationale behind the EPISODE study

PSREs are challenged with balancing the ever-present risks of seizures with pursuing a fulfilling, active life. As such, they bear a substantial disease burden that extends beyond their physical health, affecting their overall quality of life and that of their families and informal caregivers as well. Seizure dogs have been proposed as an assistive care service for them, bringing a unique combination of response behaviours and emotional support that can complement existing interventions.

Following a review of the international scientific literature available in 2012, ZIN concluded that seizure dogs did not meet the effectiveness criterion required for inclusion in the basic health insurance package [69]. This decision was based on evidence that appeared encouraging but was largely anecdotal and mainly focused on the benefits of alerting behaviour. Following ZIN's decision, a Member of Parliament in the Netherlands advocated for funding a rigorous study to collect better evidence on seizure dogs. This initiative was supported by the Ministry of Health, Welfare and Sport, which commissioned a comprehensive study to facilitate ZIN's reassessment concerning seizure dogs [70]. Known as the EPISODE (EPIlepsy SuppOrt Dog Evaluation) study, this project was coordinated by the Erasmus School of Health Policy & Management and involved a multidisciplinary consortium to explore the multifaceted potential of seizure dogs.

Thesis aim

The overarching objective of this thesis is to inform a comprehensive evaluation of the multifaceted potential of seizure dogs for adults with severe refractory epilepsy , by assessing their clinical effectiveness, cost-effectiveness, and broader impacts. While the EPISODE study was designed to inform a reimbursement decision in the Netherlands, it is also the first randomised controlled trial and economic evaluation in this field worldwide. This thesis may, therefore, also serve as a valuable resource for a broader audience. It can inform PSREs, their informal caregivers, policymakers and medical professionals on the effects and costs associated with seizure dogs. Furthermore, considering the aforementioned challenges, the EPISODE study central to this thesis serves as a case study in dealing with the complexities of broadening the scope of HTA.

The aim of this thesis branches into several research questions:

1. What is the disease burden of severe refractory epilepsy for affected adults and society?
2. How do seizure dogs impact the seizure outcomes and quality of life of adults with severe refractory epilepsy?
3. Are seizure dogs a cost-effective assistive care service for adults with severe refractory epilepsy in the Netherlands?
4. What are the experiences of people partnered with a seizure dog and their informal caregivers?

Outline

The remainder of this thesis consists of six chapters that address the research questions, followed by a general discussion. Chapter 2 introduces the study protocol of EPISODE, offering insights into the academic and practical reasoning behind the research design. Next, Chapter 3 and Chapter 4 address research question 1. Chapter 3 explores the complex task of quantifying health-related quality of life in the context of epilepsy's episodic nature, while Chapter 4 investigates the burden of illness of severe refractory epilepsy as observed in EPISODE study participants. Chapter 5 addresses research question 2 and presents the findings of the EPISODE study concerning the effectiveness of seizure dogs. Chapter 6 addresses research question 3, presenting a model-based economic evaluation exploring the cost-effectiveness of seizure dogs as assistive care service from a societal perspective. In Chapter 7, research question 4 is addressed, describing a nested qualitative study of the experiences of EPISODE study participants and their informal caregivers regarding the impacts of a seizure dog. Finally, Chapter 8 discusses the overall contribution of the research presented in this thesis and recommendations for research and policy.

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Chapter 2

Evaluating the effectiveness and cost-effectiveness of seizure dogs: study protocol for a stepped wedge randomised controlled trial (the EPISODE study)

Highlights

- The EPISODE study is designed to inform a reimbursement decision by the Dutch Ministry of Health, Welfare, and Sport.
- It uses a stepped wedge design in which all trial participants receive a seizure dog in a randomised order.
- Beyond the primary focus on seizure outcomes, the study assesses impacts on quality of life, resource use, productivity, social participation, and informal caregiver burden.

Abstract

Background and objectives

Epilepsy is associated with a high disease burden, impacting the lives of people with epilepsy, their informal caregivers, and family members. Persons with severe refractory epilepsy (PSREs) experience the greatest burden, suffering from profound physical, psychological, and social consequences. Anecdotal evidence suggests these persons may benefit from a seizure dog. As the training of a seizure dog is a substantial investment, their accessibility is limited in the absence of collective reimbursement as seen in the Netherlands. Despite sustained interest in seizure dogs, scientific knowledge on their benefits and cost impacts remains scarce. To substantiate reimbursement decisions, stronger evidence is required. The EPISODE study aims to provide this evidence by evaluating the effectiveness and cost-effectiveness of seizure dogs in adult PSREs.

Methods

The study is designed as a stepped wedge randomised controlled trial that compares the use of seizure dogs in addition to usual care, with usual care alone. The study includes adults diagnosed with epilepsy, for whom current treatment options failed to achieve seizure freedom. Participants should experience at least two seizures per week, and the seizures should be associated with a high risk of injury or dysfunction. During the three-year follow-up period, participants receive a seizure dog in a randomised order. Outcome measures are taken at multiple time points both before and after receiving the seizure dog. Seizure frequency is the primary outcome of the study and will be recorded continuously using a seizure diary. Questionnaires measuring seizure severity, quality of life, resource use, productivity, social participation, and informal caregiver burden will be completed every three months. The study is designed to include a minimum of 25 participants.

Discussion

This protocol describes the first randomised controlled trial on seizure dogs. The study will provide comprehensive data on the effectiveness and cost-effectiveness of seizure dogs in adult PSREs. The broader benefits of seizure dogs for PSREs and their informal caregivers are taken into account, as well as the welfare of the dogs. The findings of the study can be used to inform decision-makers on the reimbursement of seizure dogs.

Introduction

Epilepsy is a common neurological disorder, affecting approximately 50 million people worldwide [2,3]. The disorder is characterised by recurrent unprovoked seizures which, for most persons, can be controlled with anti-seizure medication (ASM) regimens. In about one-third of the persons with epilepsy, seizure freedom is not achieved despite the use of multiple ASM regimens at therapeutic dosage [71]. These individuals are considered to have refractory epilepsy [72]. Resective surgery, wherein a small portion of brain tissue is removed, may be a treatment option for this group of persons with epilepsy. However, only about half of them meets the strict eligibility criteria, and about 50% of procedures does not result in sustained seizure freedom [73,74]. Neurostimulation has offered new treatment options in refractory epilepsy with vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation. However, these advances seldomly result in seizure freedom [75,76]. Consequently, a group of persons continues to face the challenges of living with persistent seizures. Some of them have frequent seizures on a regular (e.g., daily to weekly) basis. In this thesis, these individuals are referred to as persons with severe refractory epilepsy (PSREs).

Burden of refractory epilepsy

Seizures are associated with several risks, leading to increased rates of morbidity and mortality in persons with epilepsy [77-82]. Individuals affected by epilepsy on average have a lower quality of life, for instance due to medication side effects and seizure-related injuries. Psychological distress is also a common concern in epilepsy, with affected individuals being twice as likely to report depression and anxiety compared to the general population [83,84]. The most important contributor to excess mortality is sudden unexpected death in epilepsy (SUDEP), that is, death occurring without finding a toxicological or anatomical cause [79,82,85,86]. Other causes for excess mortality include status epilepticus and seizure-related accidents [80,81,85]. While rare among persons with new-onset epilepsy, seizure-related deaths may account for up to 40% of all deaths in persons with refractory epilepsy [80,87,88]. While persons with refractory epilepsy represent the minority of the total epilepsy population, they account for most of the disease burden [89].

In addition to the health impact, refractory epilepsy comes with restrictions in several life domains including housing, education, occupation, transportation, and role expectations. As a consequence, affected individuals might feel restricted in their social life and independence as they generally rely heavily on informal care or community services. Finally, it is widely acknowledged that refractory epilepsy can be considered a cost-intensive disorder, with estimates of the indirect costs (productivity and informal care-related costs) generally exceeding the direct costs (epilepsy management-related costs) [90,91]. As such, refractory epilepsy imposes a burden not only on the affected individuals but also on their families and on society as a whole [92,93].

Seizure dogs

The seemingly unpredictable nature of seizures is often considered to be the most disabling aspect of the disorder. Timely detection therefore is essential and can reduce the risks that accompany seizures through early intervention. This has caused PSREs and researchers to seek out tools that can help with detecting seizures and/or alarming informal caregivers during seizures. Technological solutions so far have not been able to recognise all types of seizures [94], which may explain the sustained interest in seizure dogs. Seizure dogs can be trained to detect a variety of seizure types, as they are aware of changes in body movements as well as physiological signals. Furthermore, seizure dogs are able to interact with PSREs in an active way and can recognise seizures based on the observed level of awareness. An additional benefit is that seizure dogs are trained to act upon a seizure by showing a specific response during or immediately after the seizure. This way, seizure dogs may enable timely intervention which can help reduce subsequent seizures and physical risks. Exploratory studies have suggested a reduction in seizure frequency and improvement in quality of life of PSREs after partnering with a seizure dog [17-19,26-29], indicating benefits from their companionship.

While patient organisations and media have shown a sustained interest in seizure dogs over the last two decades, the topic remains poorly investigated

While patient organisations and media have shown a sustained interest in seizure dogs over the last two decades, the topic remains poorly investigated. Previous studies assessing seizure dogs were mainly retrospective, anecdotal reports with the risk of substantial reporting bias [17,18,27-29]. The definition of a seizure dog varied across these studies, with some studies focusing on dogs that have not received formal assistance dog training. Further limitations of the current evidence were limited or no verification of the epilepsy diagnosis and lacking control groups. The only prospective study was conducted by Strong et al. [26], following 10 PSREs in a non-randomised design. While the study suggests seizure dogs may reduce seizure frequency, no prospective studies substantiating this expectation have been published. The need for further evidence to support the effectiveness of seizure dogs has been acknowledged in recent reviews [27,95].

Political rationale for a study on seizure dogs in the Netherlands

One of the consequences of the scarce evidence in this field is that seizure dogs are not reimbursed as part of the basic health insurance package in most countries. To substantiate reimbursement decisions, decision-makers require evidence of effectiveness and safety, with randomised controlled trials generally being the preferred study design. Additional evidence requirements may apply, such as cost-effectiveness data

being a prerequisite for reimbursement decision-making on certain interventions in the Netherlands and in the United Kingdom. Without collective reimbursement, the accessibility of seizure dogs is limited as is seen in The Netherlands where PSREs generally rely on out-of-pocket payment, donations or crowdfunding for acquiring a seizure dog. Affordability issues, alongside encouraging anecdotal reports of PSREs who privately financed a seizure dog have brought the reimbursement issue to the attention of the Dutch health care authorities. As the current evidence base was determined to be insufficient to support a positive reimbursement decision [69], the EPISODE (EPIlepsy SuppOrt Dog Evaluation) study was commissioned to inform decision-makers on the reimbursement of seizure dogs in the Netherlands [70].

This Chapter describes the protocol of the EPISODE study which aims to evaluate the effectiveness and cost-effectiveness of seizure dogs combined with usual care in comparison with usual care alone in adult PSREs.

Without collective reimbursement, the accessibility of seizure dogs is limited as is seen in the Netherlands where PSREs generally rely on out-of-pocket payment, donations or crowdfunding for acquiring a seizure dog

Methods

Study design

The study is designed as a prospective stepped wedge randomised controlled trial [96,97], where randomisation occurs at the individual level. In this design, all participants begin in the control condition and sequentially move to the intervention condition by receiving a seizure dog in a randomised order. This design was chosen because it allows for rollout of the intervention to all participants. In the case of a standard randomised controlled trial the risk of drop-out during the three-year follow-up was anticipated to be substantial among those randomised to the control group, especially as blinding of the participants would be impossible. An additional advantage of the stepped wedge design is that it allows for staged implementation, which was inevitable in the context of the current study because the intervention involves intensive selection and training of dogs. The current capacity of the assistance dog organisations participating in the EPISODE study would not permit simultaneous rollout of the required number of seizure dogs to all participants.

Data collection started on June 1 2019 and is scheduled to take three years to complete. To evaluate the effectiveness and cost-effectiveness of seizure dogs, all outcome measures will be taken at multiple time points both before and after the allocation of participants to the intervention.

Participants

The study population consists of adults who experience persistent seizures despite currently available treatment options. The seizures should be associated with a high risk of injury or dysfunction. In addition, the welfare of the dog has to be ensured. Inclusion and exclusion criteria are presented in Table 1.

Recruitment and inclusion

Clinical experts at the academic centre for epileptology (Kempenhaeghe) and the expertise centre for epilepsy and sleep medicine (SEIN) will inform PSREs fulfilling the inclusion criteria about the study. In addition, the assistance dog organisations, the Dutch Epilepsy Foundation and the Dutch Epilepsy Association will bring the study to the attention of PSREs by promoting the study through their communication channels (e.g., newsletter, social media, events).

The inclusion process consists of three phases. First, the PSRE gives informed consent and hands in an eligibility statement from their treating neurologist. Subsequently, a neurologist from the study team double-checks eligibility based on the medical file and reaches out to the treating neurologist when needed. Finally, the assistance dog organisation pays a visit to the PSRE's home to assess the suitability of the living situation and the support network.

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Aged 18 years or older;	Predominance of psychogenic non-epileptic seizures;
Confirmed diagnosis of epilepsy by a neurologist with video or EEG confirmation;	A planned epilepsy surgery, deep brain simulation surgery or vagus nerve stimulation surgery within the trial duration;
Failure of adequate trials of 2 tolerated, appropriately chosen and used ASM regimen to achieve sustained seizure freedom (i.e., refractory epilepsy);	Disabilities that would require additional, non-seizure-related assistance dog tasks, e.g., dependence on a wheelchair;
Not eligible for resective surgery, not prepared to accept the risks of resective surgery, or resective surgery has not resulted in seizure freedom;	Currently in possession of a trained (either active or retired) seizure dog;
Prepared not to commence with a ketogenic diet during the study period;	Institutionalised in a 24/7 care home.
Minimum of 2 seizures per week on average over the last 6 months[1];	

Inclusion criteria	Exclusion criteria
High risk of injury or dysfunction due to seizures associated with reduced awareness and/or a loss of balance;	
Seizures are not preceded by a warning signal that allows the PSRE to act on the impending seizure;	
Capacity to take care of the dog and back-up support in the person's environment to temporarily take over the care of the dog if necessary;	
Adequacy to fill in questionnaires and seizure diaries, either alone or with the support of an informal caregiver.	

1 All types of epileptic seizures may be included in the seizure count. However, given the further criteria (e.g., high risk of injury and/or dysfunction), PSREs with tonic-clonic seizures, tonic seizures, clonic seizures, atonic seizures, and/or some focal dyscognitive seizures are most likely to be included in the study.
Keys: ASM = anti-seizure medication, EEG = electroencephalographic, PSRE = person with severe refractory epilepsy

Intervention

Seizure dogs are trained to detect seizures and to respond during or immediately after a seizure. Different seizure types require different responses. Responses include, but are not limited to: summoning help by the activation of an alarm system or warning someone, helping the person to a safe place or position during or after a seizure, blocking the PSRE during episodes of reduced awareness from walking into obstacles or dangerous areas (e.g., crossing the street), and providing comfort/emotional support to the PSRE until the seizure subsides. The specific set of tasks is tailored to the individual, taking into account the PSRE's seizure characteristics, capabilities, support network and living environment. There are reports of dogs that allegedly anticipate on impending seizures and warn their human companion [28]. However, research to confirm such innate seizure-alert abilities of dogs has been inconclusive and the presence of this behaviour cannot be guaranteed by assistance dog organisations.

As the training of seizure dogs is time intensive, two assistance dog organisations have been selected to deliver the training program for the seizure dogs that participate in the study. Both organisations adhere to the standards of Assistance Dogs International for the training of seizure dogs and use the same endpoints for qualification [46]. In both trajectories the training of a seizure dog takes around 24 months to complete. The training consists of approximately one year of basic assistance dog training, focused

at socialisation and obedience, followed by approximately one year of epilepsy-specific training, whereby the focus is on recognising and responding to seizures. While the goals of the training program were the same, the programs differed in where the various phases of training take place: primarily at a host family and kennel (pre-trained dog trajectory) or exclusively at the home of the PSRE (team coaching trajectory). In the pre-trained dog trajectory, the dog moves in with the PSRE at an age of approximately 20 months. The team coaching trajectory starts with the placement of a puppy at the PSRE's home when the dog is approximately 8 weeks old. Participants will receive a seizure dog from the organisation of their preference, striving for an equal balance between the trajectories. The detailed training schedules of both assistance dog organisations can be found in Supplement 1. Participants will continue to receive care as usual during the intervention condition next to having the seizure dog. Participants can keep their seizure dog after the study has ended.

Comparator

Participants in the control condition will receive usual care without a seizure dog. Usual care consists of ASM treatment, which may be complemented by vagus nerve stimulation and/or deep brain stimulation. Some participants might use detection and alarm devices in addition to their treatment. These devices are not commonly reimbursed in the Netherlands but can be purchased privately.

Usual care

Participants will continue to get usual care for the entire study duration. Hence, changes in ASM regimen or in the settings of the vagus nerve stimulator or the deep brain stimulator are allowed. Treatment details and the use of detection and alarm devices will be recorded to be able to adjust for these changes in the analysis.

Outcomes

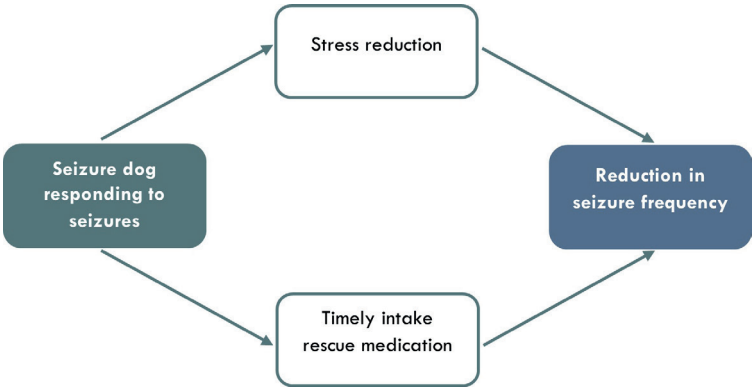
Primary outcome measure

The primary outcome of the EPISODE study is *seizure frequency,* measured per 28 days. The frequency of seizures is an important indicator for the severity of epilepsy and is therefore one of the most widely reported outcomes in the literature on seizure dogs [17,18,27-29]. As the mechanism through which the seizure dog reduces seizure frequency is unknown, the study relies on a simplified causal model (Figure 1). The knowledge that the dog will be present and is able to respond during a seizure can be reassuring for the PSRE, which may reduce seizure worry and stress. As stress is known to be an important trigger for seizures [32,98], the response behaviour of the dog is expected to result in a decreased seizure frequency. Moreover, as the dog will be trained to warn someone, this may result in administering emergency medication on

time and decreasing the likelihood of sequential seizures. Through these mechanisms. it is theorised that the companionship of a seizure dog will reduce seizure frequency.

The knowledge that the dog will be present and is able to respond during a seizure can be reassuring, which may reduce seizure worry and stress. As stress is known to be an important trigger for seizures, the seizure dog is expected to reduce seizure frequency

Figure 1. Theorised relationship between the response behaviour of a seizure dog and seizure frequency



Secondary outcome measures

In addition to the effect of seizure dogs on seizure frequency, the seizure dog might be beneficial for a broader range of outcomes. Focussing only on seizure frequency might therefore underestimate the full effect of seizure dogs, especially since not much is known about the mechanisms by which seizure dogs might impact the PSRE's health. Therefore, additional measures of health outcomes (such as quality of life) will be administered through questionnaires. Furthermore, the seizure dog might prove beneficial to the PSREs beyond their health. To capture the broader individual and societal benefits of seizure dogs, data will be collected on well-being, productivity, resource use, and social participation. Finally, as the seizure dog may have an impact on the burden of providing informal care to the PSREs, the PSRE's primary informal caregiver will be invited to fill in questionnaires as well. Table 2 provides an overview of all the outcomes that will be measured in the study. The questionnaires will be administered in Dutch.

Table 2. Overview of outcome measures

Domain	Instrument	Measured in participant	Measured in primary informal caregiver
Background and descriptives			
Demographic information (e.g., age, gender, education, living situation)	Structured questionnaire	×	×
Disease and treatment characteristics (e.g., seizure characteristics, disease duration, epilepsy treatment history, current epilepsy treatment, use of detection devices, comorbidities)	Structured questionnaire	×	
Health			
Seizure frequency (per seizure type)	Seizure diary	×	
Seizure-related injuries (categorised as light, mild or severe, use of rescue medication/ magnets to halt ongoing seizures)	Seizure diary	×	
Seizure severity (in terms of (post)ictal phenomena, postictal duration, automatisms, functional impairment, injuries, pre-seizure warnings)	Dutch adaptation on the NHS3[99]	×	
Epilepsy-specific quality of life (in terms of seizure worry, emotional well-being, energy/ fatigue, cognition, medication side effects, social function, overall quality of life)	QOLIE-31-P[100]	×	
Generic quality of life in terms of mobility, self-care, usual activities, pain/discomfort, anxiety/depression, overall quality of life	EQ-5D-5L and EQ VAS[101]	×	×
Well-being			
Well-being in terms of attachment, stability, achievement, enjoyment and autonomy	ICECAP-A[102]	×	
Resource use			
Utilisation of health care in events (e.g., emergency department visits, ambulance calls, hospitalizations) and total health care costs including informal care	iMCQ[103]	×	
Productivity			
Employment, absenteeism (days missed from work), presenteeism (reduced productivity at work), unpaid work	iPCQ[104]	×	
Social participation			

Participation in household activities, social contact, role expectations, societal participation, leisure activities	Structured questionnaire	×	×
Informal caregiver burden			
Objective burden (e.g., duration and intensity), subjective burden (e.g., perceptions of strain), health, and well-being effects of providing informal care	iVICQ[105]		×
Dog's response/alerting behaviour			
Performance of response tasks (e.g., activation of alarm system, bringing medication, blocking movements) and observations of alerting behaviour (i.e., warn prior to seizure)	Seizure diary	×	

Keys: ICECAP-A = ICEpop CAPability measure for Adults, NHS3 = National Hospital Seizure Severity Scale, iMCQ = iMTA Medical Consumption Questionnaire, iPCQ = iMTA Productivity Costs Questionnaire, iVICQ = iMTA Valuation of Informal Care Questionnaire , QOLIE-31-P= Patient-Weighted Quality of Life in Epilepsy Inventory-31

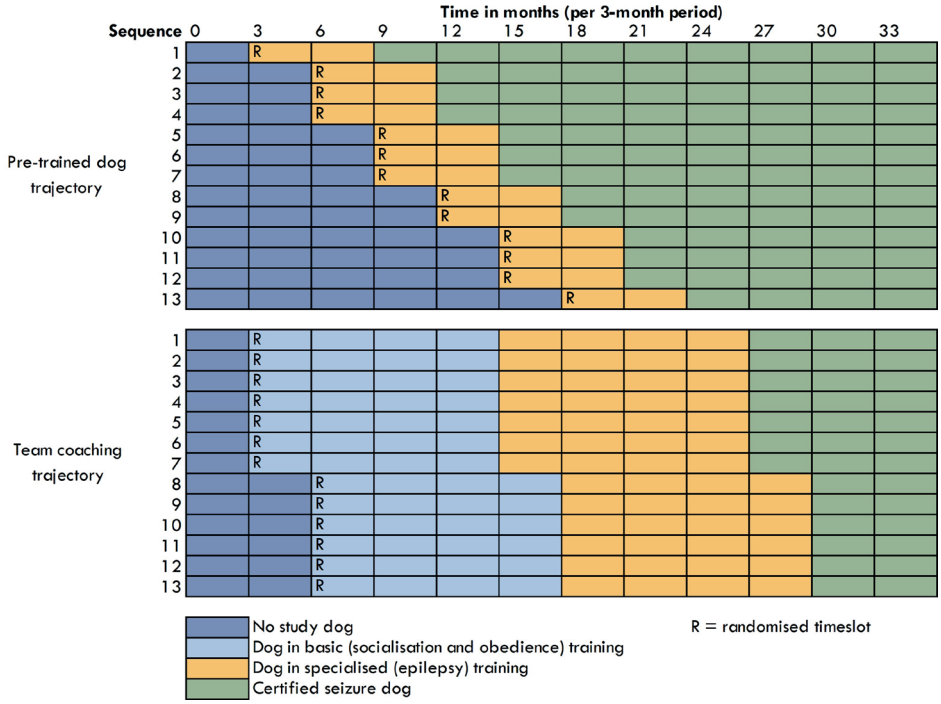
Randomisation procedure

Due to the difference in training protocols, participants can only be randomised within their assistance dog organisation group (i.e., team coaching trajectory or pre-trained dog trajectory). Hence, stratified randomisation will be applied. In the team coaching group, the randomisation determines the start of the two-month period in which the participant receives a puppy at home and begins with the basic assistance dog training. The randomisation in the pre-trained dog group determines the start of the three-month period in which the participant receives a pre-trained dog at home and continues the epilepsy-specific training. The stepped wedge schedule is designed bearing in mind that all participants have a certified seizure dog before the end of the study, while considering the capacity of the assistance dog organisations. In addition, the schedule allows for a minimum of three measurements before and three measurements after the intervention for each participant with respect to the primary outcome measure, in line with the Effective Practice and Organisation of Care (EPOC) guidelines [106]. In the team coaching group, this resulted in two allocation slots meaning that multiple participants receive a puppy within the same period. In the pre-trained dog group, participants were randomised over 13 allocation slots, as trained dogs will become available one at a time. The stepped wedge schedule for both trajectories is shown in Figure 2.

A good match with the PSRE is important for the seizure dog to function effectively. Participants in the team coaching group will therefore select their own puppy with

the guidance of the assistance dog organisation, i.e., they will select a puppy that appears to be a good fit for the PSRE and seems suitable for performing assistance dog tasks. In the pre-trained dog group, participants receive a dog that is available at that moment, i.e., a dog that has finished the basic assistance dog training, is found to be suitable for performing seizure dog tasks, and appears to be a good fit for the PSRE. While the randomisation determines the order in which participants receive a seizure dog, it might occur that the allocated dog in the pre-trained dog group does not match with the PSRE (e.g., in terms of energy level or characteristics of the living situation or support network). In that case, the participant switches places with the next participant in the randomised allocation sequence in the pre-trained dog group.

Figure 2. Stepped wedge schedule



Data collection

Daily seizure frequency will be recorded continuously using a paper seizure diary for the duration of the study (36 months). On days when the participant experiences at least one seizure, participants are asked to record seizure-related injuries and the use of rescue medication or a magnet (when the PSRE has a vagus nerve stimulator) to achieve seizure cessation. After receiving a puppy (in the team coaching group) or

dog (in the pre-trained dog group), participants are also asked to record whether the dog appears to show response and/or alerting behaviour. A smartphone application will be used to remind participants to fill in their seizure diary. In order to monitor non-response and to limit retrospective reporting of seizure frequency, the application will ask participants weekly to upload a photo of their seizure diary. Non-response will be acted on when observed by the daily study coordinator, by contacting the participant through e-mail or phone. The secondary outcome measures will be collected at the start of the trial and every three months thereafter, using paper questionnaires.

The cut-off point between control measurements and intervention measurements is determined prior to the analysis, based on the expected ability of the dog to perform seizure-related tasks at the PSRE's home. This is described hereafter.

Sample size calculation

The sample size calculation was based on the primary outcome of seizure frequency per 28 days. To determine the required sample size of the study, a simulation-based approach was adopted, using a generalised linear mixed-effects model with subject-specific random-intercepts, including a term for the time on intervention to allow for a development of the effect over time. The advantage of a simulation-based approach is that it can consider the specific features of the study including the repeated measures and the envisioned stepped wedge schedule [107]. Estimates of the intervention effect (in terms of time on intervention) were derived from a study by Strong et al. [26]. In that study the mean number of seizures in each 4-week period decreased from 13.8 in weeks 1-12 (no dog) to 9.73 in weeks 13-24 (training) to 8.8 in weeks 25-36 (follow-up) and to 8.0 in weeks 37-48 (follow-up). Four different assumptions were applied with respect to the timing of the expected decrease in seizure frequency, in line with the analysis plan in Supplement 2. The study power was calculated as the proportion among 2,500 simulation runs that detects the intervention effect at a 5% significance level. The calculation was run for two sample sizes: 20 and 25 participants. The sample size calculation showed that with both sample sizes, the study would detect the effect on seizure frequency per 28 days as observed by Strong et al. [26] regardless of the assumptions with respect to the timing of the expected decrease in seizure frequency (i.e., the power was higher than the pre-specified threshold of 0.8 in all scenarios). The study will be designed to include a minimum of 25 participants to account for dropouts.

Analysis

Effectiveness analysis

The effectiveness of seizure dogs will be measured in terms of reduced seizure frequency. All types of epileptic seizures will be included in the main analysis. Data will be described using summary statistics and scatter plots of the time series, in order

to identify any underlying trends of seizure frequency, seasonal patterns and outliers. Generalised linear mixed models (GLMM) or generalised estimated equations (GEE) are deemed as appropriate statistical methods to analyse data from stepped wedge studies [96,97]. As the primary endpoint concerns count data, a GLMM Poisson model with a logarithmic link is deemed most appropriate. The main model will include a term for time on intervention to allow for a gradual change in effect of the intervention over time.

The intervention condition consists of two distinct stages: the development stage during which the dog is taught epilepsy-specific tasks at the participant's home, and the period after the dog finished the epilepsy-specific training and is officially certified as 'seizure dog'. The cut-off point between the control and intervention period relates to the expected moment at which the dog has the ability to perform seizure-related tasks at the PSRE's home. For participants in the pre-trained dog group, the effect is expected to occur with a delay of 6 months after the dog moves from the kennel to the participant's home to account for the period of acclimatization. For participants in the team coaching group, a decrease in seizure frequency is expected as soon as the epilepsy-specific training starts, as the acclimatization period already took place during the basic assistance dog training at the participant's home. Hence, for PSRE's in the team coaching group the start of the intervention condition (i.e., time on intervention) is defined as the start of the epilepsy-specific training at the participant's home. More details on the classification of 'control' and 'intervention' measurements can be found in detail in the analysis plan (Supplement 2).

While seizure clusters are common in refractory epilepsy, there is no agreement on the definition of a cluster. This lack of consensus is revealed in the literature, where definitions that have been referenced range from episodes of multiple seizures within minutes to up to 24 hours [108,109]. The data from the EPISODE study only allows us to group seizure clusters that occur within a given day, as there is no additional granularity in the measurement of time in the seizure diary.

GLMM will be used for the secondary endpoints as well, however, the type of model (Normal, Binomial, Poisson) will be determined by the type of data for each outcome. Conclusions will be drawn from this main analysis on primary and secondary endpoints. Given the uncertainty surrounding the model assumptions, sensitivity analyses will be conducted to test the implications of the most important choices, such as the starting point of the intervention condition, the inclusion of a main effect, the types of seizures included in the count data and the definition of seizure clusters. In addition, exploratory analysis will be performed to gain insight into the relationship between the dogs response and/or alerting behaviour and the PSRE's health outcomes (e.g., seizure frequency, seizure-related injuries, anxiety).

Cost-effectiveness analysis

The cost-effectiveness analysis will follow the Dutch guidelines for economic evaluations in health care [60]. In line with this guideline, a societal perspective will be adopted. This implies that the analysis will take into account all costs within the health care sector, patient and family costs (i.e., time costs of informal caregivers and travel costs) and costs in other sectors (i.e., productivity costs). The Dutch costing manual will be used to derive unit costs [110]. The intervention costs include the purchase of a puppy, the costs of the training program and follow-up services, and costs for maintaining the dog until the dog retires.

The main outcome of the cost-effectiveness analysis concerns the incremental costs per quality-adjusted life-year (QALY) gained, expressed as the incremental cost-effectiveness ratio (ICER). The main analysis will use a lifetime time horizon. Lifetime costs and effects will be estimated, assuming that the dogs will be replaced at the time they 'retire'. Future costs and effects will be discounted according to the Dutch guidelines for economic evaluations in health care [60]. Scenario analyses will explore the cost-effectiveness of seizure dogs without the assumption that dogs will be replaced when they 'retire'. Additional uncertainties (both structural and parameter) will be tested in scenario- and sensitivity analyses.

Ensuring the dog's welfare

The current animal welfare debate has demonstrated broad acknowledgement that interventions with assistance dogs may raise welfare concerns for participating animals [111,112]. The participating assistance dog organisations apply internal protocols to monitor the health of seizure dogs and the conditions in which the seizure dogs' function, in line with international standards (Assistance Dogs International). Before PSREs enter the study, information is provided in order to make them aware of the impact of taking care of a dog. Adequacy to ensure the dogs welfare is a criterion for participating in the study. After the dog is placed at the participant's home, the welfare of the dog will be monitored regularly by the assistance dog organisations. The Institute for Anthrozoology will conduct a side-study to evaluate the welfare of the seizure dogs involved in the current study.

Discussion

The EPISODE study is the first randomised controlled trial concerning the effectiveness and cost-effectiveness of seizure dogs. The stepped wedge trial design combined with a three-year follow-up and the broad range of outcomes measured, allows for a thorough investigation of the clinical and societal benefits of this intervention. For instance, the study will look beyond health-outcomes, taking into account PSRE and

informal caregivers' well-being as well as their participation in social activities. Another neglected outcome in previous studies was the economic benefit of seizure dogs. While the costs of the training program may be considerable, and for some PSREs insurmountable when not covered by health insurance, the cost savings due to reduced medical consumption, a reduced informal caregiver burden and increased productivity might compensate this investment. As a societal perspective will be applied, these potential benefits are accounted for in the cost-effectiveness analysis, capturing the full range of expected costs and benefits attributable to seizure dogs to PSREs, informal caregivers and society.

Limitations and complications

Some limitations in the design of the study deserve mentioning. The study relies on self-reported outcome measures which, particularly in the light of the non-blinded design, have the potential of introducing reporting bias. The incentives to misrepresent responses are expected to be mitigated by several factors. First, participants can keep their dog after the study has ended, independent of the outcome of the study. As a result, the incentive to bias the results in order to increase the chance of keeping the dog will be removed. Second, participants may use the seizure diary of the study also to inform their treating neurologist. Hence, misrepresenting well-being in the seizure diary would result in misinforming one's treating neurologist as well. Third, participants have agreed that the neurologists from the study team may access their medical record for validation purposes. Finally, the analysis plan differentiates between the intervention period and the acclimatisation period, and participants are neither aware of these differences nor can forecast the impact of changing responses in different phases of the study, limiting the impact of strategic responses. Nevertheless, strategic responses may not all be avoided.

Another limitation is that the study design does not allow for a comparison of the benefits of an untrained companion dog and a trained seizure dog. It has been suggested in the literature that pet ownership at itself may have beneficial effects on their handler's health and well-being [113-115]. However, it was not feasible to include a control condition in which participants are assigned to receiving an untrained companion dog. Most importantly, there were concerns for the well-being of the participant and the dog, given the various instinctive ways in which the dog may react to seizures in their human companion when they are not trained which may include aggressive or escape behaviour [116]. Adding to this, it was expected that very few eligible PSREs would be willing to enrol in the study when they knew they could be randomised to receiving an untrained companion dog. A third limitation is that the allocation schedule for the team coaching group resulted in only two allocation slots. As a consequence, factors that might influence the results (apart from the intervention)

might be less well-balanced over 'control' and 'intervention'. However, given that the data of the team coaching trajectory and pre-trained dog group will be pooled, the impact on the results will be limited.

Some remarks should also be made with respect to the focus of the current study. The current study investigates effectiveness without a full understanding of the mechanism through which seizure dogs reduce seizure frequency as was observed in previous studies. However, the political relevance of the effectiveness and cost-effectiveness question is believed to surpass the uncertainty regarding the mode of action and hence it is warranted to measure effectiveness regardless of a clear understanding of how the effect arises. Exploratory analysis (e.g., on the relationship between response/ alerting behaviour and seizure frequency) will be conducted to test hypotheses concerning the mode of action. In addition, it should be noted that the study focusses on seizure dogs that are trained for their response behaviour, as training methods for alerting behaviour rely on hypothesised cues by dogs (e.g., variations in behaviour, scent, heart rate) and cannot be guaranteed in the way that conventional training (i.e., seizure response training) can. Nevertheless, the frequency of seizures, which will be the primary outcome of the study, might be influenced by both response and alerting behaviour. Finally, the EPISODE study is not designed to evaluate adverse events, as data on the type and number of potential adverse events related to seizure dog partnerships are not registered in a systematic way. However, several processes are in place to optimise the safety of the PSRE as well as the dog (e.g., careful selection and thorough training of the dogs as well as regular home visits by the assistance dog organisations), making adverse events seem unlikely. If major concerns regarding participant- or dog safety occur, the dog will be removed from the PSRE's home after careful consideration, with or without assigning a replacement dog. These serious adverse events will be recorded by the study team and described as part of the study results. Aspects of safety that influence a participant's well-being, quality of life or resource use will be measured throughout the study.

Based on: Wester V, de Groot S, Versteegh M, Kanters T, Wagner L, Ardesch J, Brouwer W, van Exel J, on behalf of the EPISODE-team

Value in Health. 2021;24(10)

Chapter 3

Good days and bad days: measuring health-related quality of life in episodic conditions like epilepsy

Highlights

- EPISODE participants typically complete the quarterly questionnaire on “good days” with few or no seizures.
- Lower seizure frequency corresponds to higher scores on EQ-5D-5L, an instrument which reflects health-related quality of life on the day of reporting.
- When assessments are biased towards “good days”, this may lead to overestimation of health-related quality of life in episodic conditions.
- This issue may introduce bias in the estimation of effectiveness and cost-effectiveness of interventions targeted at these populations.

Abstract

Background and objectives

Cost-effectiveness analyses typically require measurement of health-related quality of life (HRQoL) to estimate quality-adjusted life-years. Challenges with measuring HRQoL arise in the context of episodic conditions if patients are less likely - or even unable - to complete surveys when having disease symptoms. This article explored whether HRQoL measured at regular time intervals adequately reflects the HRQoL of persons with severe refractory epilepsy (PSREs).

Methods

Follow-up data from the EPISODE study on the (cost-)effectiveness of seizure dogs were used in which HRQoL is measured in 25 PSREs with EQ-5D every three months. Seizure count is recorded daily using a seizure diary. Regression models were employed to explore whether PSREs were more likely to complete the HRQoL survey on a good day (i.e., when seizures are absent or low in frequency compared with other days) and to provide an estimate of the impact of reporting HRQoL on a good day on EQ-5D utility scores.

Results

A total of 111 HRQoL measurements were included in the analysis. Regression analyses indicated that the day of reporting HRQoL was associated with a lower seizure count ($p < 0.05$) and that a lower seizure count was associated with a higher EQ-5D utility score ($p < 0.05$).

Conclusions

When HRQoL is measured at regular time intervals, PSREs seem more likely to complete these surveys on good days. Consequently, HRQoL might be overestimated in this population. This may result in an underestimation of intervention effectiveness and biased cost-effectiveness estimates.

Introduction

Cost-effectiveness analyses are often used by reimbursement agencies to inform decisions on whether or not to reimburse new health care interventions. The outcome of a cost-effectiveness analysis is commonly expressed as the incremental costs per quality-adjusted life-year (QALY). QALYs are a function of both length of life and health-related quality of life (HRQoL). Estimation of the "quality" component can be achieved with a standardised measure of HRQoL such as EQ-5D[101]. EQ-5D is a widely used preference-based instrument that has country-specific scoring algorithms available for attaching a value between 1 (full health) and 0 (a state as bad as being dead) to the recorded health state. The resulting value is EQ-5D utility score, which is often equated to HRQoL, and will also be the terminology in this study. EQ-5D is the preferred HRQoL measure of reimbursement agencies such as the National Institute for Health and Care Excellence (NICE) in England and the National Health Care Institute in the Netherlands (Zorginstituut Nederland) [60-61,117]. EQ-5D intends to capture self-reported health status on the day of completing the survey ("health today").

Individuals may be less likely - or even unable - to complete surveys on days when an episode occurred

While EQ-5D is widely applied in a variety of conditions and populations, challenges may arise in the context of its application to conditions which are characterised by considerable fluctuations in health, as in the case of migraine, multiple sclerosis and epilepsy[118-120]. Recently, Sanghera and Coast (2020) underlined the challenges in measuring HRQoL in fluctuating health states, arguing that HRQoL estimates may be biased if the timing of assessment and the recall period used do not properly account for the temporal nature of the symptoms[121]. That is to say, the symptoms may not have occurred in a representative manner within the recall period of the HRQoL instrument, individuals may be less likely – or even unable – to complete HRQoL surveys on days when an episode occurred. As a consequence, measured HRQoL may not adequately reflect (average) HRQoL and QALY estimations might be biased. This can be especially problematic when episodic symptoms are severe and infrequent, such as in epilepsy. In the context of cost-effectiveness analyses, this implies that measured HRQoL differences between intervention groups may not reflect actual intervention effectiveness adequately, hence biasing cost-effectiveness estimates and potentially misinforming subsequent decisions. However, so far, empirical evidence is lacking regarding the extent of the potential bias in HRQoL measurements in episodic conditions. The current study is a first attempt to fill this gap for the episodic condition refractory epilepsy.

Measuring HRQoL in the context of epilepsy

Epilepsy is a neurological condition that is characterised by recurrent unpredictable seizures of various types and severities. The clinical presentation of a seizure depends on the area of the brain affected, and may include unintentional body movements, unusual sensations, involuntary behaviours, and/or impaired consciousness[122]. The clinical spectrum of seizures includes focal aware or impaired awareness seizures, generalised seizures and seizures with unknown onset. Reflecting the symptoms or signs occurring at the onset of the seizure, the seizure types can further be sub-classified as 'motor' or 'non-motor', as well as 'intact awareness' or 'impaired awareness' in the case of focal seizure[123]. Seizures generally last only seconds or a few minutes and, depending on the seizure type and severity, persons with epilepsy may recover quickly or need several hours or sometimes days to recover[124]. In approximately 70% of cases, seizures can be controlled using anti-seizure medications. Refractory epilepsy is the term used to describe epilepsy that cannot be controlled and occurs when individuals do not achieve seizure freedom despite administration of at least two pharmacological treatments[72]. This occurs in about one-third of the overall epilepsy population. Among people with refractory epilepsy, seizure frequencies may range from less than one per month to several seizures per day[24,125]. In this study, persons with severe refractory epilepsy (PSREs) refers to those with seizures at a regular (i.e., daily to weekly) basis.

A change in seizure frequency has traditionally been the main measure of efficacy for epilepsy interventions. To incorporate effects of interventions in cost-effectiveness analyses, changes in seizure frequency should be accompanied by changes in HRQoL, in order for intervention benefits to be captured in QALYs. As persons are generally not able to complete an HRQoL survey during a seizure or during the post-ictal period (i.e., the altered state of consciousness after an epileptic seizure), surveys will typically be completed at another time. A study on three Phase III trials in people with refractory epilepsy showed that only 82 out of 1076 HRQoL surveys were completed on a day during which seizures were present[126]. Indeed, PSREs might be inclined to complete a survey on a good day (i.e., a day when seizures are absent or low in frequency compared to other days) rather than on a bad day. If the HRQoL of PSREs at the time of completing the HRQoL survey differs substantially from that around or during a seizure, the time since the last seizure and the applied recall period may have a considerable impact on the observed PSRE's HRQoL outcome scores and implied cost-effectiveness of (new) interventions.

The aim of this study is to explore whether HRQoL measured at regular time intervals adequately reflects the HRQoL of people with refractory epilepsy. In addition, the impact of completing the survey on a good day on EQ-5D utility scores is explored.

Methods

Data source

Data from the EPISODE study (EPIlepsy SuppOrt Dog Evaluation) were used (Chapter 2). The EPISODE study is a stepped wedge randomised controlled trial that evaluates the effectiveness and cost-effectiveness of seizure dogs in people with refractory epilepsy. Seizure dogs are trained to detect seizures and to respond during or immediately after a seizure. Responses include, but are not limited to: summoning help by the activation of an alarm system or warning someone, helping the person with epilepsy to a safe place or position during or after a seizure, blocking the person with epilepsy during episodes of reduced awareness from walking into obstacles or traffic, and providing comfort/emotional support to the person with epilepsy until the seizure subsides. The EPISODE study includes 25 adults with refractory epilepsy who experience at least two seizures per week. The study adopts a stepped wedge design, which means that all participants start in the control arm and receive a seizure dog in a randomised order during the 3-year follow-up period. The primary outcome of the study is whether the introduction of a seizure dog decreases seizure frequency. Secondary outcomes include HRQoL (generic and disease-specific), well-being, health care resource use, informal care burden, social participation and productivity. More details on the rationale and design of the study are described in the study protocol (Supplement 2).

In the EPISODE study, seizure frequency is measured using a seizure diary. Participants record the daily seizure count per seizure type in a paper diary, and upload a photograph of it every week via a smartphone application. Up to three different seizure types can be distinguished in their seizure diary. While the impact of different seizure types on HRQoL may vary, for this exploratory study the seizure count consists of the sum of all seizures experienced during one day (i.e., all seizure types get the same weight). EQ-5D-5L, which has a recall period of "today", is measured as part of a comprehensive survey that is sent to the participants every three months[101]. EQ-5D utility scores were calculated using the Dutch tariff[127]. Prior to answering EQ-5D-5L, participants are asked to record the present date. They are instructed to complete the survey preferably on the date indicated on the survey (the first day of the month), which is approximately 4 days after receipt. Participants are asked to return the survey in any case within ten days after the indicated date, allowing them a window for completing the survey of roughly two weeks. This study uses the data collected during the first year of the EPISODE trial, which includes five EQ-5D assessments (i.e., at month 0, 3, 6, 9 and 12) and daily seizure count data for 13 months. Two of the 25 participants had a pre-trained seizure dog within this time frame, one from month 10 onwards and the other starting from month 11 of the 13-month follow-up period.

Statistical methods

For each participant of the EPISODE study, a graphical display was made visualising the timing of HRQoL reporting in relation to the seizure count pattern. Subsequently, regression analyses were conducted to test the association between HRQoL reporting and seizure count, and to estimate the impact of reporting HRQoL on a good day on EQ-5D utility score. It is anticipated that the marginal impact of an additional seizure will decrease as seizure count increases. Therefore, instead of estimating a linear disutility function, previous utility prediction models in epilepsy grouped seizure counts into a categorical variable[126,128,129]. Here, seizure counts were grouped based on quartiles.

The regression analyses followed a two-step approach. First, the impact of reporting HRQoL on the seizure count quartile was explored (i.e., are participants more likely to report HRQoL on a good day). A univariate random effects ordered logistic regression model was used to estimate the relationship between the day of reporting HRQoL and the seizure count quartile on that day. Second, the association was explored between seizure count quartile and EQ-5D utility score (i.e., is the HRQoL estimate higher on a good day). For this second analysis, three types of regression models were used: generalised least squares (GLS) random effects regression, Tobit random effects regression, and repeated measures generalised estimating equations (GEE). GLS random effects regression was used because it is a common estimation method accounting for any potential impact of multiple observations from the same individual. The Tobit random effects model was used to censor predictions at the upper bound (1). GEE is a population-averaged panel-data model which accommodates both auto-correlated and non-normal data, such as the dependent variable EQ-5D utility score in this analysis. In the GEE model, a gamma distribution with a logarithmic link was used with disutility as outcome variable to have non-negative values (with disutility = 1 – EQ-5D utility score). The mean absolute error (MAE) and root-mean square error (RMSE) were calculated to examine the differences between mean observed and predicted EQ-5D utility scores. The best performing models were selected on the basis of the lowest MAE/RMSE results, with the MAE as the decisive factor in case of contrasting results. Next, the best performing model was corrected for age and gender. Finally, sensitivity analyses were performed to assess the robustness of the findings; different specifications of seizure count were explored and EQ-5D VAS scores instead of EQ-5D utility scores were used as dependent variable. Given the exploratory nature of the research questions and in order to avoid assumptions about missing observations and early patient dropout, multiple imputation of missing values was not conducted. Statistical significance was defined at the $p < 0.05$ level. All analyses were done in STATA 16 (StataCorp, College Station, TX, USA).

Results

Descriptive statistics

The EPISODE study included 25 participants, from whom at the time of analysis a maximum of 13 months of seizure data were collected. The mean age of the participants at the start of the trial was 34 years (Table 1). The daily seizure count over the first four weeks of the study was 3.59 (SD 4.70) on average, with a small proportion (8%) of the participants experiencing more than 10 seizures per day. A majority of participants had at least one seizure-free day per week (64%). The mean EQ-5D utility score at the start of the trial was 0.72 (SD 0.25). On EQ VAS, participants scored on average 66 (SD 22).

HRQoL data (i.e., complete EQ-5D-5L, date of recording and seizure count) were collected for all 25 participants for up to five assessments (baseline, $n = 23$; month 3, $n = 23$; month 6, $n = 22$, month 9, $n = 22$; month 12, $n = 21$). The main reasons for missing HRQoL observations included withdrawal from the study and no or incomplete questionnaire returned. Over all assessments, EQ-5D utility scores ranged from -0.15 to 1, with 13 (12%) observations of EQ-5D utility scores equal to 1 (i.e., perfect health). In total, 53 EQ-5D questionnaires (48%) were completed on seizure-free days. Five participants (20%) completed all EQ-5D questionnaires on a seizure-free day, whereas for eight participants all EQ-5D observations were recorded on days when at least one seizure occurred (32%). Table S3.1 in Supplement 3 presents the days on which the HRQoL measurements were completed relative to the indicated date on the survey.

Table 2 shows the average seizure count of participants on the day of reporting HRQoL for the questionnaires completed at month 3, 6, 9 and 12 *($n = 88$)* as well as the average seizure count over the preceding 7, 14, and 28 days. In general, the sample's mean and median seizure count appears to be lower on the day of reporting HRQoL as compared to the average daily seizure count over each preceding period. This is confirmed when the analysis is repeated on data without outliers in seizure count (Supplement 3 Table S3.2).

Table 1. Patient characteristics

Characteristics at the start of the trial (first 28 days)	Number of participants (n = 25)
Age, mean (SD)	33.8 (12.3)
Gender, n (percentage)	
Female	11 (44%)
Amount of seizure types distinguished by the patient, n (percentage)	
1	4 (16%)
2	13 (52%)
3	8 (32%)
Average daily seizure count	
mean (SD)	3.59 (4.70)
median (IQR)	3.86 (1.57 – 5.43)
Average daily seizure count categorised, n (percentage)	
< 1	11 (44%)
1 – < 4	6 (24%)
4 – < 7	3 (12%)
7 – < 10	3 (12%)
10 – < 19	1 (4%)
20 – < 29	1 (4%)
Average number of seizure-free days per week, n (percentage)	
< 1	9 (36%)
1 – < 4	7 (28%)
4 – 7	9 (36%)
EQ-5D utility score, mean (SD)	0.72 (0.25)
EQ VAS score, mean (SD)	66 (22)

Keys: n = number of observations, SD = standard deviation, IQR = interquartile range

Table 2. Average seizure count on day of HRQoL observation relative to the average over the preceding period[1]

Seizure count	Total (Assessment 1 to Assessment 4)		Assessment 1 (t = 3, *n* = 23)		Assessment 2 (t = 6, *n* = 22)		Assessment 3 (t = 9, *n* = 22)		Assessment 4 (t = 12, *n* = 21)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
On day of reporting HRQoL	2.98 (5.35)	1.00 (0.00 – 4.00)	2.61 (4.46)	1.00 (0.00 – 3.00)	3.55 (5.84)	0.50 (0.00 – 5.00)	1.73 (2.80)	0.00 (0.00 – 3.00)	4.10 (7.42)	1.00 (0.00 – 5.00)
Preceding 7 days	3.61 (5.41)	1.14 (0.29 – 5.00)	3.79 (5.13)	1.00 (0.29 – 5.43)	4.20 (6.56)	1.21 (0.29 – 6.00)	2.47 (3.25)	0.93 (0.29 – 2.86)	4.01 (6.37)	1.29 (0.57 – 4.43)
Preceding 14 days	3.66 (5.37)	1.07 (0.43 – 5.00)	3.38 (4.90)	1.14 (0.34 – 4.93)	4.17 (6.50)	0.82 (0.50 -6.21)	3.01 (3.92)	1.01 (0.29 – 4.58)	4.10 (6.13)	1.01 (0.64 – 5.07)
Preceding 28 days	3.62 (5.22)	1.03 (0.48 – 4.89)	3.37 (4.94)	1.11 (0.36 – 4.82)	3.95 (5.90)	0.82 (0.47 – 6.36)	3.21 (4.03)	1.31 (0.39 -4.89)	3.98 (6.13)	1.00 (0.54 – 4.39)

1 The baseline HRQoL observations (Assessment 0, t = 0, n = 23) are not included in the descriptive statistics as no preceding seizure count data were available for this measurement.
Keys: HRQoL = Health-Related Quality of Life, SD = overall standard deviation, n = number of observations, IQR = interquartile range

For illustration, two examples are presented in Figures 1 and 2. These participants record only one seizure type. The Figures visualise the daily seizure count and the timing of HRQoL assessment. The days which were indicated as preferred date for completing EQ-5D are shown as T0 to T4. Figure 1 shows data from a participant who suffers from daily seizures, who appears to complete the questionnaire on a day during which the seizure count is relatively low. Figure 2 shows data from a participant experiencing seizures a few times per week, who completed all five questionnaires on a seizure-free day.

Figure 1. Example of the seizure pattern and timing of HRQoL reporting in a patient with daily seizures

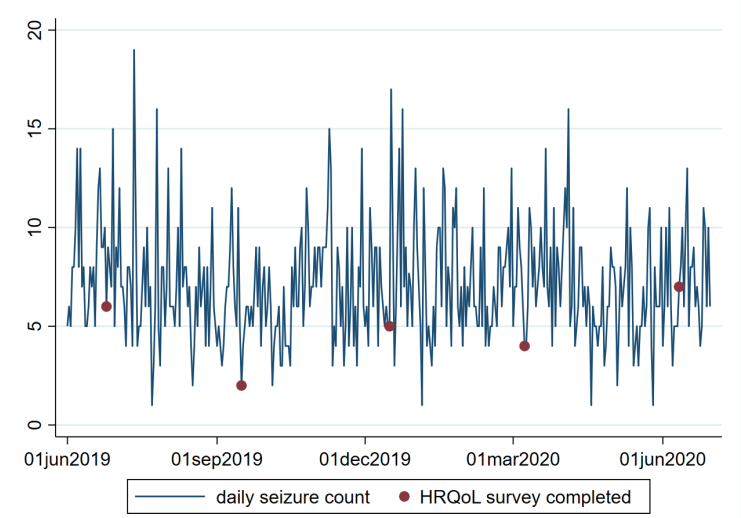
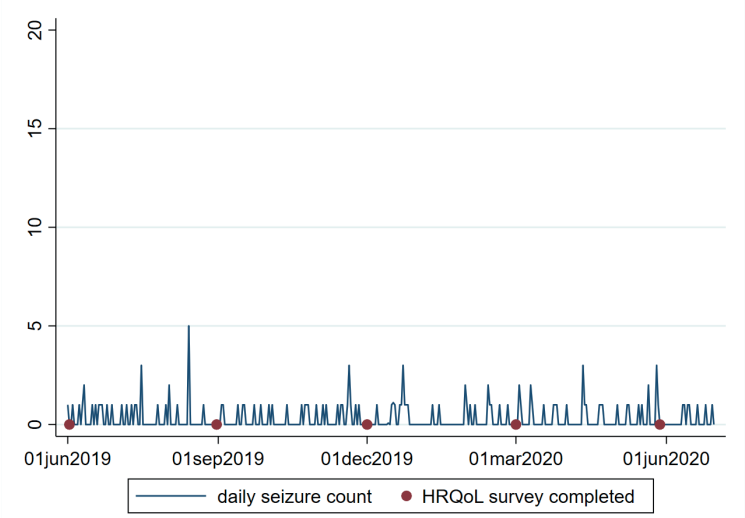


Figure 2. Example of the seizure pattern and timing of HRQoL reporting in a patient with occasional seizures.



Regression analyses

Table 3 shows the distribution of observations over the four seizure count quartiles as well as the mean seizure count and mean EQ-5D utility score within the quartiles. The mean seizure counts of these four subgroups were 0, 1, 3 and 13. On days of

reporting HRQoL, the seizure count falls most often in the lowest quartile (seizure-free). EQ-5D utility score is higher for observations reported on a seizure-free day than for observations measured on a day with seizures. Ordered logistic regression showed that completing EQ-5D was associated with a significantly lower probability of a higher seizure count quartile that day, OR 0.64, $p < 0.05$ (MAE 0.017, RMSE 0.159).

Table 3. Distribution of observations over quartiles1

Seizure count quartile (daily seizures)	Mean seizure frequency (SD)	Proportion of all observations, percentage (n = 9,199)	Proportion of observations on days of reporting HRQoL (n = 111)	Mean EQ-5D utility score (SD)
Q1 (seizure-free)	0	41.37%	47.75%	0.80 (0.16)
Q2 (1 seizure)	1	14.46%	9.91%	0.64 (0.29)
Q3 (2 to 5 seizures)	3.28 (1.14)	21.53%	26.13%	0.58 (0.30)
Q4 (6 or more seizures)	12.85 (7.33)	22.64%	16.22%	0.56 (0.27)

1 The four groups are not balanced despite the distribution over quartiles, as for example 41% of observed seizure counts was 0.
Keys: Q = quartile, SD = standard deviation, HRQoL = health-related quality of life, n = number of observations

The three regression models for predicting EQ-5D utility score from the seizure count quartiles performed broadly similarly, with MAE scores ranging between 0.184 and 0.187 and RMSE scores ranging from 0.239 to 0.241. All three models showed a significant negative association between each of the three seizure count quartiles and EQ-5D utility score, compared to the first seizure count quartile (seizure-free), $p < 0.05$. The Tobit model performed the best, followed by the GEE model, and the GLS random effects model performed least well (see Table S3.3 in Supplement 3). The performance of the Tobit model increased by including demographic factors (MAE 0.169; RMSE 0.232). The details of the best performing model are given in Table 4. Several sensitivity analyses have been performed to assess the robustness of the findings. These analyses, which explored the impact of different specifications of seizure count and investigated EQ VAS score as outcome variable to test for sensitivity, were in line with the observation from the main analysis that a lower seizure count is associated with a higher HRQoL estimate ($p < 0.05$) (Tables S3.4 – S3.7 in Supplement 3).

Table 4. Regression coefficients and predictive performance of best performing utility model

Tobit model, right censored at 1	
Parameter estimate (SD)	
Seizure count Q2 (1 seizure)	-0.13† (0.06)
Seizure count Q3 (2 to 5 seizures)	-0.17§ (0.05)
Seizure count Q4 (6 or more seizures)	-0.19‡ (0.07)
Age	-0.00 (0.00)
Gender	-0.18† (0.09)
Constant	0.87§ (0.14)
Predictive performance	
MAE	0.169
RMSE	0.232
Estimates within SD 0.05 of true value	25.23%
Estimates within SD 0.10 of true value	34.23%
Estimates within SD 0.25 of true value	57.66%

Keys: SD = standard deviation, Q = quartile, MAE = mean absolute error, RMSE = root-mean square error
† $p < 0.05$
‡ $p < 0.01$
§ $p < 0.001$

Discussion

Obtaining reliable estimates of HRQoL in the context of an episodic condition such as refractory epilepsy can be challenging, as the symptoms may not have occurred in a representative manner within the recall period of the HRQoL instrument. Using data from the EPISODE study, this analysis indicated that people with refractory epilepsy appear more likely to complete HRQoL assessments on good days rather than bad days in terms of seizure count. Sanghera and Coast (2020)[121] illustrated that, at the time of HRQoL assessment, people with episodic conditions may be either at the worst or best point of the fluctuation in symptoms, or at some point in-between. Graphical displays of the EPISODE data showed that participants appear to complete the HRQoL survey at a relatively good point of the fluctuation in seizures and this hypothesis was confirmed by statistical analysis. Regression analysis revealed that HRQoL reporting was associated with a lower seizure count on that day, and that a lower seizure count was associated with a higher HRQoL score. It is therefore possible that when HRQoL is measured at regular time intervals, the assessments result in an overestimation of average HRQoL in the refractory epilepsy population and, consequently, an underestimation of the potential effect of seizure control on HRQoL.

This might help to explain why some studies in epilepsy treatments failed to detect a significant difference in HRQoL when measured with EQ-5D, even when a clinically meaningful intervention effect in terms of seizure frequency (i.e., a 50% reduction) was observed[126,130,131].

Our analysis has a number of limitations, which should be considered in interpreting these results. First of all, the current study did not differentiate for seizure severity. Seizure types vary from muscle twitches or short absence seizures to drop-seizures and may not all have a similar impact on HRQoL. The majority of PSREs in this study distinguished their seizures into different types when completing their seizure diary, which indicates that using an unweighted total seizure count as indicator for disease severity on a given day likely constitutes an oversimplification of the burden they experience. In addition to seizure count, the type of seizures and the time intervals between seizures will likely have an impact on HRQoL on a given day, as well as on the ability or motivation of a person to complete a HRQoL survey. Secondly, EQ-5D observations were matched with the seizure count recorded in the seizure diary as a proxy for seizures that occurred within EQ-5D recall period, which is "today". However, seizures may still have occurred on that day *after* completing the survey. Thus, the seizure count from the seizure diary presents the maximum number of seizures that could be reflected in EQ-5D utility scores, but likely is an overestimation. In contrast, it may occur that the prolonged aftermath of a severe seizure on the day(s) preceding HRQoL observation is captured within EQ-5D utility scores, for example, because of a long recovery period or because of injuries incurred. Moreover, EQ-5D observations on both seizure-free days and days with at least one seizure were only available for a part of the (already limited) sample, the ability to perform within-subject analyses was limited. Utility differences between different seizure count quartiles should therefore be interpreted with caution, as what might be considered as a good day by one PSRE might be perceived as a bad day by another PSRE. Finally, this study had a limited sample size which comes with a higher likelihood of observing coincidental findings. The findings described concern a secondary analysis on data collected for a (cost-) effectiveness study, and power calculations were therefore not performed for the current analyses. Hence, the study should be considered as explorative. Nonetheless, the sensitivity analyses that were conducted confirm the results regarding the impact of seizure count on the day of completing EQ-5D on HRQoL estimates.

Experimenting with consecutive measurements over a period of time might contribute to a better understanding of how health-related quality of life fluctuates within persons with severe refractory epilepsy

The issue of measuring HRQoL in episodic conditions has been previously described mainly from a theoretical point of view, and the study described here is a first attempt

to explore this issue in practice, by investigating the timing of reporting HRQoL relative to symptom severity within the EPISODE trial. For a better understanding of the impact of fluctuating symptoms on HRQoL estimates in PSREs, it would be interesting to investigate the impact of using modified recall periods. Moreover, experimenting with consecutive measurements over a period of time (i.e., intensive longitudinal assessment) might contribute to a better understanding of how HRQoL fluctuates within PSREs and provide more insight into HRQoL on bad days and into the extent of overestimation of HRQoL when the timing of reporting HRQoL relative to the occurrence of seizures is not accounted for. Findings in refractory epilepsy are not necessarily generalisable to other episodic conditions. Hence, future research may help identify for which episodic conditions the timing of completing the survey is particularly relevant, by considering disease characteristics such as the frequency, duration, severity, and time intervals of symptom episodes.

Conclusions

This exploratory study showed that PSREs are more likely to complete HRQoL surveys on relatively good days in terms of seizure counts. If seizures do not occur in a representative manner within the recall period of a HRQoL instrument, the observed impact of seizures on HRQoL may be biased. In particular when the intervention reduces the frequency or intensity of bad days, HRQoL measured at regular time intervals may not be sufficiently responsive to changes in seizures over time, especially when measured with instruments with a short recall period such as EQ-5D. Not accounting for the finding that HRQoL reporting in the context of refractory epilepsy is more likely on relatively good days may result in a biased estimation of the HRQoL of PSREs and, consequently, in a biased estimation of the (cost-)effectiveness of interventions in this patient population.

Based on: van Hezik-Wester V, de Groot S, Kanters T, Versteegh M, Wagner L, Ardesch J, Brouwer W, van Exel J, on behalf of The EPISODE-team

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Chapter 4

Burden of illness in persons living with severe refractory epilepsy: 12-month follow-up of participants in the EPISODE study

Highlights

- Participants of the EPISODE trial show considerably lower health-related quality of life than both the general population and broader epilepsy populations.
- Intensive health care use and high dependency on informal care contribute to considerable societal costs.
- This emphasizes the need for novel treatment options and assistive care services to alleviate the burden of this condition for patients, their informal caregivers, and society.

Abstract

Background and objectives

A subset of persons with epilepsy suffers from frequent seizures despite the available pharmacological and non-pharmacological interventions. The impact of epilepsy on these persons with severe refractory epilepsy (PSREs) extends beyond health-related quality of life (HRQoL), impacting their broader well-being and ability to participate in society. This study describes the burden of severe refractory epilepsy in terms of HRQoL, well-being, and societal costs.

Methods

Data from the first 12 months of the EPISODE study on (cost-)effectiveness of seizure dogs were used. The data were collected from a sample of 25 adults with daily to weekly seizures, before they were partnered with a certified seizure dog. Data comprised seizure diaries covering 365 days and five three-monthly surveys, including EQ-5D-5L, QOLIE-31-P, and ICECAP-A to measure HRQoL and well-being. A societal perspective was applied to estimate costs using the iMCQ and iPCQ questionnaires on health care use, informal care, and productivity losses.

Results

Daily seizure frequency and survey data were collected from 25 patients. A minimum of 114 observations was available for each instrument included in the survey. A total of 80% of participants experienced seizures on three or more days per week, with a median ranging from 1 to 17 seizures per seizure day. The mean EQ-5D-5L utility score was 0.682 (SD 0.235), which is considerably lower than the age-adjusted general population average of 0.890. The mean QOLIE-31-P and ICECAP-A scores were 55.8 (SD 14.0) and 0.746 (SD 0.172), respectively. The average annual total cost amounted to €39,956 (range €3,804 – €132,264). Informal care accounted for the largest share of costs (50%); those who received informal care reported, on average, 26 hours per week (SD 30).

Conclusions

Severe refractory epilepsy is associated with a considerable burden of illness at the patient and societal level. People with this condition have significantly reduced HRQoL and well-being and are limited in their ability to work, while incurring substantial medical costs and relying heavily on informal care.

Introduction

Persons with refractory epilepsy do not achieve sustained seizure freedom despite adequate provision of multiple pharmacological treatment regimens, known as anti-seizure medications (ASM) [72]. Refractory epilepsy is associated with excess disability, morbidity and mortality and is ranked fourth in terms of disability weight among the 220 health conditions included in the Global Burden of Disease 2010 study [132]. Next to expanding opportunities for pharmacological treatment, for some persons, non-pharmacological treatments such as epilepsy surgery, deep brain stimulation (DBS), vagus nerve stimulation (VNS), and the ketogenic diet, can be effective alternative or complementary therapies to reduce or eliminate seizures [133,134]. Despite this, the burden of refractory epilepsy has remained almost unchanged for several decades.

The prevalence of refractory epilepsy (at least one seizure per year) is estimated to be 1.36 per 1,000 (95% CI: 1.07–1.66) in Western Europe. Within this group, 32% of individuals had more than one seizure per week [135]. This is well below the prevalence of overall active epilepsy (that is, newly diagnosed and refractory epilepsy), which is estimated at 8.23 per 1,000 [136]. A study in four European countries considering all ages, found that 9% of persons classified with definite and probable epilepsy had daily or weekly seizures [137]. While these persons represent a small proportion of the epilepsy population, they account for an important share of the total burden of illness.

While persons with severe refractory epilepsy represent a small proportion of the epilepsy population, they account for an important share of the total burden of illness

The health-related quality of life (HRQoL) of persons with refractory epilepsy is threatened by the seizures, the unpredictability of their occurrence, and medication side effects. Moreover, adaptations in everyday life are generally required to limit the chances of seizure-related injuries [138]. Precautionary measures impact these persons's mobility (e.g., restrictions to drive a car or ride a bicycle) as well as their ability to participate in daily activities of normal life such as sports, leisure, education and work. Consequently, the burden of illness of refractory epilepsy extends beyond HRQoL, impacting a person's broader well-being and ability to participate in society [139,140]. The challenge for these persons, therefore, is balancing between staying safe and living a fulfilling life. Interventions for this patient population could be targeted at limiting the impact of seizures on everyday life and helping them maintain their independence. Examples include self-management interventions, assisted living facilities, protective gear, home safety equipment, and technical devices designed to monitor seizures and notify informal caregivers. More recently, there is a growing interest in dogs that are trained to detect seizures and to assist a person during or after a seizure.

While epilepsy is the fourth most common neurological condition, studies investigating the characteristics and burden of persons with refractory epilepsy are scarce, with most studies focusing on the paediatric population. Although previous studies have measured the HRQoL of adults with refractory epilepsy or the socioeconomic impact of this disease, only few studies assessed these issues jointly [141-144]. Moreover, these studies often measured HRQoL using disease-specific rather than generic instruments, hampering the comparability of outcomes with other patient populations and the use in economic evaluations. Furthermore, well-being measures are generally not included in studies assessing the burden of illness of persons with refractory epilepsy while the impact of this condition on well-being is expected to be substantial. Finally, most cost-of-illness analyses in epilepsy are performed from a limited health care perspective and, therefore, do not account for the entire socioeconomic burden of illness [145-150]. Examples of important costs that are not typically included are treatment of seizure-related injuries, protective garment or home safety equipment, monitoring devices, informal care, and productivity losses in paid and unpaid work. The aim of the current study is therefore to describe the burden of severe refractory epilepsy in terms of HRQoL, well-being, and societal costs. By taking a societal perspective the study aims to provide a more complete picture of the burden of this disease.

To study the burden of illness, data from the EPISODE study were used. The EPISODE study follows 25 adults in the Netherlands before and after they are partnered with a seizure dog. Persons were eligible for participation in the EPISODE study when they had a minimum of two seizures per week despite having explored both pharmacological and non-pharmacological treatment options. Also, the seizures had to be associated with a high risk of injury or dysfunction. As such, the study population reflects a population of persons with severe refractory epilepsy (PSREs). Over a period of three years, the study investigates the effectiveness and cost-effectiveness of seizure dogs, as well as the effects on broader outcomes such as well-being, participation in society, and informal caregiver burden (Chapter 2). The EPISODE study, therefore, provides unique insight into the lives of PSREs, and the impact seizure dogs can have on their health and well-being, and the societal costs of this difficult to treat illness. While the EPISODE study is based on a relatively small sample of 25 participants, its structured set-up, longitudinal nature, as well as the broad array of instruments used offer a unique overview of the impact and costs of refractory epilepsy in an understudied group of affected individuals, their environment, the health care sector, and society. For the current study the data collected during the 12 months before participants were partnered with a certified seizure dog were used.

Methods

Data source

This study describes data from 25 participants in the EPISODE study on the (cost-) effectiveness of seizure dogs in the Netherlands who were followed over time. The main inclusion criteria were an age of 18 years or older, a confirmed diagnosis of epilepsy, an average seizure frequency of two seizures per week or more, failure of two or more ASM treatment regimens, and having had epilepsy surgery or not being eligible for epilepsy surgery (Table 1 of Chapter 2). While there was no restriction on the type of epileptic seizures, seizures should be associated with a high risk of injury or dysfunction. The EPISODE study adopted a stepped wedge design, wherein the order in which participants were allocated to a seizure dog was randomly assigned before the start of the study. There were no restrictions in the use of care during the study, participants received usual care when needed. That is, participants could receive pharmacological and non-pharmacological treatments and were allowed to use epilepsy-related technologies. Participants are followed over a period of three years, during which they record their seizures daily using a seizure diary and complete a questionnaire every three months. The questionnaire includes instruments for measuring seizure severity, HRQoL, well-being, health care use, informal care use, and productivity losses from paid and unpaid work. In addition, at baseline, sociodemographic information was collected as well as disease characteristics and details on treatment history. The rationale and design of the study are described in the study protocol (Chapter 2). In the current study the data collected during the first 12 months of the EPISODE study were used, before participants were partnered with a certified seizure dog.

Health-related quality of life

Generic outcome measures of HRQoL enable the comparison of health outcomes between different diseases and their use in economic evaluations. However, generic HRQoL measures are considered less sensitive to detect small but clinically important health impacts related to a specific disease. Therefore, the EPISODE study included both generic and epilepsy-specific measures of HRQoL.

EQ-5D-5L and EQ VAS

Generic HRQoL was measured with EQ-5D-5L questionnaire. This instrument measures HRQoL on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [101] . Each item has five answer categories (levels): no problems, some problems, moderate problems, severe problems, and extreme problems/unable to. EQ-5D utility scores were calculated using the Dutch tariff [127] , and could take a value between -0.446 and 1, with 0 representing the state “death” and 1 representing

the state "full health"; negative values represent health states considered worse than death by the general public. In addition, overall health was assessed with a visual analogue scale (EQ VAS). EQ VAS scores range from 0 to 100 with higher scores indicating better health. EQ-5D and EQ VAS adopt a recall period of 'today'.

QOLIE-31-P

Disease-specific HRQoL was assessed using the Patient Weighted Quality Of Life In Epilepsy (QOLIE-31-P). QOLIE-31-P is designed to assess HRQoL in adults with epilepsy. Using a 100-point scale, the instrument covers seven domains of epilepsy: seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning [151]. QOLIE-31-P includes seven items asking the subjects to rate the degree of 'distress' related to the topic of each domain [100]. The instrument has a recall period of four weeks.

Well-being

ICECAP-A

To measure well-being, the ICEpop Capability Measure for Adults (ICECAP-A) instrument was used. The ICECAP-A is a measure of capability well-being focused on the adult population and comprises five domains related to attachment, stability, achievement, enjoyment, and autonomy [102]. Each of these domains has four response levels, ranging from the absence of capability to full capability. Index scores were calculated using the Dutch tariff [152]. The index score was scaled to range from 0 [11111] to 1 [44444], indicating no capability and full capability respectively. The ICECAP-A adopts a recall period of 'at the moment'.

Medical costs

To collect data on health care use, the iMTA Medical Consumption Questionnaire (iMCQ) was utilised [103]. This questionnaire includes items related to the number of visits to health care providers and care institutions. Furthermore, the iMCQ was applied to assess the use of medication and home care. The questionnaire was complemented with questions that are relevant specifically for persons with epilepsy, such as consultations with a social worker, psychomotor therapist, day care in an outpatient facility, diagnostics and procedures, and the purchase of medical equipment (e.g., protective garments, home safety equipment, monitoring devices). Health care use was assessed using a three-month recall period.

Health care use was combined with reference prices, as provided in the Dutch costing manual, to estimate total costs [110]. When reference prices were not available in the Dutch costing manual, prices were derived from the Dutch Health care Authority for surgical procedures and from the Dutch Health care Institute or, when not available,

from websites from suppliers for medical equipment. The measurements included in this analysis were taken before participants were partnered with a certified seizure dog. When purchases were made in anticipation of the seizure dog, such as alarm systems, these were excluded from the current analysis in order to provide estimates of the costs of severe refractory epilepsy without the intervention. Drug prices were collected from the Dutch Health care Institute. To estimate drug costs without VAT, prices obtained from this website were corrected. A fee of €6.50 per drug, once every three months, was applied to account for pharmacy dispensing costs.

Non-medical costs

Informal care

Informal care was also assessed with the iMCQ. Participants reported the cumulative number of hours of informal care received over the past three months, which might be provided by more than one informal caregiver [103]. In the questionnaire, informal care was defined as care falling in one of the following three categories: household activities (e.g., cleaning, grocery shopping, food preparation, taking care of children), personal care (e.g., help with dressing/undressing, washing, eating and drinking, medication), and practical support (e.g., providing support during walking, visiting family or friends, accompanying someone to hospital appointments, managing professional help, assisting with financial tasks). The total of informal care hours was valued using the replacement cost method [110].

Travel costs

Travel costs related to visits to health care providers were included in this analysis. For hospital visits, data on the mode of transportation and travel distance were collected via the iMCQ. For other health care services, the assumption was made that participants travelled by car (and were driven by an informal caregiver) and the average travel distance was taken from the Dutch costing manual [110]. Costs were estimated in line with the Dutch costing manual.

Productivity costs

Productivity costs were assessed with the iMTA Productivity Cost Questionnaire (iPCQ). The iPCQ measures absenteeism (being absent from work) and presenteeism (decreased productivity while at work), as well as losses of unpaid work [104]. The questionnaire uses a recall period of four weeks. Presenteeism was estimated by multiplying the number of workdays during which efficiency loss was experienced with the efficiency score (0 – 1, with 0 representing no productivity and 1 representing full productivity), multiplied by the hours of work on a working day. In line with the Dutch health economic guidelines [60], costs of absenteeism were estimated using the

friction cost method, which limits societal costs due to absenteeism to the average period required to replace an ill worker [153], which was estimated to be 14.55 weeks in 2021 [154]. For the monetary valuation of lost productivity (both absenteeism and presenteeism) and losses of unpaid work, the Dutch costing manual was followed. As the recall of the iPCQ on short-term absenteeism and presenteeism covers 4 weeks, short-term productivity loss was extrapolated to a period of three months. Where needed, inflation correction was applied, using the general price index from the Central Bureau of Statistics of the Netherlands. All costs were expressed in 2021 euro.

Statistical analysis

Descriptive statistics for all variables of interest were calculated. Numerical variables are shown with mean and standard deviation, while categorical variables are represented by numbers and percentages. Owing to loss to follow-up, item non-response and invalid answers, the dataset was unbalanced. To give equal weight to all participants in the dataset, missing values were imputed. A missing value on a domain prohibits the calculation of index scores for EQ-5D-5L and ICECAP-A. In these cases, i.e., when partial information was available, missing domain scores were imputed using the mean of the prior and posterior observation. When the posterior observation was missing, the last observation carried forward was applied. For item non-response on QOLIE-31-P, the scoring manual was followed. In case of unit non-response on either of the three instruments, i.e., in the absence of information, the index score was imputed with the mean of non-missing values of the participant. The same approach was adopted to impute missing values for medical and non-medical costs, with the exception of long-term productivity loss which was not imputed to prevent double counting as the friction cost method was applied. Whereas the measurements were performed during a 12-month time span, the data cover a maximum period of 15 months owing to the recall periods of instruments used (i.e., the questionnaire contained instruments with recall periods ranging up to three months). To aid interpretability and comparability, data covering a period of more than 12 months are recalculated and presented for a 12-month period where relevant. For the HRQoL and well-being measures the average scores are presented, while for resource use the accumulated yearly costs are provided. Stata/MP 16 was used to analyse the data.

Results

Study population

Data were collected from 25 participants who were followed over 12 months. The mean age at baseline was 33.8 years (SD 12.3, range 20 – 57) and 56% was male. The majority of participants lived either with their parents (48%) or with their

partner (44%). The majority of participants did not have a paid job (76%). On average, participants had been living with the epilepsy diagnosis for 22.6 years (SD 14.1, range 2 – 54). Sixty-four percent was diagnosed with focal onset seizures, generalised onset seizures were reported by 28% of participants. About one-third of participants reported daily seizures. The median 12-month seizure count was 476 (range 49 – 6,223) which is equal to 9 seizures a week. On a seizure day, the median seizure count was 3 (range 1 – 17). Comorbidities were reported by 60% of participants, of which the majority had more than one comorbidity. The most frequently reported comorbidities were cognitive impairment ($n = 6$), developmental, learning or behavioural disorder ($n = 5$), motor impairment ($n = 4$), respiratory disease ($n = 4$) or mental disorder ($n = 3$). Additional clinical and demographic information is provided in Table 1.

HRQoL and well-being

Table 2 shows the mean HRQoL and well-being scores reported by the 25 participants during the first year of the EPISODE study, that is, the mean across the five three-monthly measurements. For the instruments EQ-5D-5L, EQ VAS, ICECAP-A and QOLIE-31-P, the number of observations before imputation was 114, 116, 114, and 117 (i.e., a response rate between 91.2% and 93.6%), respectively. After imputation, a balanced dataset of 125 observations was obtained.

The mean EQ-5D-5L utility score across all observations was 0.682 (SD 0.235) (Table 2). Figure 1 shows the proportion of participants reporting problems by EQ-5D dimension, taking into account all observations. The health domain on which participants felt most impaired was usual activities, with 44% experiencing moderate or severe problems on average during the follow-up. On average, 36% of participants reported to be moderately or severely anxious or depressed and 36% reported moderate or extreme pain or discomfort. The majority of participants reported no problems with mobility (64%) or self-care (80%). The mean score on EQ VAS was 68.3 (SD 16.0) (Table 2).

On ICECAP-A, the average score during the first year was 0.746 (SD 0.172) (Table 2). Figure 2 shows the proportion of participants reporting problems by ICECAP-A dimension, taking into account all observations. The domains most affected were autonomy and stability, with 64% and 40% of participants reporting on average little or no capability. Attachment was the least affected domain, with 12% of participants reporting on average full capability and 68% reporting a lot of capability.

Table 1. Demographic characteristics at baseline (n = 25)

Characteristics	n (%)
Sociodemographic characteristics	
Gender	
Male	14 (56%)
Female	11 (44%)
Age (mean (SD, range))	33.8 (12.3, 20 – 57)
Living situation	
Alone	2 (8%)
With parents	12 (48%)
With partner and/or children	11 (44%)
Education attainment	
Primary school or lower	4 (16%)
Secondary school	9 (36%)
Secondary vocational education	9 (36%)
Higher professional education	1 (4%)
University	2 (8%)
Daily occupation	
Paid job	3 (12%)
Unpaid job	10 (40%)
Paid job and unpaid job	3 (12%)
None	9 (36%)
Clinical characteristics	
Duration of disease in years (mean (SD))	22.6 (14.1)
Type of epilepsy	
Focal onset	16 (64%)
Generalised onset	7 (28%)
Unknown onset	2 (8%)
Frequency of seizures1	
Daily	8 (32%)
Three to six times a week	12 (48%)
Twice a week or less	5 (20%)
Seizure frequency on a seizure day[1] (median (range))	3 (1 – 17)
Comorbidity	
No comorbid conditions	10 (40%)
1 comorbid condition	2 (8%)
2 – 3 comorbid conditions	9 (36%)
4 or more comorbid conditions	3 (12%)
Missing	1 (4%)

Keys: n = number of observations, SD = standard deviation

1 Seizures for which the participant could not record daily frequencies (i.e., because the seizures are difficult to notice or occur at a high frequency) are not considered

The average score on QOLIE-31-P during the first year was 55.8 (SD 14.0). Figure 3 shows the average domain scores on QOLIE-31-P (before multiplication with the distress score). Lowest average scores were observed in the social function, seizure worry, and cognition domains with scores of respectively 27 (SD 12), 28 (SD 20) and 29 (SD 22). Across all domains, the lowest impact was observed on emotional well-being and medication effects, both with a mean score of 45. The distress score, which reflects the weight of the degree of distress felt by the individual about each domain, revealed that participants were most distressed by cognition and seizure worry. Medication effects and emotional well-being were least bothersome to participants.

Table 2. Summary statistics for EQ-5D-5L, EQ VAS, ICECAP-A, and QOLIE-31-P over five assessments within a one-year follow-up (n = 25)

Instrument (Possible range)	Average score Mean (SD)	Range across participant means Min, Max	Range across individual observations Min, Max
EQ-5D-5L (-0.446 –1)	0.682 (0.235)	0.221, 1	-0.149, 1
EQ VAS (0 – 100)	68.3 (16.0)	33.4, 96.0	10.0, 100
ICECAP-A *(0 – 1)*	0.746 (0.172)	0.328, 0.945	0.208, 0.964
QOLIE-31-P *(0 – 100)*	55.8 (14.0)	29.9, 76.4	19.0, 81.9

Keys: ICECAP-A = ICEpop CAPability measure for Adults, QOLIE-31-P = Patient-Weighted Quality of Life in Epilepsy Inventory-31, SD = standard deviation

Figure 1. EQ-5D-5L domain scores (a higher score reflects worse health)

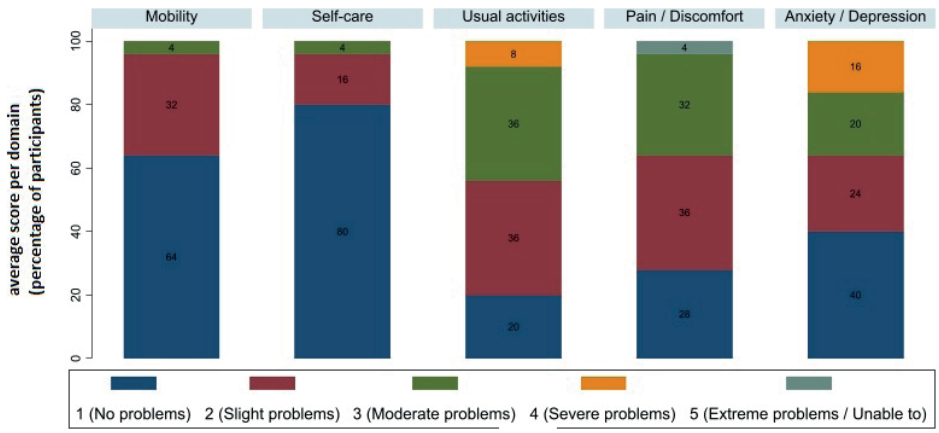


Figure 2. ICECAP-A domain scores (a higher score reflects better well-being)

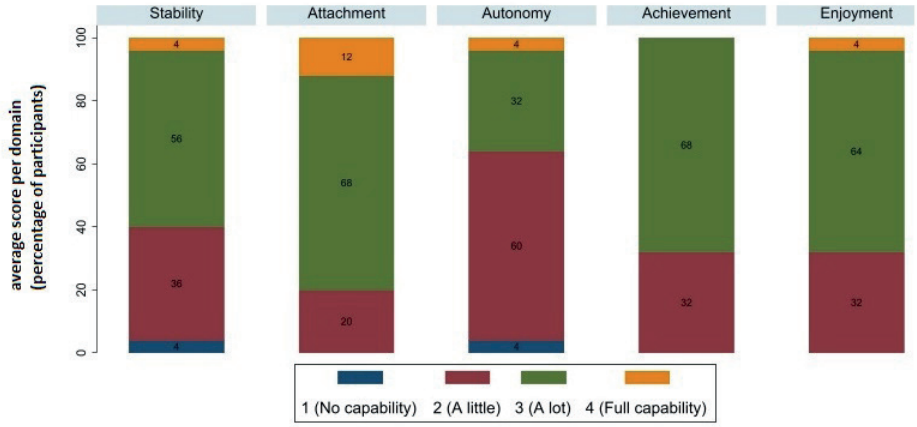
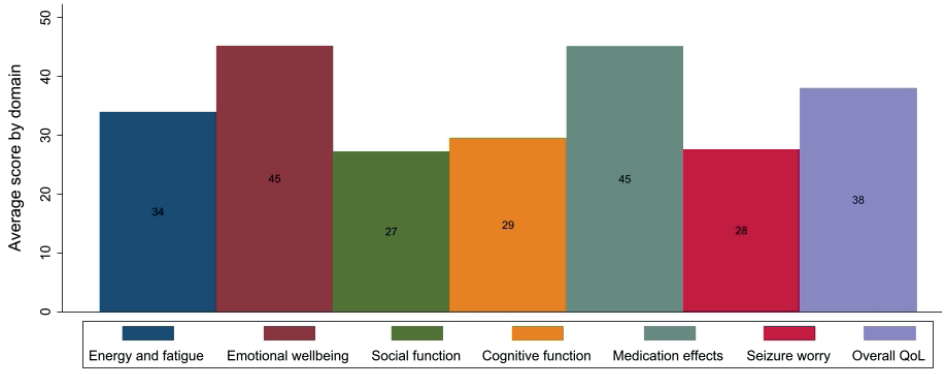


Figure 3. Average QOLIE-31-P domain scores (a higher score reflects better quality of life)



Medical costs

Table 3 summarises the medical and non-medical costs of the 25 participants in the first year of the EPISODE study. In total, annual medical costs accumulated to an average of €15,823 (range €1,617 – €73,319). Overnight treatment was the most important contributor to the total medical costs (30%), but its costs varied widely among participants (range €0 – €65,627). Participants reported on average 25 visits to a primary care professional, mostly a physiotherapist, a general practitioner or a psychologist with an average of 13, 4, and 5 visits per year across the sample. Home care was used by 25% of participants, who received on average 3 hours of

assistance per week. All participants reported outpatient visits to the hospital or tertiary care centre, mostly to visit a neurologist or nurse specialist (on average, 9 times per year) or a social care worker (on average, 4 times per year). Annual costs for outpatient visits amounted to €1,412 with a range of €440 – €4,683. Day treatment was used by one-third of the participants, mostly at an activity centre or revalidation centre. Approximately half of the participants received emergency care, with ambulance calls accounting for a larger proportion of costs as compared to visits to the emergency department. Diagnostic tests or medical procedures were reported by 40% of participants, most frequently electroencephalogram (EEG) diagnostics or replacement of VNS or DBS batteries. All participants used medication, with the average annual costs amounting to €1,837 (range €344 – €4,915). Purchase of medical equipment was reported by 24% of participants, which included monitoring devices, home safety equipment and orthoses.

Non-medical costs

In total, annual non-medical costs accumulated to an average of €24,133 (range €203 – €86,925), comprising of informal care costs, productivity losses and travel costs. All but one participant received informal care. Those who received informal care reported on average 26 hours of informal care per week (Table 3). The average annual costs of informal care across the sample amounted to €20,041 (range €0 – €86,575). Approximately half of the hours of informal care received comprised practical assistance. The primary informal caregiver was most often the parent of the participant (60%), followed by a spouse or partner (40%). In total, 52% of participants experienced reduced productivity due to their health status due to presenteeism or absenteeism. Two participants had stopped working due to their disease during the data collection. Overall, average annual productivity losses amounted to €3,734 with a range of €0 – €36,952 per year. Participants made 49 trips to care providers in a year on average, with travel costs amounting to €359 (range €5 – €2,784).

Total costs for persons with severe refractory epilepsy accumulated to €39,956 per year (range €3,804 – €132,264). Non-medical costs accounted for 60% of total costs. The largest cost components were informal care (50%), inpatient care (12%) and productivity loss (9%).

Table 3. Average resource use in natural units and costs per participant over one year, in euro (n = 25)

Type of care	Unit description	Participants using resource	Average units if using Mean (SD)	Range of costs if using Mean (SD)	Average units per participant Mean (SD)	Average costs per participant Mean (SD)
Primary care consultation	Appointments	100%	25 (35)	15 – 6,365	25 (35)	1,369 (1,780)
Home care	Hours	25%	139 (100)	220 – 11,511	28 (71)	896 (2,559)
Outpatient visit	Appointments	100%	15 (12)	440 – 4683	15 (12)	1,412 (1,040)
Day treatment	Days admitted	32%	50 (55)	119 – 14,991	16 (39)	1,790 (3,971)
Overnight treatment	Nights admitted	36%	30 (50)	423 – 65,627	11 (33)	4,740 (13,257)
Emergency care	Events	48%	7 (9)	230 – 16,210	3 (7)	1,669 (3,529)
Medical diagnostics and interventions	Procedures	40%	1 (1)	296 – 14,804	0 (1)	1,931 (4,760)
Medical technologies	N/A	24%	1 (1)	132 – 1,200	0 (1)	179 (383)
Medication	N/A	100%	NA	344 – 4,915	NA	1,837 (1,071)
Total medical costs				1,617 – 73,319		**15,823** (16,765)
Informal care	Hours	96%	1,342 (1,561)	377 – 86,575	1,288 (1,552)	20,041 (24,131)
Productivity loss	Hours	52%	195 (279)	121 – 36,952	101 (223)	3,734 (8,208)
Travel costs	Trips	100%	49 (55)	5 – 2,785	49 (55)	359 (626)
Total non-medical costs				203 – 86,925		**24,133** (23,789)
Total costs				3,804 – 132,264		**39,956** (32,073)

Keys: SD = standard deviation. N/A = not applicable

Discussion

Using data from the first year of the EPISODE study, a detailed account of the burden of illness of PSREs was provided. Quantifying the burden of illness can increase the awareness and understanding of the importance of (research into) interventions for this particular patient population, and may be used to develop policies and inform resource allocation in this specific area. The findings showed that PSREs experience substantial deterioration in their HRQoL and well-being and incur considerable societal costs. With informal care accounting for 60% of total costs, persons with severe refractory epilepsy rely heavily on their family and friends in daily life. This is reflected by the majority of participants reporting problems with autonomy (ICECAP-A) and usual activities (EQ-5D-5L). Furthermore, while the proportion of participants with a paid job is limited, productivity losses in this population should not be ignored and can be attributed mainly to long-term absenteeism and losses from unpaid work. The disease burden, however, varied considerably between participants.

Quantifying the burden of illness can increase the awareness and understanding of the importance of (research into) interventions for this particular patient population, and may be used to develop policies and inform resource allocation in this specific area

With an average EQ-5D-5L utility score of 0.682, participants scored considerably lower than the average Dutch population for the age group 30-39 (0.903) [127]. Participants scored also considerably lower than other epilepsy populations. For example, a study by Wijnen et al describes pooled data on EQ-5D-5L and QOLIE-31-P collected in adults participating in an epilepsy self-management study in the Netherlands and the United Kingdom [155]. The baseline scores were 0.86 on EQ-5D-5L and 65.7 on QOLIE-31-P, relative to 0.68 and 55.8 in the current study. A Dutch study looking into three types of epilepsy populations, those treated by the general practitioner, university hospital, and tertiary epilepsy centre observed the lowest quality of life scores and highest societal costs in the latter population which most closely matches the population in the current study [141]. With an average QOLIE-31-P score of 62.9 and annual societal costs of €4,292 (which would compare to 5,648 in 2021 euros), their estimate of the HRQoL of persons treated at an epilepsy centre is higher while their estimate of the costs is considerably lower than the findings of the current study (55.8 and €39,956) [141]. These findings demonstrate the high burden of illness of persons with severe refractory epilepsy compared to other epilepsy populations. Similarly, a study in Germany reported lower direct costs in all subgroups [156]. The higher costs in the current study may result from a broader approach to costing, as well as from a higher disease severity.

The main strengths of this burden of illness study lie in the evaluation of the burdens experienced by persons with severe refractory epilepsy from a broad societal perspective (HRQoL, well-being and costs) and in the detailed approach to costing. The one-year follow-up period allowed for capturing fluctuations in outcomes over time, which is relevant as seizure patterns may fluctuate and seizure-related injuries can have a substantial yet temporal impact on HRQoL, well-being, health care use, reliance on informal care and productivity.

If symptom relief is not possible, interventions could focus on improving coping and self-management skills, and reducing the risk and severity of seizure-related injuries.

Some limitations need noting. First, the analyses were based on data from a relatively small sample of 25 persons with severe refractory epilepsy, which is an obvious limitation. Persons with severe refractory epilepsy represent a small proportion of the total epilepsy population. With this data this study was, however, able to provide insight in this understudied and hard to reach population. Nevertheless, it should be noted that the data used in the current study were collected in the context of the EPISODE study on seizure dogs for adults with severe refractory epilepsy. It is uncertain to which extent the results of the current study are generalisable to other populations with severe refractory epilepsy. The criteria used to determine eligibility for participating in the study extend beyond refractory epilepsy alone (Table 1 of Chapter 2). For example, it was important to ensure the suitability of participants and their environment to own a seizure dog and guarantee its well-being. Furthermore, a seizure dog may not be a desirable solution for all persons with severe refractory epilepsy, for example, if they are unwilling or unable to care for a seizure dog under their current living circumstances. Therefore, only a specific subset of the population eligible may have applied for participation in the EPISODE study. Such a selection bias cannot be ruled out and the impact of these aspects on the outcomes presented remains unclear. The results might provide reliable estimates for persons with frequent and severe seizures, who have been exploring both pharmacological and non-pharmacological treatment options, and fulfil the requirements for participating in an assistance dog programme. Second, owing to the limited sample size as well as probable violation of the missing at random assumption, the ad-hoc method of mean imputation has been applied to address missing data. This approach reduces the within variance in the dataset which may result in standard errors which overstate the actual precision and certainty. Third, it should be noted, however, that EQ-5D may not accurately reflect average HRQoL in participants as it only considers HRQoL on the day of questionnaire completion, whereas participants may have days with numerous seizures, and other days where they have no seizures at all (Chapter 3). A further

limitation lies in the potential of double counting between the various categories of care received within hospitals or tertiary epilepsy centres. The data did not allow for linking consultations with specialists to procedures or hospitalisations. Given the considerable costs of hospitalisations and procedures relative to the costs of a specialist consultation, the impact of double counting is expected to be limited. Finally, the current estimates do not distinguish between the burden due to refractory epilepsy and the burden that may result from other, comorbid conditions. Notwithstanding these limitations, these findings represent an important addition to the literature on an understudied group of severely burdened persons with epilepsy.

Conclusions

This study has investigated and detailed the burden of illness of a sample of Dutch persons with severe refractory epilepsy. It has shown that the impact on these persons, in terms of their health, well-being and daily lives, as well as the impact on their informal caregivers and the health care system and society as a whole, are substantial. Novel treatment options are needed to alleviate the burden of this disease for this patient population. If symptom relief is not possible, interventions could focus on improving coping and self-management skills, and reducing the risk and severity of seizure-related injuries.

Based on: Based on van Hezik-Wester V, de Groot S, Kanters T, Wagner L, Ardesch J, Brouwer W, Corro Ramos I, le Cessie S, Los J, Versteegh M, van Exel J, on behalf of the EPISODE-team

Neurology. 2024;00:e209178

Chapter 5

Effectiveness of seizure dogs in persons living with severe refractory epilepsy: results from the EPISODE study

Highlights

- The EPISODE study shows seizure frequency reduces over time with the seizure dog.
- Improvements in quality of life are observed across all measures, most notably in health-related quality of life.
- Data do not indicate when the seizure dog's full effect is reached.
- Discontinued seizure dog trajectories highlight the need for further research on the suitability of seizure dogs for different individuals.

Abstract

Background and Objectives

The aim of this study was to evaluate whether persons with severe refractory epilepsy (PSREs) benefit from a seizure dog.

Methods

An individual-level stepped wedge randomised controlled trial was conducted. The study was carried out in the Netherlands among adults with daily to weekly seizures. All participants were included simultaneously, on 1 June 2019, and initially receiving usual care. Then, during the 36-month follow-up, they received a seizure dog in a randomised sequence. Participants kept a seizure diary and completed three-monthly surveys. Seizure frequency was the primary outcome. Secondary outcomes included seizure-free days, seizure severity, health-related quality of life (HRQoL), and well-being. Data were analysed using generalised linear mixed modelling (GLMM). The models assumed a delayed intervention effect, starting when the seizure dog reached an advanced stage of training. Effects were calculated as changes per 28-day period with the intervention.

Results

Data were collected from 25 participants, of whom 20 transitioned to the intervention condition. The median follow-up was 19 months with usual care and 12 months with the intervention. On average, participants experienced 115 (SD 164) seizures per 28-day period in the usual care condition and 73 (SD 131) seizures in the intervention condition. Seven participants achieved a reduction of 50% or more at the end of follow-up. GLMM indicated a 3.1% decrease in seizure frequency for each consecutive 28-day period with the intervention (0.969, 95% CI 0.960 – 0.977). Furthermore, an increase in the number of seizure-free days was observed (1.012, 95% CI 1.009, 1.015), but no effect on seizure severity measured with the NHS3. Generic HRQoL scores improved, as reflected in the decrease in EQ-5D-5L utility decrement (0.975, 95% CI 0.954 – 0.997). Smaller improvements were observed on overall self-rated HRQoL, epilepsy-specific quality of life, and well-being, measured with EQ VAS, QOLIE-31, and ICECAP-A, respectively.

Conclusions

Seizure dogs reduce seizure frequency, increase the number of seizure-free days, and improve the quality of life of PSREs. The magnitude of the effect on generic HRQoL indicates that seizure dogs benefit PSREs beyond the impact on seizure frequency alone. Early discontinuation of seizure dog partnerships suggests that this intervention is not suitable for all PSREs and requires further study.

Introduction

Epilepsy imposes a significant clinical and economic burden on societies. Despite the development of numerous anti-seizure medications over the past 15 years, approximately 20–30% of people with epilepsy experiences persistent seizures [24]. While epilepsy surgery can be effective in eliminating seizures, only a small minority of people with epilepsy is eligible for surgery [157]. Neurostimulation is another treatment alternative but does not often result in seizure freedom [158]. Hence, a proportion of people with epilepsy experiences frequent seizures despite the wide and continuously expanding range of treatments. People with severe refractory epilepsy (PSRE) bear the greatest burden of epilepsy-related disabilities and are at risk of falls, drowning, and burn wounds [9]. Furthermore, depression and anxiety disorders are important comorbid conditions in those who experience frequent seizures [159,160].

The unpredictable nature of seizures is generally considered the most disabling aspect of the condition [161,162]. Many seizures are accompanied by loss of consciousness, and PSRE are often unable to call for help. Timely intervention on the occurrence of a seizure, such as administering emergency medication, can reduce the risk of seizure-related injuries, status epilepticus, and sudden unexpected death. Therefore, over the last few years, wearable devices have been developed to detect seizures and alert informal caregivers [163]. Yet, no device is currently able to recognise all types of seizures due to their different clinical manifestations. Moreover, the risk of false positives resulting from everyday activities restricts the usability of most devices to nighttime.

Because it concerns a costly intervention that not many persons with epilepsy can afford, the current number of seizure dogs is very low and (opportunities for collecting) observational data thus also limited

Seizure dogs may help overcome some of the limitations of seizure detection devices. These formally trained dogs recognise seizures and respond when they occur. They are trained to identify seizures activity in the person they are partnered with by observing body movements, sounds, and physiological signals. The set of response tasks depends on the care needs of the person with epilepsy, but generally includes the activation of an alarm system, fetching medication or a phone, blocking the person's movement, or changing the person's body position. Furthermore, the dog can provide companionship as the seizure subsides, a period during which the person may feel disoriented and anxious. Previous exploratory studies suggested that seizure dogs could potentially reduce seizure frequency and improve quality of life [19,26,29]. Stress is the most common trigger for seizures, with half of people with epilepsy reporting stress-precipitated seizures [162,164-166]. The tasks seizure dogs perform and their companionship may

alleviate (seizure-related) anxiety, potentially reducing stress-precipitated seizures. Furthermore, seizure dogs may facilitate rapid action when a seizure occurs, limiting the risk of seizure clusters and seizure-related injuries. However, current evidence for the benefits of seizure dogs is limited, which hinders their consideration as routine (reimbursed) care [25,27]. At the same time, because it concerns a costly intervention that not many people with epilepsy can afford, the current number of seizure dogs is very low and (opportunities for collecting) observational data thus also limited.

The primary aim of the EPISODE (EPIlepsy SuppOrt Dog Evaluation) study was to evaluate whether seizure frequency is reduced by the provision of a seizure dog in addition to usual care, relative to usual care alone, in adults with severe refractory epilepsy (Chapter 2). Because previous studies suggest that seizure dogs may affect the lives of PSRE more broadly, the secondary aim was to evaluate the impact of seizure dogs on seizure-free days, seizure severity, health-related quality of life (HRQoL), and well-being.

Methods

The methods employed in this study are described further. A detailed description of the EPISODE study rationale and methods can be found in the study protocol (Chapter 2).

Study design

An individual-level stepped wedge design was adopted. This is a subtype of randomised controlled trials (RCTs) in which the intervention is gradually introduced to the study population. Randomisation determines the point in time during which participants receive the intervention, rather than whether or not they receive the intervention at all as in traditional RCTs. The study was conducted in the Netherlands. Participants were enrolled on June 1 2019, and followed up for three years, until May 31 2022. Participants were first observed for a baseline period (i.e., usual care condition), after which they sequentially received a seizure dog at their assigned time slot and were transferred to the intervention condition .

Eligibility criteria and screening process

People were eligible for study participation if they had refractory epilepsy, an average seizure frequency of two per week or more, seizure characteristics associated with a high risk of injuries or dysfunction, and the ability to care for a seizure dog (full set of criteria available in Chapter 2, Table 1). Eligibility was assessed by the treating neurologist and had to be confirmed by a neurologist in the study team. In addition, the assistance dog organisation advised on the feasibility of starting a seizure dog

trajectory considering the applicant's personal circumstances (e.g., housing conditions and support network to help with dog care and training).

Intervention characteristics

The intervention was defined as the partnership with a dog that is being trained or has finished a training trajectory focused on recognising seizures and responding when they occur. Seizure dogs may also develop alerting behaviour, which consists of anticipating on an impending seizure [27]. Seizure dog trainers were attentive to signs of such behaviour, but the cues that allow some dogs to anticipate seizures are unknown and, therefore, alerting behaviour cannot be trained. Seizure dogs were provided through either a pre-trained dog trajectory or a team coaching trajectory. In the pre-trained dog trajectory, the participant was partnered with a dog that had finished socialisation and obedience training, after which the training of epilepsy-specific tasks was continued at the participant's home. In the team coaching trajectory, participants were coached in training a puppy in their own home from the start. Participants were allocated to the trajectory of their preference. Because both trajectories aimed to provide a seizure dog that adheres to the standards of Assistance Dogs International [46], the effect of the trajectories was assumed to be identical. Usual care included treatments to control seizures, such as anti-seizure medications and neurostimulation, as well as assistive care services and technologies, such as occupational therapy and wearable alarm devices.

Randomisation

Before the start of data collection, participants were randomly assigned to a time point at which their seizure dog trajectory would start. The randomisation was conducted separately for the pre-trained dog trajectory and the team coaching trajectory, taking into account the assistance dog organisations' capacities, and a minimum follow-up of three months without a study dog and three months with a certified seizure dog for each participant. As a good fit with the dog was considered a crucial factor for the success of a seizure dog partnership, deviation from the randomised order was allowed when there was no match between the participant and the dog(s) available at the assigned time point.

Stepped wedge design specification

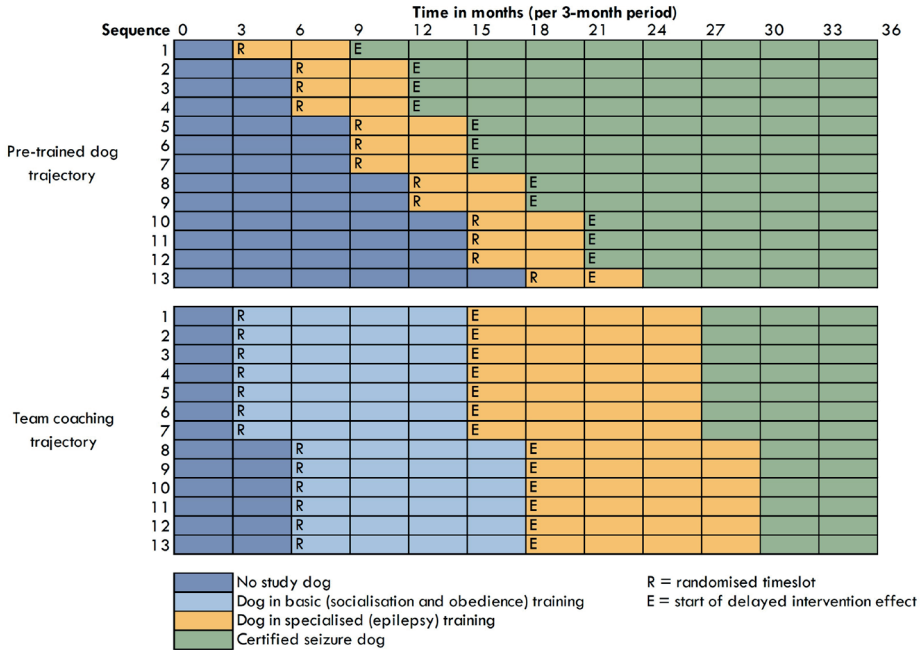
Figure 1 presents the stepped wedge schedule reflecting the individual pathways to which participants were randomised, stratified by seizure dog trajectory. The crossover from usual care to the intervention condition was defined as 6 months after placement in the pre-trained dog trajectory, and as the seizure dog passing the socialisation and obedience test in the team coaching trajectory (approximately 12 months after placement of the puppy). This cut-off was defined before data collection and

considered in the statistical analyses (Supplement 2). It was based on the hypothesis that the dog starts providing seizure dog-specific benefits when the participant and the dog have bonded, and training is focused on epilepsy-specific tasks.

Data collection

Seizure frequency was the primary outcome of the study. Using paper seizure diaries, participants recorded their daily seizure counts for up to three most frequently occurring and countable seizure types. Each week, participants submitted a photograph of their seizure diary via a smartphone application. For the analysis, daily seizure counts were converted to obtain cumulative seizure frequencies over 28-day periods. Participants completed a survey every three months. The survey consisted of a set of validated questionnaires, including NHS3 [99] to measure seizure severity, EQ-5D-5L [101], EQ VAS [101], and QOLIE-31-P [151] to measure HRQoL, and ICECAP-A [102] to measure well-being.

Figure 1. Stepped wedge schedule reflecting the planned rollout and different stages of seizure dog trajectories



Each row reflects one participant. Based on the inclusion at the time of randomisation, the schedule was designed to randomise 26 participants. They were equally divided over the two seizure dog trajectories. The columns reflect time in three-month periods, totalling to the three-year follow-up. As time progressed, more participants were scheduled to have transitioned from the usual care condition to the intervention condition.

Sample size calculation

In an observational study by Strong et al., an average decrease of 43% in 28-day seizure frequency of tonic clonic seizures was observed in ten individuals 24 to 36 weeks after pairing with a pre-trained seizure dog [9]. To determine statistical power for this study, 2,500 simulations were run incorporating the planned analyses and stepped wedge schedule. The power was calculated as the proportion of simulations that detected the intervention effect at a 5% significance level. Two sample sizes were tested: one with 20 participants and another with 25 participants. With both sample sizes, the study would have more than 80% power to identify a reduction in seizure frequency similar to the effect previously demonstrated (Chapter 2).

Handling missing data

When information on an outcome measure was missing in full (i.e., unit nonresponse), no imputation was conducted. When information was missing partially (i.e., item nonresponse), missing values were imputed to retain observations in the dataset. For 28-day seizure frequency, a missing daily seizure count was imputed with the participant's mean seizure count in the particular period. An exception was made when a participant noted the seizure count was missing because of the unusual high frequency, for example due to clustering or status epilepticus. In those cases, the missing daily seizure count was imputed with the highest seizure count recorded by the participant over the entire follow-up. For NHS3, EQ-5D-5L, and ICECAP-A, missing item scores were imputed with the mean of the participant's nearest non-missing prior and posterior observations for that item [167]. For QOLIE-31-P, the scoring manual was followed for handling missing data [151].

Statistical analysis

Data were analysed in accordance with a pre-specified statistical analysis plan (Supplement 2). To account for repeated measures of participants over time, the effects of seizure dogs were examined using a generalised linear mixed modelling (GLMM) approach. For all outcomes, effects were assumed to develop linearly over time with the intervention. Time was expressed in 28-day periods, and consequently, effects were reported as changes per 28-day period with the intervention. Specifically, the GLMM analyses included a parameter for time with the intervention as a fixed effect and a random effect for each participant.

For the primary outcome, the statistical analysis plan prescribed a GLMM approach with a Poisson distribution and a log-link. The observed seizure frequency data exhibited an unexpected high degree of overdispersion, which may result in biased parameter estimates and invalid conclusions when using this distribution [168]. Therefore, an observation-level random effect was added where each data point receives its own random effect [168]. To test the robustness of the results for model specifications

and assumptions, sensitivity analyses were performed. These analyses included the exclusion of absence and myoclonic seizures and different approaches to accounting for the effect of time.

For secondary outcomes, an appropriate distribution family and link function were chosen depending on the observed distribution of the dependent variable. For EQ-5D-5L and ICECAP-A, utility scores were calculated using tariffs for the Netherlands [152,127]. Utility decrements (= 1 minus the utility score) were used in the effect estimations for EQ-5D-5L. Details of all models are presented in Supplement 4, Table S4.1. Data analysis was performed in R software.

Results

Inclusion and rollout of the intervention

Twenty-five PSRE participated in the study. Table 1 presents the characteristics of the participants at the start of the study. The trial flow diagram is presented in Figure 2. Six participants discontinued their seizure dog trajectory, and consequently their study participation, before the end of the trial follow-up. Of them, three participants discontinued before placement of the seizure dog. Three additional participants discontinued after placement, two of whom before the assumed start of the intervention effect and one thereafter. Consequently, 20 participants were observed under both the usual care and intervention conditions. Figure S4.1 in Supplement 4 presents the final stepped wedge schedule. Data on seizure frequency were available for 99% of the observed 28-day periods (846 out of 851), and 95% of the surveys were returned (270 out of 283). More information on missing data for each outcome measure is included in Table S4.2 of Supplement 4.

Table 1. Sociodemographic and clinical characteristics at the start of the study (n = 25)

Characteristics	n (%)
Sociodemographic characteristics	
Gender	
Male	14 (56.0%)
Female	11 (44.0%)
Age (mean (SD, range))	33.8 (12.3, range 20 – 57)
Living situation	
Alone	2 (8.0%)
With parents	12 (48.0%)
With partner and/or children	11 (44.0%)
Dog owner (prior to start of the study)	
Yes	8 (32.0%)
No	17 (68.0%)
Clinical characteristics	
Duration of disease in years (mean (SD))	22.6 (14.1)
Type of epilepsy	
Focal onset	16 (64.0%)
Generalised onset	7 (28.0%)
Unknown onset	2 (8.0%)
Number of seizure types recorded in seizure diary1	
1	3 (12.0%)
2	12 (48.0%)
3	10 (40.0%)
Number of participants recording seizure type	
Focal onset tonic-clonic seizure	13 (52.0%)
Generalised onset tonic-clonic seizure	6 (24.0%)
Unknown onset tonic-clonic seizure	1 (4.0%)
Focal motor seizure impaired awareness	10 (40.0%)
Focal non-motor seizure impaired awareness	8 (32.0%)
Focal motor seizure aware	1 (4.0%)
Focal non-motor seizure aware	1 (4.0%)
Generalised motor seizure	6 (24.0%)
Generalised non-motor seizure (absence)	5 (20.0%)
Not classifiable / unknown	6 (24.0%)
Frequency of seizures during first 28-day period1	
Daily	9 (36.0%)

Three to six times a week	9 (36.0%)
Twice a week or less	7 (28.0%)
Seizure frequency on a seizure day during first 28-day period[1] (median (range))	4 (1 – 29)
Comorbidity at baseline	
No comorbid conditions	10 (40.0%)
1 comorbid condition	2 (8.0%)
2 – 3 comorbid conditions	9 (36.0%)
4 or more comorbid conditions	3 (12.0%)
Missing	1 (4.0%)

1 Seizure types for which the participant could not record daily frequencies (e.g., because the seizures are difficult to notice or occur at a high frequency) are not considered.
Keys: SD = standard deviation, n = number of observations

Seizure frequency, seizure-free days, and seizure severity

The median follow-up consisted of 21 28-day periods in the usual care condition (range 3 – 36) and 13 28-day periods in the intervention condition (range 0 – 27), with a total follow-up ranging from 3 to 39 28-day periods (median 39). The number of observations for seizure frequency over time with the intervention can be found in Supplement 4, Figure S4.2.

Participants experienced an average of 115 (SD 164) seizures per 28-day period in the usual care condition and 73 (SD 131) seizures per 28-day period in the intervention condition (difference of -36.5%). The median seizure frequencies were 37.5 and 24, respectively (difference of -36.0%). The average seizure frequency over the last three 28-day periods (i.e., 12 weeks) of follow-up in the intervention condition was 31.1% lower when compared with the average seizure frequency in the usual care condition. A 25% – 49% reduction in seizure frequency was observed in four participants, and a 50% – 100% reduction in seven participants (Figure 3). One participant had a 25% – 50% increase in seizure frequency, and two participants showed an increase of 50% or more. For the remaining six participants, the change in seizure frequency was less than 25%, with four participants reporting a decrease and two an increase

Figure 2. Trial flow diagram of screening, randomisation, and follow-up

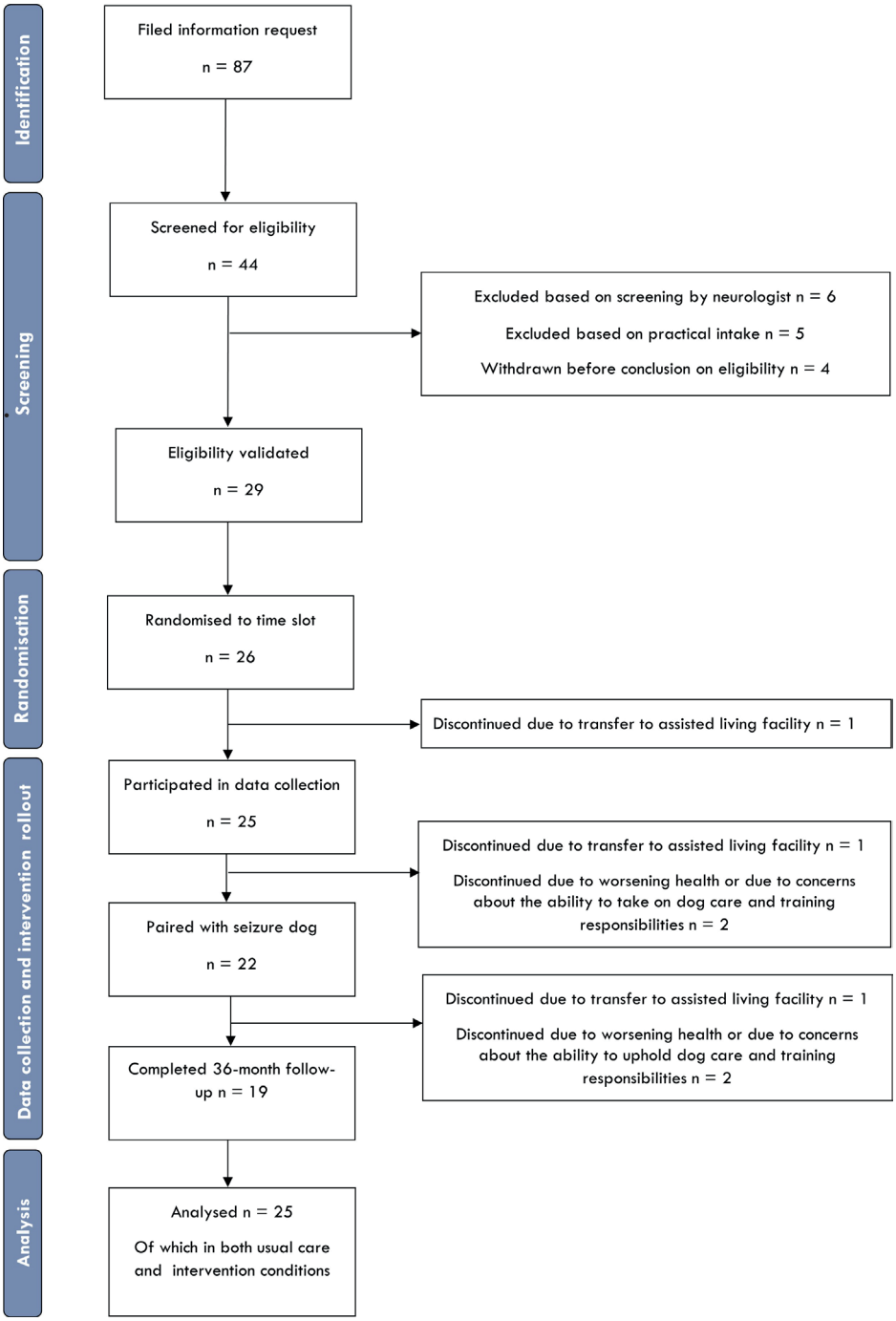
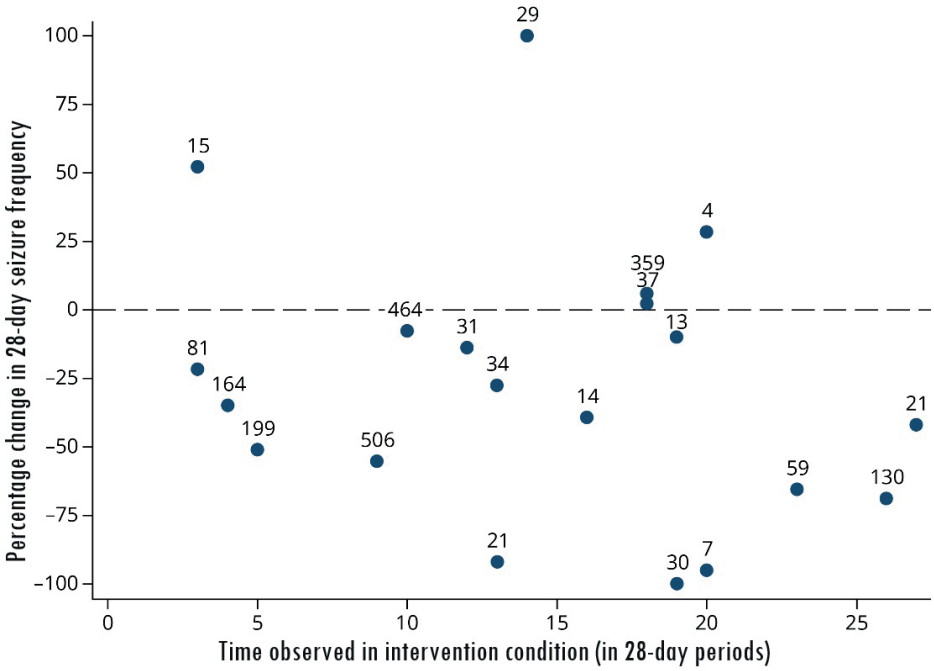


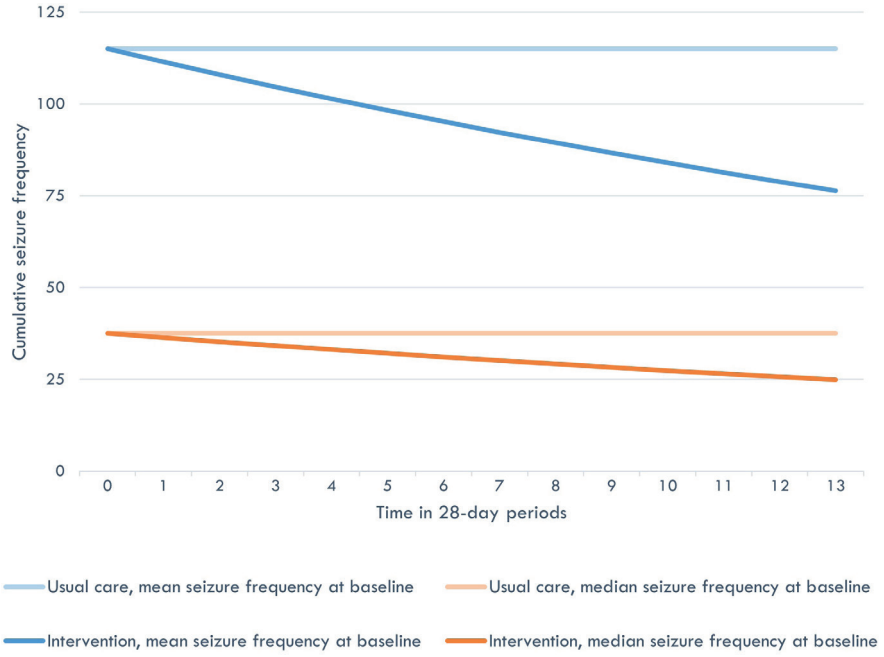
Figure 3. Change in seizure frequency as percentage change over the last three 28-day periods in the intervention condition relative to the average over the total time in the usual care condition



Each dot reflects one participant. Only participants observed with the intervention are presented. The number above each dot reflects the participant's average seizure frequency in the usual care condition. The x-axis reflects the time the participant is observed in the intervention condition.

For each consecutive 28-day period with the intervention, seizure frequency decreased on average by 3.1% (0.969, 95% CI 0.960 – 0.977) (Table 2). Figure 4 presents the estimated change over one year, using the mean and median seizure frequency of the study population at baseline as a reference.

Figure 4. Estimated effect plotted over one year, comparison between usual care and intervention arm using mean and median seizure frequency at baseline as a reference



Sensitivity analyses on 28-day seizure frequency showed effects in the same direction (Supplement 4, Table S4.3). Excluding absence and myoclonic seizures resulted in an average reduction of 3.4% for each consecutive 28-day period (0.966, 95% CI 0.957 – 0.974).

In the usual care condition, participants reported on average 11 (SD 9.8) seizure-free days per 28-day period, while in the intervention condition, this was 15 (SD 9.6). The number of seizure-free days increased on average by 1.2% for each consecutive 28-day period with the intervention (1.012, 95% CI 1.009 – 1.015) (Table 2). The intervention duration did not affect seizure severity as measured with the NHS3 (1.001, 95% CI 1.000 – 1.002).

Table 2. Study results on seizure frequency, seizure severity, HRQoL, and well-being: outcomes of the generalised linear mixed models

	28-day seizure count	28-day seizure-free day count	NHS3 score	EQ-5D-5L utility score decrement	EQ VAS score	QOLIE-31-P score	ICECAP-A index score
Regression results							
Exponentiated coefficient for time with the intervention	0.969	1.012	1.001	0.975	1.001	1.002	1.004
95% CI	0.960 – 0.977	1.009 – 1.015	1.000 – 1.002	0.954 – 0.997	1.001 – 1.002	1.001 – 1.002	1.001 – 1.006

Keys: CI = Confidence interval, ICECAP-A = ICEpop CAPability measure for Adults, NHS3 = National Hospital Seizure Severity Scale,QOLIE-31-P= Patient-Weighted Quality of Life in Epilepsy Inventory-31

HRQoL and well-being

Participants completed the surveys a median of seven times in the usual care condition (range 1 – 12) and three times in the intervention condition (range 0 – 9), with a total ranging from one to thirteen completed surveys per participant (median 13).

The average utility score in the usual care condition was 0.674 (SD 0.262) on EQ-5D-5L. In the intervention condition, the average score was 0.748 (SD 0.214). EQ-5D-5L utility decrements decreased on average by 2.5% per consecutive 28-day period with the intervention, reflecting an increase in generic HRQoL (0.975, 95% CI 0.954 – 0.997).

The average scores on EQ VAS and QOLIE-31-P were 69.0 (SD 19.4) and 55.4 (SD 15.8), respectively, in the usual care condition, and 73.9 (SD 16.9) and 58.7 (SD 13.9), respectively, in the intervention condition. Therefore, for each consecutive 28-day period with the intervention, EQ VAS scores increased by 0.1% (1.001, 95% CI 1.001-1.002), reflecting an increase in the overall self-rated HRQoL. QOLIE-31-P scores increased by 0.2% each period (1.002, 95% CI 1.001-1.002), reflecting an increase in epilepsy-specific quality of life. Figure S4.3 in Supplement 4 provides a graphical representation of the estimated changes over one year for each QoL instrument.

In the usual care condition, the average ICECAP-A utility score was 0.738 (SD 0.187). In the intervention condition, the average score was 0.781(SD 0.164). ICECAP-A utility scores increased on average by 0.4% per consecutive 28-day period with the intervention (1.004, 95% CI 1.001 – 1.006), reflecting an increase in well-being.

Dimension score analyses indicated improvements over time with the intervention on the anxiety / depression dimension of EQ-5D-5L and on the stability and achievement dimensions of ICECAP-A. Moreover, improvements were observed on five out of seven dimensions of QOLIE-31-P, with largest improvements on the social function and seizure worry dimensions. Scores on the other two dimensions worsened (cognition and medication side effects). More detailed results on dimension scores are presented in Tables S4.4a-c of Supplement 4.

Discussion

The EPISODE study is the first to evaluate the effectiveness of seizure dogs using a randomised design. The intervention was targeted at a difficult-to-treat population, for whom currently no further treatment options exist. This population bears a substantial burden of illness, leaving a high unmet need for care (Chapter 4). The study showed that partnering of PSRE with a seizure dog reduced seizure frequency, increased the number of seizure-free days, and improved quality of life.

The magnitude of the effect on seizure frequency observed here is remarkable considering the uncertainty about the mechanism of action of a seizure dog to affect seizure frequency

Seizure frequency decreased by a rounded 3.1% each consecutive 28-day period with the intervention, resulting in a cumulative reduction of 33.9% after one year (i.e., 13 periods). This effect remained consistent across various modelling assumptions, consistently showing a decrease in seizure frequency with time with the intervention. Previously, only one study evaluated the effectiveness of trained seizure dogs. In that study, baseline seizure frequency was compared with the seizure frequency in the last 12 weeks of follow up with the seizure alert dog. Four out of ten PSREs achieved a 50% reduction or more in tonic clonic seizures [26]. Considering all seizure types, this cut-off was achieved by seven out of 20 PSREs who were observed in the intervention condition in this study. In a systematic review and meta-analysis on adjunctive anti-seizure medications versus placebo, Beyenburg et al. found a weighted pooled risk difference of 21% for reaching the aforementioned cut-off [169]. Batson et al. reported an odds ratio of 2.27 in their systematic review and meta-analysis on the efficacy of vagus nerve stimulation versus placebo [170]. While differences in study design and follow-up time complicate a direct comparison of effect sizes between these studies and the current study, the magnitude of the effect on seizure frequency observed here is remarkable considering the uncertainty about the mechanism of action of a seizure dog to affect seizure frequency. The potential for a seizure dog to reduce seizures may be explained by the bidirectional pathophysiological relationship between stress and

epilepsy [30,160,171]. That is, while the role of stress in the causal pathway of seizures is complex and incompletely understood, previous studies on cognitive and behavioural interventions focused on stress reduction have demonstrated improvements in seizure frequency [172,173].

Patient-reported seizure frequency is commonly used in clinical studies evaluating epilepsy interventions. However, management of epilepsy is not only about controlling seizures but also about enhancing quality of life. Particularly among PSRE, for whom treatments have repeatedly failed to achieve seizure freedom, improving self-management and self-efficacy, and appropriately managing anxiety symptoms and comorbidities is of fundamental importance for their quality of life. Therefore, to provide insight into the full potential of seizure dog partnership, it is crucial to consider secondary outcomes. Besides a reduction in seizure frequency, this study showed an improvement on different quality of life outcomes. An improvement in quality of life after partnering with a seizure dog is consistent with findings from two self-reported survey studies [19,29]. Among the several quality of life instruments included in this study, the intervention effect was most evident for EQ-5D-5L, which is an established instrument for obtaining generic HRQoL values for inclusion in cost-effectiveness analyses [60,61]. With a 2.5% reduction in utility decrement for each consecutive 28-day period with the intervention, the mean utility score is expected to increase from 0.674 to 0.764 after one year of seizure dog partnership. Taking into account the age-adjusted general population utility value of 0.890, the average utility decrement attributable to epilepsy and comorbidities reduces by 41.7% (from 0.216 to 0.126). The results on EQ VAS, QOLIE-31-P, and ICECAP-A indicate smaller improvements on the respective outcomes. It is relevant to consider that previous studies have been unable to find statistically significant improvements in QOLIE-31-P and EQ-5D utility scores, even when a clinically relevant reduction in seizure frequency of 50% or 75% was observed [120,155,174]. Hence, the impact of changes in seizure frequency on the quality of life of PSREs might not be fully captured by the instruments used in this study. Nevertheless, this study detected a sizeable change in EQ-5D-5L utilities, which could indicate that seizure dogs affect the HRQoL of PSREs through changes in seizure frequency and through other mechanisms. Analyses on the dimension scores of the quality of life instruments showed reductions in (seizure-related) stress and improvements in social function, stability, and achievement. While a regular companion dog might also provide such benefits [27], the results from this analysis are expected to reflect the impact of the training of a seizure dog because one-third of participants already had a regular companion dog at the start of the study. Furthermore, observations taken during the first months after partnering with the seizure dog were attributed to the usual care condition due to the assumed delayed

intervention effect. Thus, any quality of life effects similar to those of an untrained companion dog are likely captured in observations in the usual care condition.

The study reported a discontinuation rate of 24% (i.e., 6 out of 25). In most cases, the decision to discontinue was made by the participant and assistance dog organisation jointly, primarily due to changes in participants' health or living situations. A seizure dog trajectory is a time-intensive and cost-intensive intervention. Discontinuation of a partnership can affect may both the person with epilepsy and the dog. Hence, one should weigh the reported benefits of seizure dogs against the risk of discontinuation and its consequences.

In particular among persons with severe refractory epilepsy, for whom treatments have repeatedly failed to achieve seizure freedom, improving self-management and self-efficacy as well as appropriately managing anxiety symptoms and comorbidities is of fundamental importance

Limitations

The study has several limitations. First, with 25 participants of whom 20 were observed in the intervention condition, this study has a limited sample size. Although the sample size calculation indicated these numbers were sufficient to detect changes in seizure frequency of the magnitude observed in an earlier study (Chapter 2) [26], the limited sample size does have implications for the ability to detect changes in secondary outcomes and limits the possibilities for subgroup analyses. As a consequence, the assumption that the effects are identical between the pre-trained dog trajectory and the team coaching trajectory could not be verified. Furthermore, small sample sizes may raise concerns about generalisability. However, because the total population of PSRE is small, the participants of this study constitute a considerable proportion of the total population in the Netherlands eligible for this intervention. Hence, the study findings are expected to be generalisable to the current target population. A second limitation is that blinding of participants was not possible. The impact on the study results is expected to be limited because in the analyses, the start of the intervention effect was defined at a later time point than the partnering with the dog, and this delay period was unknown to participants. A third limitation is that the study relied self-reported seizure frequency data. While self-reported seizure diaries are a common instrument for collecting seizure frequency data in clinical and research settings, the quality of such data depends on accurate recognition and recording of seizures by the person with epilepsy. This can be challenging, especially for seizure types that occur at high frequencies or are non-disabling such as absence seizures of myoclonic jerks. Sensitivity analyses showed that excluding these seizure types did not result in meaningful changes to the effect size. Fourth, the stepped wedge study design

complicates the estimation of the intervention effect at fixed time points of follow-up as the number of participants decreases with increasing time with the intervention. That is, data for 20 participants were available for the time point 12 weeks (3 periods) with the intervention, while for one year (13 periods) with the intervention data were available for 13 participants. Because no indication of a stabilisation of the intervention effect was observed in the data, more participants or a longer follow-up would be required for determining the point in time at which the intervention has reached its full potential. Furthermore, follow-up after discontinuation is required to understand the impact of ending the seizure dog partnership on the outcomes reported here. Lastly, the COVID-19 pandemic coincided with part of the data collection, which may have affected the training and coaching processes as well as the outcomes measured in this study. An additional survey was administered during a lockdown period (May 2020) to gain insight into the potential influence of the pandemic on the outcomes of this study. These data showed no clear impact of the pandemic on seizure frequency and resource use. This is in line with a study conducted in the same period in the United States, which indicated that most people with epilepsy in their sample reported no change in seizure frequency during the pandemic [175]. Moreover, as PSREs transitioned to the intervention condition at different points in time, any impact of the COVID-19 on study outcomes would have been present in both study conditions and, consequently, have a limited impact on the observed effects of the intervention.

Conclusions

This study represents the most comprehensive and scientifically rigorous examination of the impact of seizure dogs on seizure frequency, seizure-free days, seizure severity, HRQoL, and well-being in PSREs to date. This research showed improvements across all outcome measures over time with the intervention, except for seizure severity. Improvements in seizure frequency and generic HRQoL were most sizeable. The high discontinuation rate suggests that seizure dogs may not be suitable for all PSRE, and the prevention and consequences of discontinuation require further study.

Chapter 8

General discussion

For a subgroup of persons with epilepsy, available treatments are not effective in fully eliminating seizures. Amongst them are those who have seizures on a regular basis, known as persons with severe refractory epilepsy (PSREs). These individuals face the daily challenge of minimising the risks of frequent unpredictable seizures, while striving for a fulfilling, active life. Seizure dogs have been suggested as an assistive care service for this group. These dogs receive specialised training, focusing on the unique seizure characteristics and care needs of their human companion, with the goal of enhancing safety in everyday activities and offering emotional support. Anecdotal accounts and exploratory studies have indicated that seizure dogs may contribute to improvements in quality of life and seizure frequency outcomes [17,26-28]. Yet, the lack of robust evidence of effectiveness has hindered their inclusion in basic health insurance packages. The EPISODE (EPIlepsy SuppOrt Dog Evaluation) study was initiated with the objective of informing a reimbursement decision in the Netherlands. By conducting a comprehensive assessment of the impacts of seizure dogs, the trial addresses a broader, global knowledge gap concerning the effectiveness of seizure dogs in reducing seizure frequency and improving quality of life. At the same time, it presents a case study in the trend of broadening the application of Health Technology Assessment (HTA) to non-pharmacological interventions.

The primary aim of this thesis was to conduct a thorough assessment of the potential of seizure dogs as an assistive care service for adults with severe refractory epilepsy. This involved examining several aspects, including the burden of illness of adult PSREs and the clinical effectiveness, cost-effectiveness, and broader impacts of seizure dogs. In this concluding Chapter, the overall research findings and their implications for clinical practice and policy are discussed. Additionally, this Chapter provides insights into the challenges of the application of the HTA framework in this dynamic indication-intervention combination and identifies directions for future research.

Main findings

The study protocol of EPISODE, the clinical trial central to this thesis, was outlined in **Chapter 2** . The protocol highlights the complex methodological and logistic considerations inherent to the intervention. Given these complexities, a stepped wedge design was selected, differing from a conventional randomised controlled trial. This approach involves randomly assigning participants to timeslots for receiving a seizure dog, transitioning them gradually from usual care to the intervention, rather than assigning them directly to either one of the study conditions. Alongside clinical criteria, eligibility for participation required a suitable living environment and a reliable support network to ensure proper accommodation for a seizure dog (Table 1 of Chapter 2). The EPISODE study was designed to determine clinical effectiveness in

terms of seizure frequency reduction, during a follow-up period of three years. In addition to monitoring seizure frequency through diaries, quarterly surveys assessed seizure severity, quality of life, health care utilisation, reliance on informal care, and productivity losses. It was anticipated that the effect of the intervention would begin with a delay, which would then increase over time. These details were incorporated into the analysis plan through estimation of a delayed time on intervention effect. The trial commenced on 1 June 2019, with 25 participants.

Building on data from the first year of trial follow-up, **Chapter 3** highlighted an important limitation in using EQ-5D to assess the impacts of severe refractory epilepsy on HRQoL and the influence of seizure dogs in this context. The Chapter revealed that participants typically completed EQ-5D, which inquires about their health status 'today', on days without or with relatively few seizures. This pattern indicates that among those who experience seizures on a non-daily basis, EQ-5D utility scores may predominantly capture the health status during seizure-free days, potentially overlooking the immediate impact of seizures. Consequently, this could lead to an underestimation of the true HRQoL burden associated with severe refractory epilepsy and the potential benefits of interventions targeted at mitigating the seizure burden.

Chapter 4 described an evaluation of the burdens posed by severe refractory epilepsy, focusing on seizure outcomes, quality of life, and societal costs. Insights were drawn from data on the EPISODE trial prior to the anticipated start of the intervention effect, which suggested a considerable burden of illness at both the individual and societal levels. Regular occurrences of seizures, ranging from daily to weekly instances, and a median count of three seizures on a seizure day, characterised the disease severity in the study participants. Participants had an average EQ-5D-5L utility score of 0.682, constituting a 24% decrease in HRQoL compared to the age-adjusted general population in the Netherlands. This impaired quality of life was also observed on the other instruments included in the data collection, reflecting impacts on epilepsy-specific quality of life (QOLIE-31-P) and self-rated quality of life (EQ VAS) that exceeded levels within broader epilepsy populations reported in the literature [155,214,215]. Additionally, the data showed intensive reliance on formal and informal care: participants visited health care providers 49 times a year and received around 25 hours of informal care weekly. The broad impact of the disease is further substantiated by a significant proportion of participants not engaging in paid employment. Those who have paid jobs or volunteering roles reported losing about 4 hours of productivity per week due to health-related reasons. All cost categories combined, average societal costs were almost €40,000 per PSRE per year.

In **Chapter 5** , the effectiveness of seizure dogs for adult PSREs was addressed. The trial revealed a 3.1% reduction in seizure frequency for every 28-days with a seizure

dog. This accumulates to a 33.9% reduction in seizure frequency after one year, which was the median follow-up time with a seizure dog in the EPISODE study. Additionally, participants experienced more seizure-free days and reported better quality of life as measured by EQ-5D-5L, QOLIE-31-P, EQ VAS, and ICECAP-A instruments. Among these, EQ-5D-5L showed the most notable improvements, with an average estimated improvement of 13.6% after one year with the seizure dog. The impacts on the other instruments were smaller, with improvements between one and five percent over the same period. Domain score analyses of the instruments indicated improvements on anxiety and stress (EQ-5D-5L and QOLIE-31-P), stability and achievement (ICECAP-A), and social functioning (ICECAP-A, QOLIE-31-P). While the study did measure seizure severity, no significant change was found in the sum score of the NHS3. Discontinuation prior to the start and across various phases of the seizure dog trajectory led to an overall drop-out rate of 24.0%.

Chapter 6 evaluated the cost-effectiveness of seizure dogs compared to usual care alone for PSREs. The study used a microsimulation model that showed considerable QALY gains for both PSREs and their primary informal caregivers over a 10-year partnership with the seizure dog. The analysis further highlighted that an important share of intervention costs is offset by savings, with approximately half of these savings occurring in the health care sector and the other half resulting from a reduced need for informal care. In the Netherlands, the willingness-to-pay threshold for interventions for PSREs is €50,000 per quality-adjusted life year (QALY), given the disease severity in this population. The intervention's incremental cost-effectiveness ratio (ICER) was estimated at about €2,300 per QALY. This indicates that seizure dogs are a cost-effective addition to usual care, a conclusion that remains consistent across all explored scenarios. This consistency underscores the relative certainty of the claim that total heath benefits of seizure dogs outweigh the associated societal costs.

Chapter 7 explored the experiences of PSREs and their informal caregivers with seizure dog partnership using a qualitative research method. Semi-structured interviews with 17 participants and their informal caregivers revealed the various roles that seizure dogs may take on, acting as a first responder, an emotional support companion, a responsibility, a spotlight drawing public attention, and as a seizure predictor. Participants reported a diverse range of advantages, such as improved emotional well-being, including a sense of security and upliftment, enhanced personal capabilities like more autonomy and the ability to pursue ambitions, improved social functioning, highlighted by greater confidence and better relationships with their informal caregivers, and improved seizure outcomes. The responsibilities of caring for the dog, the impact on one's daily routine, interactions with strangers, and the visibility of epilepsy were seen as advantageous to some, but as challenging to others. Informal caregivers experienced relief knowing the seizure dog is present but

remained vigilant and ready to respond when the seizure dog detects a seizure. The seizure dogs' abilities did not always align with expectations. Overall, seizure dog partnership resulted in mixed experiences, with some participants benefiting greatly and perceiving it as a life-altering intervention, while others emphasised challenges and disappointment from unfulfilled expectations.

Strengths and limitations

The EPISODE study is the first randomised controlled trial in the field of seizure dogs, providing evidence of their clinical effectiveness, cost-effectiveness, and broader outcomes. Employing a stepped wedge design contributing to efficiency, combined with a thorough follow-up, the trial established a strong framework to critically assess the multifaceted potential of seizure dogs, even with a limited number of participants. Alongside the innovative study design and the unconventional intervention under evaluation, the trial is unique in that its scope goes beyond clinical effectiveness alone, by considering various spillovers on others than the PSRE. Furthermore, the nested-qualitative study provided insights from PSREs and informal caregivers that add context and nuance to the quantitative outcomes. The EPISODE study not only is the first effort in providing robust evidence in the field of seizure dogs, but also serves as an exemplary case study of the application of established HTA methodologies to non-pharmacological interventions.

Alongside the innovative study design and the unconventional intervention under evaluation, the trial is unique in that its scope goes beyond clinical effectiveness alone, by considering various spillovers on others than the person with severe refractory epilepsy

A key limitation of the study lies in the limited sample size, resulting in uncertainty about the impact of seizure dogs on some outcomes and prohibiting subgroup analyses. The uncertainty of the impact of seizure dogs on costs, used to inform the cost-effectiveness model, was most profound. A larger sample size could have revealed more distinct effects on these outcomes. Although the delayed onset of the intervention effect, which was not disclosed to participants, may have acted as a form of implicit blinding, the risk of response bias remains, especially due to the reliance on self-reported outcome measures. The study's stepped wedge design also presented challenges in estimating the overall effect of the intervention, given the varying follow-up times that covered a small fraction of the expected duration of the continuously evolving seizure dog partnership. As a result, making assumptions became necessary both for assessing the clinical significance of the observed effects and for estimating cost-effectiveness over the lifespan of the intervention. For instance, the assumptions as to when the intervention starts taking effect, the period over which the effect develops, and how long the effects lasts were made based entirely on expert opinions, without

empirical backing. These factors collectively introduce an element of uncertainty to the quantitative findings. In addition, both the quantitative and qualitative investigations did not follow-up on individuals who discontinued their seizure dog partnership. This omission resulted in an incomplete portrayal of the diverse experiences and outcomes related to the intervention, thereby offering only a partial perspective on its suitability for different PSREs in different contexts.

Finally, the study was conducted without a clear understanding of the mechanisms through which seizure dogs impact outcomes. The observed improvements in stress-related quality of life areas might suggest that seizure dogs help reduce stress, thereby potentially lowering the frequency of stress-precipitated seizures. Insights from the nested qualitative study lend further support to this theory, while also hinting at the potential role of stability and daily routine brought by the dogs presence. Furthermore, the qualitative study highlighted the diverse and context-specific impacts seizure dogs bring about, which appear not uniformly attributable to the trained behaviour. As such, considering the notion that the bond between the seizure dog and their owner strengthens over time, the inclusion of a delayed intervention effect in the study design may not have completely isolated the general impact of having a dog from the estimated effects of having a seizure dog.

Conclusions

Concluding, seizure dogs effectively reduce seizure frequency and improve the quality of life of adult PSREs. Their impact transcends health benefits, enriching various facets of PSREs' well-being, with spillovers to their informal caregivers and society. While the overall results are promising, it is important to note that seizure dogs might not be the right fit for every PSRE, as evidenced by the drop-out rate of the trial and the qualitative findings. Yet, from a societal perspective, seizure dogs offer a cost-effective complement to usual care for adult PSREs in the Netherlands. As such, seizure dogs have shown potential to lower the substantial disease burden of severe refractory epilepsy at both an individual and societal scale. The insights from the qualitative study highlight the underlying complexity of the impacts of seizure dogs on PSREs and their support networks, showing both benefits and challenges that emerge from these partnerships. This underscores the importance of evaluating seizure dog partnerships based on a spectrum of outcomes, not just seizure frequency.

Seizure dogs have shown potential to lower the substantial disease burden of severe refractory epilepsy at both an individual and societal scale

Implications for policy and clinical practice

The findings of the EPISODE study underscore the potential of seizure dogs in the management of severe refractory epilepsy. Their integration into clinical practice largely depends on whether they are covered by health insurance, given the significant costs involved in training and caring for these dogs. In the Dutch health care system, for an intervention to be included in reimbursed care, it must meet the standards of 'established medical science and medical practice' (in Dutch: Stand van de Wetenschap en Praktijk). When assessing this legal criterion, the following question needs to be answered: 'is the additional value desired, relevant, and sufficient/large enough, and is there sufficient confidence that it will actually occur?' [56]. This assessment considers two main aspects: the clinical relevance of the intervention and the strength of the evidence supporting the health benefits. Alongside these aspects, medical arguments related to the intervention or condition under evaluation may be considered.

Clinical relevance

Evaluating clinical relevance often involves comparing observed effects to a clinical relevance threshold, typically known as the minimal clinically important difference (MCID). Although the EPISODE study did not predefine an MCID, studies about the effectiveness of epilepsy treatments generally consider a reduction of 50% or more in seizure frequency as meaningful [216-219]. The EPISODE study's distinctive design makes direct comparisons to such benchmarks complex, as follow-up time with the intervention vary widely (i.e., from three months to two years). Nevertheless, about one-third of participants who completed the study achieved this level of improvement by the end of the follow-up. Furthermore, in a conservative scenario where the full potential of seizure dogs is realised after one year, the estimated cumulative average reduction in seizure frequency of 34% seems comparable with other interventions for this population which are part of usual care, like some anti-seizure medications and neurostimulation options, but potentially with fewer negative side effects [169,170].

Beyond the primary outcome, the study's exploration of secondary outcomes broadens the understanding of the clinical relevance of seizure dogs. While the primary focus on seizure frequency is justified by its central role in epilepsy treatment and its objective measurability, the participants' narratives revealed PSREs might seek other health-related benefits from seizure dogs such as improvements in their mental health. This makes it important to factor in secondary outcomes in the appraisal of seizure dogs' clinical relevance. For HRQoL, measured with EQ-5D-5L, even under conservative assumptions, the study meets the literature-reported MCID benchmarks reported in the literature, indicating clinical relevance for PSREs [220]. However, analyses in Chapter 3 suggested that EQ-5D-5L may not fully capture the impact of changes in episodic conditions like epilepsy, in particular among those who have seizures on a less than

daily basis, as measurements then primarily reflect health status on relatively good days in terms of episodes of symptoms (i.e., seizure-free days) rather than average health status. Therefore, the effect of seizure dogs on HRQoL through changes in seizure frequency is potentially underestimated.

As for the other quality of life measures, MCIDs have not been defined. Yet, the smaller effect sizes suggest that changes in these outcomes are less likely to be clinically relevant. Interestingly, ICECAP-A, which measures capability well-being, showed only minor changes after partnership with a seizure dog. This finding contrasts with the accounts of PSREs, whose anticipated and perceived benefits were centred in this area of their lives. This could indicate that the follow-up period of the trial (with a median of one year with the intervention) was insufficient for capturing the well-being benefits of adapting to a new health status. PSREs have often adapted their lifestyles, expectations, and behaviours to manage their condition. The introduction of a seizure dog creates a new situation, requiring changes in self-perception and modification of these long-standing coping strategies, as reflected in the narratives. Over time, as trust in the seizure dog grows and seizure frequency reduces, PSREs might begin to perceive a reduction in barriers to daily activities and improved well-being. This gradual process may explain why the improvements in health status, as reflected in improvements on HRQoL and seizure frequency outcomes, do not immediately translate into proportional gains in broader well-being. Yet, more research in this area is needed.

The introduction of a seizure dog creates a new situation, requiring changes in self-perception and modification of long-standing coping strategies

Appropriateness of evidence

The second aspect of the "established medical science and medical practice" criterion, next to clinical relevance, involves the evaluation of the robustness of the evidence. As discussed above, the study has several limitations which increase uncertainty. However, despite these limitations, it is noteworthy that the trial's outcomes consistently confirm the benefits of seizure dogs across various measures. Furthermore, scenario analyses testing the impact of varying assumptions, uniformly reinforce the conclusion that seizure dogs are both effective and cost-effective in adult PSREs. This underscores the reliability and significance of the findings despite the inherent uncertainties. Nevertheless, the trial's substantial dropout rate of 24% points to the considerable uncertainty regarding the suitability of seizure dogs at an individual level.

As the first study of its kind to achieve a Class III evidence rating according to the standards of Neurology for therapeutic studies [221], the EPISODE study sets a

high standard for research in this area. With a self-reported primary outcome, and the nature of the intervention precluding blinding, this also represents the best achievable evidence level for the indication-intervention combination. Although this is the only randomised study on seizure dogs, its conclusions are supported by external sources such as anecdotal evidence and exploratory research, which suggest similar benefits [17-19,27-29]. These factors can be weighted when determining what can serve as 'appropriate evidence' in view of the particular reimbursement question concerned [56].

Although EPISODE is the only randomised study on seizure dogs, its conclusions are supported by external sources such as anecdotal evidence and exploratory research

Broader considerations

Two other arguments that may receive consideration in determining whether an intervention adheres to the "established medical science and medical practice" criterion are the severity of the disease and the availability of treatment alternatives for the targeted population [56], which reflect the urgency of expanding the current clinical pathway. The burden of illness study highlighted the substantial toll of this condition. Affected individuals endure frequent, unpredictable seizures that severely diminish their HRQoL and overall well-being. The qualitative study further emphasised the extensive impacts on various facets of their daily lives. Furthermore, the influence of this disorder is not limited to the individuals with PSRE: it has considerable spillovers on informal caregivers and society. Adding to this, the patient population targeted for the provision of seizure dogs consists of individuals who have consistently shown insufficient response to conventional treatments. These PSREs, having navigated the clinical pathway for several years, continue to face challenges due to the inadequacy of existing medical solutions. As such, there exists a severely affected population with a persistent gap in care needs, which seizure dogs have the potential to mitigate effectively.

While the criterion of "established medical science and medical practice" is the sole legal requirement for inclusion in the basic health insurance package in the Netherlands, additional criteria may be used to assess whether an intervention belongs in the basic health insurance package. One such criterion is cost-effectiveness, an increasingly important element in these decisions [58,222]. The EPISODE study demonstrates that seizure dogs present a cost-effective addition to usual care for PSREs. Notably, while initial costs are significant, they are largely offset by savings in health care costs and informal care. The costs that remain are proportionate to the health benefits produced by the intervention, in terms of QALY gains in both PSREs and informal caregivers. Another aspect of interest is assessing the financial consequences of reimbursement for the health care budget. Inclusion of seizure dogs into the basic health insurance

package is expected to result in additional costs for the health care system, as roughly half of the cost savings fall outside this sector. Nonetheless, given the limited size of the eligible population and the likelihood that not all suitable candidates will choose this intervention, the overall budgetary impact is expected to be modest.

Finally, the qualitative study revealed the emphasis placed by PSREs and their informal caregivers on non-health-related benefits from seizure dogs, like improvements in autonomy and other aspects related to their broader well-being. Although the improvements in overall well-being found in the trial were less pronounced than anticipated, the observed enhancements in specific domains of well-being such as social functioning and stability are noteworthy and were reaffirmed in the qualitative study. While it remains debatable if investments in well-being gains should be sourced from health care budgets, the finding that seizure dogs yield benefits also beyond health introduces a compelling normative argument to be considered in the appraisal of this intervention and reimbursement decision-making. Finally, the studies in this thesis showed that both the burden of severe refractory epilepsy and the benefits of seizure dogs' spillover to informal caregivers, highlighting the dual potential benefit of this intervention.

From potential to practice

The ball is now in the court of neurologists, patient organisations, and insurers to carefully assess the outcomes presented. The findings described in this thesis illustrated the multifaceted potential of seizure dogs in managing severe refractory epilepsy, providing these stakeholders with the tools to balance the considerations of clinical effectiveness, cost-effectiveness, and broader impacts, but also the limitations of the intervention. Given the complexity and novelty of this intervention, these key stakeholders may hold different views regarding the desirability of incorporating seizure dogs into clinical practice and health insurance schemes. In that case, the role of the National Health Care Institute (Zorginstituut Nederland) may become crucial, potentially stepping in to provide guidance when consensus is not reached.

A case study of broadening the horizon of HTA

The EPISODE study also represents a unique effort in applying established methods of HTA to a dynamic and personalised intervention. Despite the unique nature of the intervention and the small, heterogeneous target population, the study attempted to adhere to conventional methods and standards for effectiveness research and economic evaluations. This approach positions the trial as an exemplary case study of expanding the application of HTA beyond pharmacological interventions. Nevertheless, several challenges and key considerations emerged that underscore the need for an

adaptive and context-sensitive approach in HTA when expanding its application to a broader range of health care services. These include the challenges in selecting an appropriate study design, capturing multifaceted outcomes, and establishing funding.

Challenge 1: Settling for a non-traditional study design

The EPISODE study required adaptations from the traditional double-blinded randomised controlled trial design, the gold standard for evaluating health technologies. The nature of the intervention, involving live animals with epilepsy- and partnership-specific training, made blinding impossible. The characteristics of the intervention necessitated a stepped wedge design to address logistic and ethical concerns, as described in the study's protocol. Also, the need for personalised matches between PSREs and dogs and the varying training time needed for each pair demanded flexibility in the trial's implementation. Additionally, the severity of the disease precluded restricting PSREs from adjusting their treatments during the trial. These intervention and population characteristics not only limited the achievable sample size but also restricted the possibility of a highly controlled setting, which is generally preferred in clinical trials. This situation underscores the importance of balancing the burden of proof and the required level of evidence against what is achievable and appropriate for the indication-intervention combination under evaluation.

The intervention and population characteristics not only limited the achievable sample size but also restricted the possibility of a highly controlled setting, which is generally preferred in clinical trials

Challenge 2: Capturing multifaceted outcomes

Pharmacological interventions often involve standardised products targeting a known mechanism of action, which facilitates the selection of an objective, quantifiable clinical primary outcome measure. However, the impacts of assistive care services like seizure dogs are generally less predictable and direct, complicating the a-priori selection of a single primary outcome measure for the purpose of conducting sample size calculations, determining clinical relevance, and designing cost-effectiveness models. Furthermore, non-pharmacological interventions sometimes aim to achieve broader benefits beyond immediate health outcomes, which standard outcome measures used in HTA may not fully capture. For instance, rather than focusing on health outcomes, PSREs and their informal caregivers sought relief from seizure dogs in terms of enhancing patient independence and societal participation, and to ease the practical and emotional burdens of informal caregivers. Alongside the wide reach of seizure dogs' benefits, the intervention brings disadvantages that extend beyond the health domain as well. Seizure dogs were described to demand considerable effort

from PSREs and their support network in terms of training and care responsibilities, adaptations to daily routines, and the necessity for back-up support for the dog's care. For a nuanced understanding of the impact of the intervention, these elements should also be considered in the evaluation. As exemplified in this thesis, integrating qualitative research into HTA may help provide deeper insights into the full extent of an intervention's impacts. The diverse outcomes of services like seizure dogs call for societal dialogue about the range of benefits that should be considered in the context of reimbursement decisions from the health care budget, and consequently should be considered within HTA.

The diverse outcomes of seizure dogs call for societal dialogue about the range of benefits that should be considered in the context of reimbursement decisions

Challenge 3: Establishing funding for conducting clinical trials and HTA

The EPISODE study is an encouraging example of HTA for non-traditional interventions, made possible by exceptional funding support from the Dutch Ministry of Health, Welfare, and Sport. For pharmacological products, rigorous marketing authorization processes and proprietary rights provide motivation and financial incentives and possibilities for evidence generation [63]. However, for assistive care services such as seizure dogs, these elements generally are absent, hindering the conduct of robust clinical trials, which poses a significant challenge in extending HTA to these types of interventions.

For a transparent and consistent evaluation process, a clear framework is necessary to specify the expected level of evidence and the scope of benefits to be measured and considered. In addition, identifying who bears the responsibility for funding and executing the research needed to generate this evidence is crucial for equitable application of HTA in health care decision-making.

Avenues for further research

There were several interesting issues that fell beyond the scope of this thesis. Constrained by its limited sample size, the EPISODE study did not facilitate the conduct of subgroup analyses. Nevertheless, the observed heterogeneity in study outcomes indicates that investigating subgroups could yield valuable insights into differential costs and effects from the intervention for different PSREs in different contexts. Several potential subgroups warrant such exploration. For instance, a subgroup analysis based on the classification of seizures carries significance not only in estimating their varying impact on quality of life but also in delineating which response tasks can be effectively

trained for whom. The reported variability in training effectiveness for certain response behaviours suggests that seizure dogs may struggle to recognise seizures without clear motor symptoms or those that occur irregularly. Furthermore, the necessity for immediate action in response to a seizure, such as notifying informal caregivers, may be less pressing for certain seizure types where the associated risks are minimal. This raises the possibility that individuals who endure more severe seizures, or experience them at a higher frequency, may derive greater benefit from the assistance of a seizure dog. Moreover, variations in outcomes might be influenced by factors such as when seizures occur (day or night) and the PSREs' living situation (independent or with their informal caregiver(s)). Closer examination of these elements in future studies could assist in more precisely targeting the intervention to those who stand to benefit the most.

In addition, seizure dogs can assist in two distinct ways, providing a warning prior to seizures (alerting behaviour) or assisting during and after a seizure (response behaviour). The EPISODE study primarily centred on response behaviour since the assistance dog organisations did not formally train alerting behaviour. Nevertheless, it is worth noting that about one-third of interviewed participants reported observing alerting behaviour in their seizure dog. The potential to predict seizures holds significant promise for PSREs as it can offer them time to prepare or seek assistance, potentially reducing the risks associated with seizures. Consequently, this group of participants may have derived benefits from both types of behaviour exhibited by their seizure dogs. As a result, any potential advantages stemming from this dual behaviour role might be reflected in the study's findings. While accounting for alerting behaviour and its effects is not undesirable, as this behaviour mirrors real-world situations, it would be intriguing to investigate how the benefits differ between those who have a seizure dog performing solely response behaviour, and those who have a seizure dog exhibiting alerting behaviour as well. In addition to conducting a subgroup analysis on this matter, delving further into alerting behaviour, its underlying mechanisms, and the dog or PSRE characteristics linked to this behaviour could enhance the understanding of its trainability and aid in identifying PSREs who are most likely to derive benefits from it. However, until sufficient knowledge is gained about the reliability and trainability of alerting behaviour (for subgroups of PSREs), it is imperative to transparently communicate to PSREs contemplating a seizure dog partnership that this behaviour cannot be assured and should not be the primary objective when pursuing the intervention.

Another avenue for further research arises from the trial's follow-up time. The median follow-up period with the seizure dog of one year is considerably shorter than the expected lifespan of the intervention. This limited timeframe is particularly relevant given the hypothesis that the effects of seizure dogs develop gradually as the bond

between the PSRE and the seizure dog strengthens over time, and as the seizure dog's trained behaviour is consistently reinforced, potentially improved, and even expanded. However, the study, constrained by its sample size and a varying follow-up time with the seizure dog, was not equipped to discover when the full potential of the intervention is realised, including whether a seizure dog has the potential to impact mortality. This limitation introduces a degree of uncertainty regarding the whole extent of the intervention's impact and, hence, its cost-effectiveness. To gain a more comprehensive understanding of the long-term effects of seizure dogs, further research focusing on extended follow-up periods is essential. Such research should ideally span beyond the duration of the seizure dog partnership to consider the impacts following its discontinuation or transition to a new partnership.

Lastly, the qualitative study underscored the diverse mechanisms by which seizure dogs impact the lives of PSREs and their informal caregivers. This encompasses a blend of trained and natural behaviours, as well as characteristics specific to owning an assistance dog and those associated with dog ownership in general. Future research should focus on comparing the benefits and challenges provided by seizure dogs to those of untrained companion dogs to better understand the distinct potential of each in supporting individuals with seizures.

Final remarks

The aim of this thesis was to conduct a thorough assessment of the potential of seizure dogs as an assistive care service for adult PSREs, exploring their clinical, economic, and broader impacts. Based on the findings, this thesis concludes that seizure dogs reduce seizure frequency and improve the quality of life of adult PSREs, offering a cost-effective complement to usual care by relieving the condition's significant burden at the level of the PSRE, their support network, and society. Looking forward, these findings highlight the need for decision-makers in policy and clinical practice to consider integrating seizure dogs into usual care and reimbursement schemes, while acknowledging the intervention comes with variable outcomes and presents challenges at the individual level, and hence, may not be the solution for all PSREs.

Appendices

List of abbreviations

ASM	Anti-Seizure Medication
CE	Cost-Effectiveness
CI	Confidence Interval
DBS	Deep Brain Stimulation
EEG	ElectroEncephaloGram
EPISODE study	EPIlepsy SuppOrt Dog Evaluation study
GEE	Generalised Estimating Equations
GLMM	Generalised Linear Mixed Models
GLS	Generalised Least Squares
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICECAP-A	ICEpop CAPability measure for Adults
ICER	Incremental Cost-Effectiveness Ratio
ILAE	International League Against Epilepsy
iMCQ	iMTA Medical Consumption Questionnaire
iMTA	institute for Medical Technology Assessment
iPCQ	iMTA Productivity Costs Questionnaire
IQR	Interquartile Range
iVICQ	iMTA Valuation of Informal Care Questionnaire
IRR	Incidence Rate Ratio
MAE	Mean Absolute Error
MCID	Minimal Clinically Important Difference
NHS3	National Hospital Seizure Severity Scale
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PSRE	Person with Severe Refractory Epilepsy
Q	Quartile
QALY	Quality-Adjusted Life Year
QOLIE-31-P	Patient-Weighted Quality of Life in Epilepsy Inventory-31
RCT	Randomised Controlled Trial
RMSE	Root-Mean-Square Error
SD	Standard Deviation
Std. Error	Standard Error
SUDEP	Sudden Unexpected Death in Epilepsy
VNS	Vagus Nerve Stimulation
ZIN	Zorginstituut Nederland (in English: the National Health Care Institute)

Supplemental content

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Figure S4.3 Estimated effect plotted over one year, comparison between usual care and intervention arm using mean score at baseline as a reference

Table S4.1 Model specifications

Chapter 6

Supplement 5. Supplemental Tables to Chapter 3

Chapter 2

Supplement 1. Training programs of participating assistance dog organisations

Figure S1.1 Training program of pre-trained dog trajectory

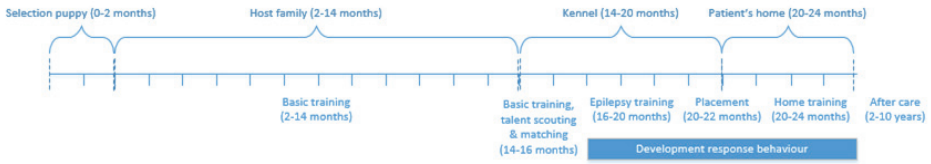
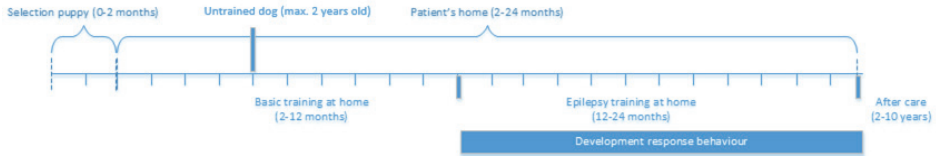


Figure S1.2. Training program of team coaching trajectory



Supplement 2 Statistical Analysis Plan for the (Cost)-Effectiveness Analyses for the EPISODE trial (version May 22 nd 2019)

1. Purpose

The purpose of this statistical analysis plan is to provide the details of the statistical analyses that are planned for the data on clinical effectiveness, cost-effectiveness, and broader outcomes (e.g. well-being, participation and informal caregiver burden) of the EPISODE trial evaluating seizure dogs.

2. Study design

The EPISODE study is a 3-year stepped wedge randomised controlled trial [223,224] that compares the use of seizure dogs with the usual care for adults with severe refractory epilepsy. In this study, seizure dogs will be introduced sequentially to participants over time in which the order is chosen at random. In other words, participants will progressively move from the control group to the intervention group at random time points. At the end of the trial all participants have received a seizure dog. This staged implementation is inevitable, because simultaneous rollout of trained dogs to all participants is impossible for logistical reasons (i.e. the time and capacity needed

to train seizure dogs). The schedule of the staged implementation is designed in such a way that, in line with the Effective Practice and Organisation of Care (EPOC) guidelines on what study designs to include in a systematic review [106], at least three measurements before and three measurements after the intervention will be planned for each participant.

Due to the difference in training protocols, participants will be randomised within their training stratum (i.e. team coaching trajectory or pre-trained dog trajectory), meaning that randomisation is stratified according to training cluster and that there are effectively two randomisation procedures. To determine the order in which participants receive the intervention (i.e. the seizure dog) within their stratum, each participant gets assigned a random number between 0 and 1. The participant with the smallest number will be the first one to receive the intervention within the stratum, the participant with the highest number will be the last one.

To evaluate the effectiveness and cost-effectiveness of seizure dogs, all outcome measures (summarised in the next section) are taken at multiple time points both before and after the random allocation to the intervention. This implies that we have for each participant a time series of measurements for each of the outcomes of interest. This time series of measurements will be used to establish an underlying trend, which is 'interrupted' by the intervention at a known (and randomly assigned) point in time [225]. In this way, we may detect whether the intervention has had an effect significantly greater than any underlying trend over time [226].

3. Study endpoints

3.1 Primary outcome measure

Seizure frequency over 28 days

Seizures are recorded daily using a paper seizure diary for 36 months. A smartphone application will be used to remind participants to fill in their seizure diary. In order to monitor non-response and to limit retrospective entry of seizures, the application will routinely ask participants to photograph their seizure diary. Non-response will be actioned upon when observed by the daily study coordinator. Participants will be asked to record all epileptic seizure types. While participants will be asked to record psychogenic non-epileptic seizures as well, these will be excluded from the main analysis given their non-epileptic nature.

3.2 Secondary outcome measures

- Seizure severity: seizure diary and NHS3 [99]
- Generic health-related Quality of Life: EQ-5D-5L [101]
- Disease-specific health-related Quality of Life: QOLIE-31-P [100]
- Well-being: ICECAP-A [102]
- Utilisation of health care in events (ED visits, ambulance calls, hospitalizations, inpatient days): iMCQ [103]
- Total health care costs (including informal care): iMCQ [103]
- Productivity losses: iPCQ [104]
- Social participation: covering the domains social contact, daily activities and leisure activities (patient and primary informal caregiver)
- Informal caregiver burden: iVICQ [105]

The secondary outcome measures are collected every three months using a set of questionnaires. The timing of the three-monthly questionnaire is calculated from the start of the study (t=0), and will be reset after transitioning from control to intervention. These questionnaires will be administered on paper.

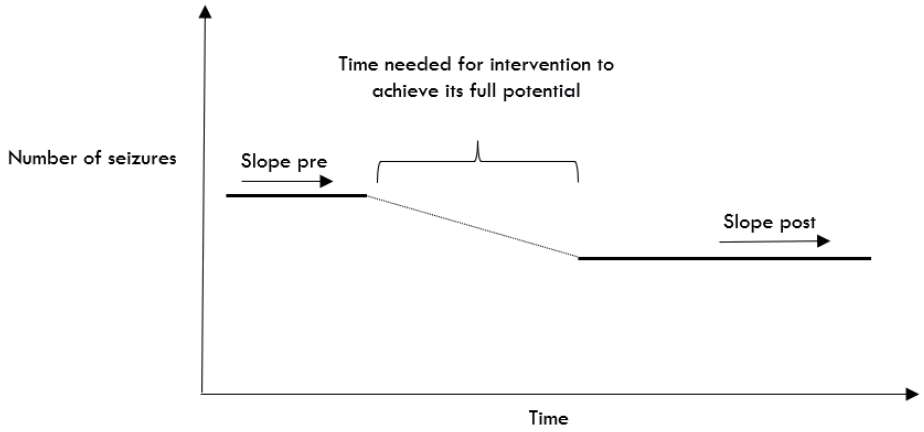
4. (Clinical) assumptions underlying the analysis plan

4.1 Primary outcome measure

Seizure frequency is expected to be affected by the introduction of a seizure dog. People with severe refractory epilepsy may experience less anxiety due to the companionship of a seizure dog, even when the dog is only responding to seizures. A decrease in seizure worry may reduce stress, which is known as an important trigger for seizures. Reducing stress may be a result of the response function of the seizure dog and may cause a decreased seizure frequency. Moreover, the activation of an alarm button by the dog can inform family members or neighbours quickly, resulting in administering the emergency medication on time. Timely medication might reduce seizure frequency due to a decreased likelihood of sequential seizures [227].

Although it might take some time before the dog has learned how to accurately respond to a seizure, we expect a decrease in seizure frequency shortly after the dog starts epilepsy training (at home), in line with the study by Strong et al. [26]. Since there is no evidence of any secular trend (i.e. the number of seizures does not decrease with time), or any cyclical or seasonal effects (i.e. there is no cyclical pattern in the number of seizures that occur over time), a slope change leading to a level change in the number of seizures is expected. The slope is assumed to continue until the intervention has reached its full potential (which depends on the time needed for the dog to improve its sensitivity to seizures), after which we expect to observe a plateau (Figure 1).

Figure S2.1 Expected effect of the intervention over time



4.2 Secondary outcome measures

Besides the effect of seizure dogs on seizure frequency, an effect may be observed on seizure severity. Seizure severity consists of several domains including secondary damage (e.g. cuts, burns or fractures) and the time to recovery, and both may be influenced by the presence of a seizure dog. To elaborate, the dog can get help when the PSRE has lost consciousness, the dog may block the PSRE from putting him/herself in danger during impaired consciousness, and the seizure dog's presence might reduce stress and anxiety during or immediately after the seizure. As such, the seizure dog may have an impact on other outcomes measures as well, such as well-being (e.g. because dogs provide greater independence), health-related quality of life (e.g. due to a reduction of problems with performing usual activities or less feelings of anxiety/depression), productivity losses and social participation. Furthermore, seizure dogs may reduce health care resource use, because they could help prevent prolonged hospital stays due to a reduction of secondary damage, such as sequential seizures, or simply because unnecessary ambulance arrivals are avoided. In addition to the effect of seizure dogs on their human companion, there might be an impact on their informal caregivers, i.e. PSREs may need less help of family members and friends and, therefore, the burden on their informal caregivers may be reduced.

For the secondary outcomes the effect is expected to follow a similar pattern to the effect on seizure frequency. Therefore, outcomes are assumed to be affected shortly after the dog starts epilepsy training (at home) and a temporary slope is expected to appear. Although the causal pathway is unknown, some outcomes may show a

delayed intervention effect, for example informal caregiver burden and participation. These outcomes might not improve immediately, but only after the decreased seizure frequency has been stable for a while. This will be tested in the exploratory analyses.

5. Data analysis

5.1 Effectiveness analysis

The effectiveness of seizure dogs will be measured in terms of a change in seizure frequency. Data will be described using summary statistics and scatter plots of the time series in order to identify any underlying trends of seizure frequency, seasonal patterns and outliers [96]. A simple before-and-after comparison will be conducted by calculating per person the average of the measurements before the seizure dog's epilepsy training starts, during the seizure dog's epilepsy training at home and after the training of the seizure dog is completed. It will be reported how often the seizure dog responded to seizures, and how often they detected an oncoming seizure.

5.1.1 Main analysis on primary and secondary endpoints

Generalised linear mixed models (GLMM) or generalised estimated equations (GEE) are deemed as appropriate statistical methods to analyse data from stepped wedge studies [96,97]. The models specified by Hussey and Hughes include time as a fixed effect for each step [97]. Thus, for example, for continuous (and normally distributed) outcomes, a model with random effect for cluster and fixed effect for each step (time) is suggested. Note that in the case of the EPISODE study, the size of the cluster is 1 PSRE. Likewise, for binary outcomes a logistic regression model is recommended and for count outcomes a Poisson regression model is appropriate.

Primary endpoint

The primary endpoint involves count data (number of seizures over 28 days ranging from 0 to n) and since seizure frequency is not normally distributed, a GLMM Poisson model with a logarithmic link will be used. The main model will include a term for the time on intervention , to allow for a gradual increase in the intervention effect over time.

A decrease in seizure frequency is expected shortly after the dog starts epilepsy training. Therefore, in the team coaching trajectory, the time on intervention is defined from the start of the epilepsy training, which commences 12 months after basic training. In the pre-trained dog trajectory, the epilepsy training commences 14 months after basic training while the dog is still in the kennel. During this 8-month long epilepsy specific training, the seizure dog is placed at the home of a PSRE. The assistance dog trainers have experienced that the dog and person with severe refractory epilepsy first experience a period of acclimatization during which they bond and the dog needs

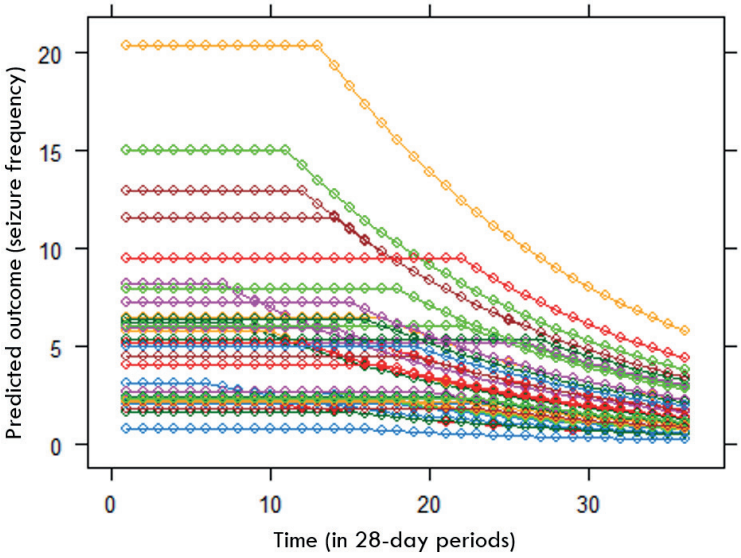
to get comfortable with the new environment. Therefore they expect that outcomes start improving slightly later due to the disruption in the living environment of the dog: six months after the dog starts living at the home of the PSRE. In the team coaching trajectory this acclimatization phase took place during the first year of basic training with the dog. Hence, in the main analysis time on intervention is defined from the start of the epilepsy training in the team coaching trajectory, and 6 months after the dog has been placed in the home of the PSRE in the pre-trained dog trajectory. Figure S2.2 shows how predictions from the main model may look like.

Secondary endpoints

For the secondary endpoints, different distributions for the outcomes are applicable. The model structure described for the primary outcome will be used for the secondary outcomes (listed under point 3) as well, but the assumptions concerning the distribution of the data will be amended. The type of model (Normal, Binomial, Poisson) will be determined by the type of data for each outcome (continuous outcomes should use Normal, binary outcomes Binomial and count outcomes Poisson).

Conclusions will be drawn from this main analysis on primary and secondary endpoints. The analyses described below are exploratory.

Figure S2.2 Simulation of predictions for the main model



This Figure shows how predictions from the main model may look like, using one simulated dataset from the sample size calculation. The y-axis shows the predicted number of seizures over 28 days, and the x-axis shows time in months. The number of seizures at time zero varies across patients, as illustrated by the random intercepts. The number of seizures decreases when time on intervention is no longer zero.

5.1.2 Exploratory analyses

In the exploratory analyses, alternative assumptions will be explored. The exploratory analyses will be performed on both the primary and the secondary endpoints (where applicable).

Assumptions with respect to the timing of the expected improvement in seizure frequency

- The timing of the expected improvement in seizure frequency will be changed. The parameter 'time on intervention ' will be defined from the start of the epilepsy training (in the team coaching trajectory) and from 6 months after the home placement (in the pre-trained dog trajectory) in line with the main analysis:
- plus two months (2/12 epilepsy training in the team coaching trajectory; home placement +6 +2 months in the pre-trained dog trajectory);
- plus four months (4/12 epilepsy training in the team coaching trajectory; home placement +6 +4 months in the pre-trained dog trajectory);
- plus six months (6/12 epilepsy training in the team coaching trajectory; home placement +6 +6 months in the pre-trained dog trajectory).
- The timing of the expected improvement in seizure frequency will be changed in the pre-trained dog trajectory only, and this parameter will be defined from:
  - home placement;
  - home placement +2 months;
  - home placement +4 months.

Assumptions with respect to a main effect besides the effect of time on intervention

- A parameter for having a dog in epilepsy training will be added to the main model, to explore whether a main effect is observed in addition to the effect of time on intervention;
- A parameter for having a trained dog will be added to the main model, to explore whether a main effect is observed in addition to the effect of time on intervention . A trained / certified dog is defined as a dog that has successfully completed the assistance dog exam;
- A parameter for having a dog in basic training (i.e. time on intervention[basic training]) will be added to the main model, to explore whether having a dog has an effect even before the dog has learned epilepsy-specific tasks. This parameter will be estimated on data from patients in the team coaching trajectory only, as they receive a pup that will learn basic tasks in the first year. Dogs of patients in the pre-trained dog trajectory stay in a kennel during the first year, so these dogs cannot have any impact on any of the outcomes specified.

Assumptions regarding the type of seizures that an epilepsy dog can react on

- The dependent variable in the main model will be changed such that it excludes absence seizures and myoclonic jerks;
- The dependent variable in the main model will be changed such that it only includes the worst seizure type in each patient as defined by the baseline NHS3 scores;
- The dependent variable in the main model will be changed such that it includes psychogenic non-epileptic seizures;

Besides testing those assumptions, the following alternative (exploratory) analyses will be run:

- The main model will be rerun after transforming seizure count to seizure-free days;
- The main model will be rerun after changing the parameter 'time on intervention ' from 0 = not on treatment, 1 = on treatment to fractions between 0 and 1 representing the phase of epilepsy training. E.g. after two months epilepsy training, a patient in the pre-trained dog trajectory training cluster is assigned a time on intervention fraction of 0.50 (2 out of 4 months completed), whereas a patient in the team coaching trajectory training cluster is assigned a fraction of 0.17 after two months in epilepsy training (2 out of 12 months completed). This analysis allows for two different slopes, as well as for two different starting points for the time on intervention;
- Hybrid measurements (i.e. including only those measurements where the dog is not in epilepsy training) will be disregarded and a model will be run including a main effect for having a trained dog only.

5.1.3 Missing and invalid data

An advantage of mixed models, including GLMM, is that they can be used in combination with unbalanced data. Unbalanced data means that the number of measurements and measurement times may vary across patients. Since GLMM can be used in combination with unbalanced data, all participants can be included in the analyses, even if they have missing values or when they left the study prematurely. When it can be assumed that any missing data were missing at random or missing completely at random (i.e. not related to either control or intervention), unbiased results will be produced. In the presence of severe missing data, general approaches to this problem (e.g. multiple imputation) will be considered.

This study might also suffer from incorrect data, due to, for example, incorrect data entry (by patients or one of the researchers). In order to evaluate the possible impact

of incorrect data, standard statistical techniques will be used to detect potential outliers. In case, it is suspected that the model results will be affected by the presence of outliers, the main model will be run without outliers.

5.2 Cost-effectiveness analysis

The cost-effectiveness analysis will follow the Dutch guidelines for economic evaluations in health care [60]. The main outcome of the analysis are the incremental costs per quality-adjusted life-year gained, expressed as the incremental cost-effectiveness ratio. The Dutch tariff will be used to calculate utilities from EQ-5D-5L scores [127].

In line with the Dutch guidelines for economic evaluations in health care, the cost-effectiveness analysis will adopt a societal perspective [60]. The analysis will take into account all significant health outcomes and costs that result from seizure dogs, regardless of who experiences the outcomes or costs. This means all costs within the health care sector are included as well as patient and family costs (i.e. time costs of informal caregivers and travel costs) and costs in other sectors (i.e. productivity cost). The intervention costs include the costs of the training program of the dog and lifetime costs for maintaining the dog. The Dutch costing manual will be used to derive unit costs where possible [110].

The working life of a seizure dog is approximately eight years (calculated from certification). Lifetime costs and effects will be estimated, assuming that the seizure dog will be replaced at the time they 'retire'. In scenario analyses, the cost-effectiveness of seizure dogs using a lifetime time horizon will be explored, without taking into account that the dogs will be replaced when they 'retire'. Furthermore, the cost-effectiveness of seizure dogs will be explored using a 8-year time horizon, in line with the working life of one dog.

The discount rates will be set at 4.0% for costs and 1.5% for effects as recommended by the Dutch health economic guidelines [60].

6. Implementation

All analyses will be led by Isaac Corro Ramos, statistician working at iMTA. He gave his consent on this analysis plan.

Chapter 3

Supplement 3. Supplemental Tables to Chapter 3

Table S3.1 Distribution of HRQoL observations relative to the indicated date

Day relative to the indicated date	Number of HRQoL observations recorded (n=111)
-5	1
-4	1
-3	1
-2	5
-1	5
Indicated date	11
+1	13
+2	12
+3	8
+4	15
+5	6
+6	4
+7	3
+8	6
+9	4
+10	2
≥11	14

Keys: n = number of observations, HRQoL = health-related quality of life

Table S3.2 Average seizure count on day of HRQoL observation relative to the average seizure count over the preceding period, after removing two outlier participants[1]

Seizure count	Overall (Wave 1 t/m Wave 4, *n* = 81)		Wave 1 (t = 3, *n* = 21)		Wave 2 (t = 6, *n* = 20)		Wave 3 (t = 9, *n* = 21)		Wave 4 (t = 12, *n* = 19)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
On day of reporting HRQoL	1.99 (3.01)	0.00 (0.00 -3.00)	1.90 (3.08)	1.00 (0.00 -3.00)	2.15 (3.45)	0.00 (0.00 -3.50)	1.81 (2.84)	0.00 (0.00 -3.00)	2.10 (3.20)	1.00 (0.00 -3.00)
Preceding 7 days	2.45 (3.10)	0.86 (0.29 – 3.71)	2.98 (3.66)	0.71 (0.29 -5.23)	2.37 (2.90)	1.00 (0.29 -4.21)	2.14 (2.91)	0.71 (0.29 -2.43)	2.31 (2.98)	1.00 (0.29 -4.00)
Preceding 14 days	2.46 (3.03)	0.93 (0.36 – 4.29)	2.54 (3.21)	1.07 (0.36 -4.71)	2.35 (2.89)	0.70 (0.46 -4.36)	2.49 (3.15)	1.00 (0.29 -3.86)	2.46 (3.08)	0.86 (0.29 -4.00)
Preceding 28 days	2.47 (2.99)	0.86 (0.43 – 3.93)	2.49 (3.14)	1.07 (0.36 -3.39)	2.35 (2.86)	0.77 (0.45 -4.16)	2.65 (3.12)	1.00 (0.39 -4.68)	2.38 (3.06)	0.82 (0.81 – 3.93)

1 outlier participants are participants that experience more than 10 seizures per day on average. The baseline HRQoL observations (Wave 0, t = 0, *n* = 21) are not included in the descriptive statistics as no preceding seizure count data were available for this measurement.
Keys: HRQoL = Health-Related Quality of Life, SD = standard deviation, n = number of observations, IQR = interquartile range

Table S3.3 Models for predicting EQ-5D utility scores based on seizure count quartiles[1]

	Model 1: GLS random effects. Outcome = utility	Model 2: Tobit random effects, right-censored at 1. Outcome = utility	Model 3: GEE (gamma family, log link) Outcome = 1-utility
Parameter estimate (SD)			
Seizure count Q2 (> 0 < 2)	-0.11† (0.05)	-0.13† (0.06)	1.48‡ (0.21)
Seizure count Q3 (>= 2 <= 5)	-0.16‡ (0.06)	-0.17§ (0.05)	1.60‡ (0.29)
Seizure count Q4 (> 5)	-0.17§ (0.05)	-0.19‡ (0.07)	1.72§ (0.25)
Constant	0.77§ (0.04)	0.80§ (0.05)	-1.49§ (0.04)
Predictive performance			
Predicted mean (observed: 0.69)	0.68	0.70	0.69
Predicted minimum (observed: -0.15)	0.60	0.62	0.61
Predicted maximum (observed: 1)	0.77	0.80	0.78
Predicted median (observed: 0.774)	0.66	0.67	0.67
RMSE	0.239	0.239	0.241
MAE	0.187	0.184	0.186

1 Reference category is seizure count Q1 (0 seizures).
Keys: GLS = generalised least squares, GEE = generalised estimating equations, SD = standard deviation, Q = quartile, MAE = mean absolute error, RMSE = root-mean square error
† $p < 0.05$
‡ $p < 0.01$
§ $p < 0.001$

Table S3.4 Alternative model for predicting EQ-5D utility scores based on seizure freedom

Tobit random effects model, right-censored at 1	
Parameter estimate (SD)	
Seizure-free	0.16§ (0.04)
Age	-0.00 (0.00)
Gender	-0.17 (0.09)
Constant	0.75§ (0.14)
Predictive performance	
Predicted mean (observed: 0.69)	0.70
Predicted minimum (observed: -0.15)	0.53
Predicted maximum (observed: 1)	0.88
Predicted median (observed: 0.774)	0.70
RMSE	0.232
MAE	0.170

Keys: SD = standard deviation, MAE = mean absolute error, RMSE = root-mean square error
† $p < 0.05$
‡ $p < 0.01$
§ $p < 0.001$

Table S3.5 Alternative model for predicting EQ-5D utility scores based on seizure count terciles[1]

Tobit random effects model, right-censored at 1	
Parameter estimate (SD)	
Seizure count T2 (>= 1 < 3)	-0.13‡ (0.05)
Seizure count T3 (>= 3)	-0.20§ (0.06)
Age	-0.00 (0.00)
Gender	-0.17† (0.09)
Constant	0.89§ (0.14)
Predictive performance	
Predicted mean (observed: 0.69)	0.70
Predicted minimum (observed: -0.15)	0.50
Predicted maximum (observed: 1)	0.89
Predicted median (observed: 0.774)	0.70
RMSE	0.230
MAE	0.168

1 reference category is seizure count T1 (0 seizures).
Keys: SD = standard deviation, MAE = mean absolute error, RMSE = root-mean square error
† $p < 0.05$
‡ $p < 0.01$
§ $p < 0.001$

Table S3.6 Model for predicting EQ-5D utility scores based on seizure count

Tobit random effects model, right-censored at 1	
Parameter estimate (SD)	
Seizure count (continuous)	-0.01 (0.00)
Age	-0.00 (0.00)
Gender	-0.19 (0.10)
Constant	0.87§ (0.15)
Predictive performance	
Predicted mean (observed: 0.69)	0.71
Predicted minimum (observed: -0.15)	0.23
Predicted maximum (observed: 1)	0.84
Predicted median (observed: 0.774)	0.71
RMSE	0.249
MAE	0.183

Keys: SD = standard deviation, MAE = mean absolute error, RMSE = root-mean square error
† p < 0.05
‡ p < 0.01
§ p < 0.001

Table S3.7 Model for predicting EQ-VAS scores based on seizure count quartiles1

Tobit random effects model, right-censored at 100	
Parameter estimate (SD)	
Seizure count Q2 (> 0)	-9.07† (4.11)
Seizure count Q3 (>= 2 & <= 5)	-10.83† (4.99)
Seizure count Q4 (> 5)	-15.35‡ (5.51)
Age	-0.10 (0.24)
Gender	-9.99 (5.73)
Constant	82.81§ (8.99)
Predictive performance	
Predicted mean (observed: 68.92)	68.06
Predicted minimum (observed: 10)	52.93
Predicted maximum (observed: 100)	80.82
Predicted median (observed: 70)	68.66
RMSE	18.51
MAE	14.08

1 reference category is seizure count Q1 (0 seizures).
Keys: SD = standard deviation, Q = quartile, MAE = mean absolute error, RMSE = root-mean square error
† p < 0.05.
‡ p < 0.01
§ p < 0.001

Chapter 5

Supplement 4. Supplemental material to Chapter 5

Figure S4.1 Stepped-wedge schedule reflecting the planned and actual rollout of seizure dog trajectories

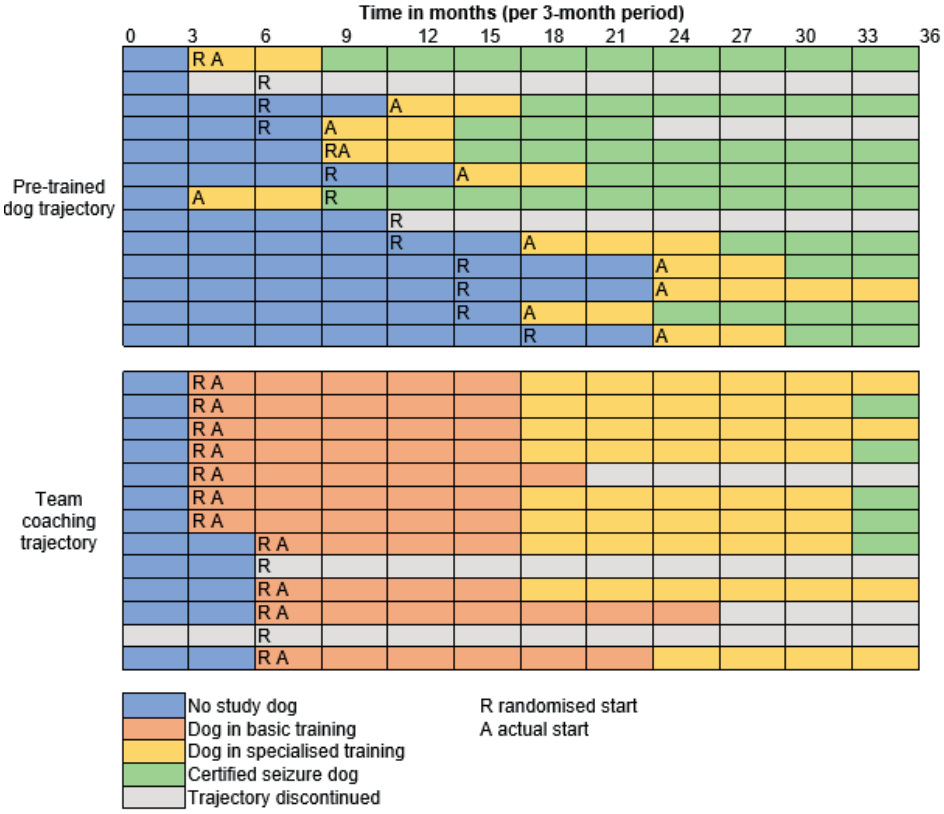


Figure S4.2 Number of observations for each follow-up duration in the intervention condition

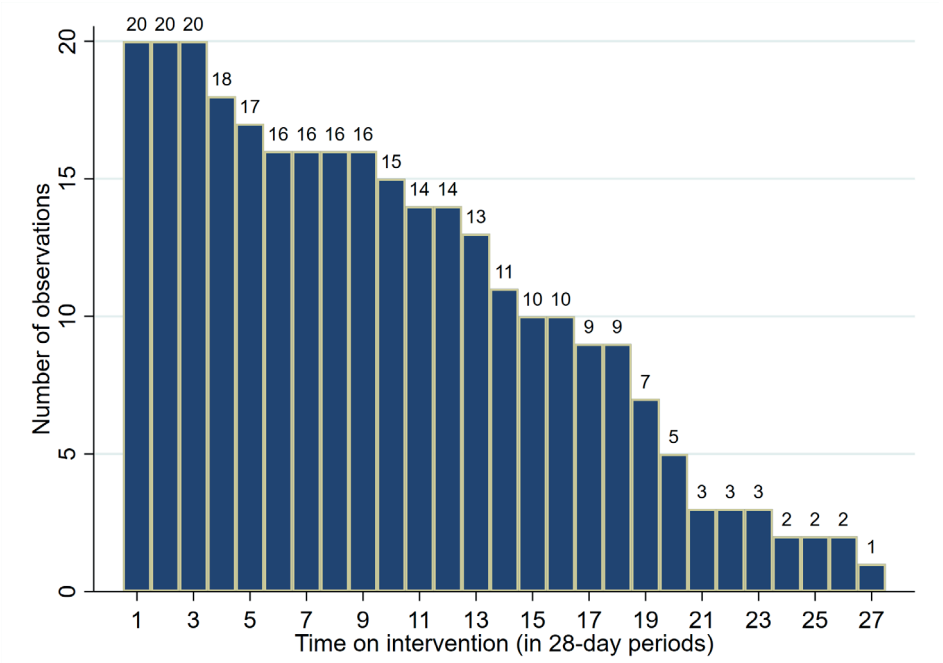
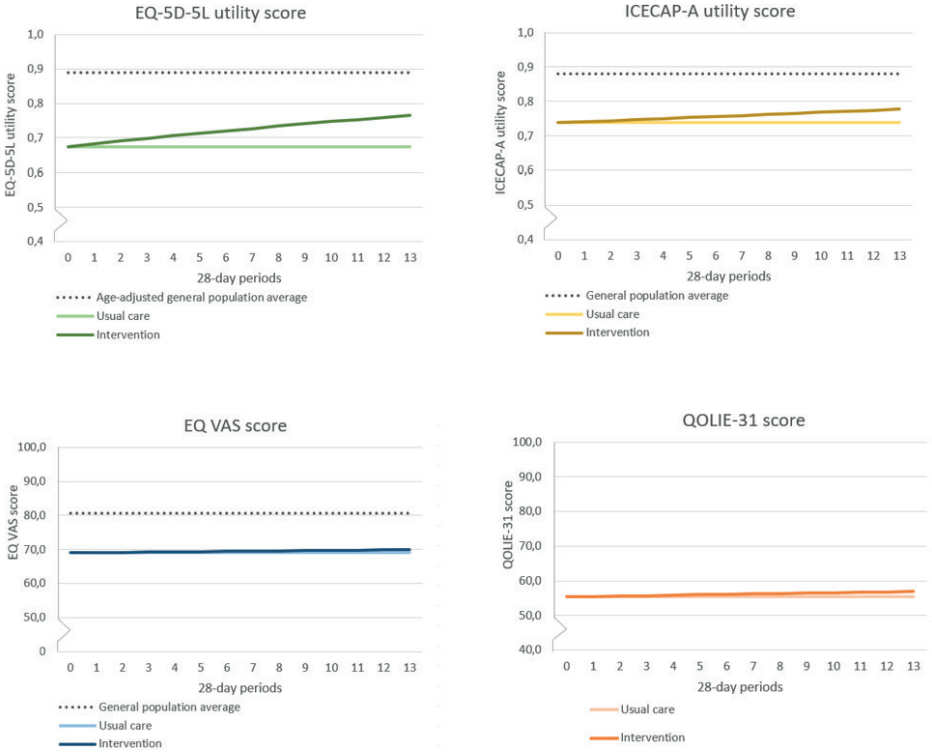


Figure S4.3 Estimated effect plotted over one year, comparison between usual care and intervention arm using mean score at baseline as a reference



Reference general population average EQ-5D-5L and EQ-VAS: 127
Reference general population average ICECAP-A: 152

Table S4.1 Model specifications

Outcome measure	Distribution family, link function	Random effect specification	Number of quadrature points
Seizure frequency	Poisson, log	(1 | id) + (1 | obs_ effect)	Not applicable
Seizure-free days	Poisson, log	(1 | id)	11
NHS3	Gaussian, log	(1 | id)	11
EQ-5D-5L disutility	Gamma, log	(1 | id)	11
EQVAS	Gaussian, log	(1 | id)	11
QOLIE-31	Gaussian, log	(1 | id)	11
ICECAP-A	Gaussian, log	(1 | id)	11

All analyses performed in R as Generalised Linear Mixed Model using the 'lme4' package (version 1.1-31) and 'glmer' function.

Table S4.2 Missing values per outcome measure

Outcome measure	Number of usable responses	Number of times imputation was required
Seizure frequency	846 / 851 (99%)	65[1] / 846 (8%)
Seizure-free days	846 / 851 (99%)	65 / 846 (8%)
NHS3	270 / 283 (95%)	23 / 270 (9%)
EQ-5D-5L disutility	270 / 283 (95%)	5 / 270 (2%)
EQVAS	269 / 283 (95%)	N/A (only one item)
QOLIE-31	270 / 283 (95%)	N/A (not required according to scoring manual)
ICECAP-A	270 / 283 (95%)	2 / 270 (1%)

1 in the majority of cases, only one or two seizure counts within the 28-day period had to be imputed

Table S4.3 Coefficients and confidence intervals for the main analysis and the sensitivity analyses on 28-day seizure frequency

Model	Exponentiated coefficient	Lower limit 95% CI	Upper limit 95% CI
Main analysis1			
Time on intervention	0.969	0.960	0.977
Sensitivity analyses			
Excluding absence and myoclonic seizures			
Time on intervention	0.966	0.957	0.974
Time as fixed effect			
Time on intervention	0.981	0.968	0.994
Time	0.992	0.986	0.998
Time as subject-specific random effect			
Time on intervention	0.982	0.965	0.999

All analyses performed in R as Generalised Linear Mixed Model using the 'lme4' package (version 1.1-31) and 'glmer' function.
1 Poisson distribution with a log-link and a subject-level and observation-level random effect, all epileptic seizures considered.
Keys: CI= Confidence Interval.

Table S4.4a Regression results from a Cumulative Link Mixed Model on EQ-5D-5L dimension scores, where a higher value reflects worse generic HRQoL

	Mobility	Self-care	Usual Activities	Pain / Discomfort	Anxiety / Depression
Coefficient time on intervention	0.029	0.068	-0.035	-0.028	-0.082
Std. Error	0.032	0.037	0.022	0.024	0.026
Pr (>|z|)	0.360	0.065	0.112	0.230	0.002

Analysis performed in R using the 'ordinal' package (version 2022.11-16) and 'clmm''function.
Keys: Pr (>|z|) = p-value resulting from a z-test, Std. = standard

Table S4.4b Regression results from a Generalised Linear Mixed Model with Gaussian family distribution and log link function on QOLIE-31 subscale scores, where a higher value reflects better epilepsy-specific quality of life

	Seizure worry	Overall QoL	Emotional well-being	Energy / Fatigue	Cognitive function	Medication effects	Social function
Coefficient time on intervention	0.008	0.005	0.003	0.004	-0.006	-0.003	0.009
Std. Error	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Pr (>|z|)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Analysis performed in R using the 'lme4' package (version 1.1-31) and 'glmer' function.
Keys: Pr (>|z|) = p-value resulting from a z-test, Std. = standard

Table S4.4c Regression results from a Cumulative Link Mixed Model on ICECAP-A dimension scores, where a higher value reflects better capability well-being

	Stability	Attachment	Autonomy	Achievement	Enjoyment
Coefficient time on intervention	0.064	0.041	0.049	0.067	0.011
Std. Error	0.024	0.027	0.030	0.028	0.026
Pr (>|z|)	0.009	0.122	0.106	0.015	0.672

Analysis performed in R using the 'ordinal' package (version 2022.11-16) and 'clmm''function.
Keys: Pr (>|z|) = p-value resulting from a z-test, Std. = standard

Summary
Samenvatting

Summary

For a small group of persons with epilepsy, seizures persist on a regular basis despite having tried available treatments. These persons have severe refractory epilepsy. Seizure dogs have gained attention as a potential solution to help address the seizure-related risks and emotional challenges faced by these individuals. Seizure dogs undergo specialised training to recognise and respond to the unique characteristics of their owner's seizures. The aim of a seizure dog partnership is to enhance safety and provide emotional support during episodes. Anecdotal reports and exploratory studies hint at the potential of seizure dogs to improve quality of life and reduce seizure frequency in their owners. Yet, there is no robust, scientific evidence on the benefits of seizure dogs and this has been a barrier to their inclusion in reimbursed care packages. The goal of this thesis, embedded in the EPISODE (EPIlepsy SuppOrt Dog Evaluation) study, was to conduct an extensive evaluation of the potential of seizure dogs as an assistive care service for adult PSREs. The chapters of this thesis describe the results of studies into the burden of illness of adults with severe refractory epilepsy and the clinical effectiveness, cost-effectiveness, and broader impacts of this intervention.

The protocol of the EPISODE study is detailed in Chapter 2. The study was designed as a stepped wedge trial, a variant of randomised controlled trials. Participants started at the same time, and initially received usual care. During the three-year follow-up period, participants gradually received a seizure dog in addition to their usual care, in a randomised order. The study's primary focus was evaluating the clinical effectiveness of seizure dogs in reducing seizure frequency. Data on seizure frequency were collected using seizure diaries. In addition, data on seizure severity, quality of life, use of health care and informal care, and labour were collected using quarterly questionnaires. To isolate the impact of trained seizure dog behaviours from any effects of the mere presence of a dog, a delay in the start of the intervention effects was incorporated into the analyses. It was assumed the effects would start when the dog has mastered the basic skills and when the participant and dog have had time to bond. In addition, the effects were assumed to grow as time with the seizure dog increases. The trial began on 1 June 2019, with 25 participants.

Chapter 3 used data over the first year of follow-up of the EPISODE study to shed light on the challenges of evaluating health-related quality of life (HRQoL) in the context of episodic conditions. The analysis showed that participants often completed the quarterly surveys on days when they were seizure-free, or when they experienced fewer seizures. This pattern indicates that EQ-5D-5L, the instrument used for assessing HRQoL, might not accurately represent the average health status of participants, since it focuses on the day the survey was completed (i.e., reflecting on "your health today"). Moreover, the analysis found that a lower seizure count on the day of reporting

corresponded with a better HRQoL score. These findings indicate that the use of the EQ-5D could potentially lead to an underestimation of the health burden associated with episodic conditions, and may consequently downplay the benefits of interventions aimed at these populations.

The burden of illness in the participants of the EPISODE study was explored in Chapter 4. The data of the first year of the study, prior to partnering with a seizure dog, revealed a significant disease burden. Participants typically experienced seizures multiple times a week, with multiple seizures on the days they occur. A small majority of participants reported comorbidities. Only about a quarter of participants had a paid job. The average HRQoL score was 24% lower than age-adjusted reference values for the general population in the Netherlands. Epilepsy-specific quality of life scores were lower than reported for broader epilepsy populations in the literature. The societal costs associated with severe refractory epilepsy were about €40,000 per participant per year. This involved for example expenses for, on average, nearly weekly visits to a health care institution, and three-and-a-half hours of informal care daily.

In Chapter 5 the findings of the trial regarding clinical effectiveness of the intervention are described. For 20 out of the 25 participants, follow-up with the seizure dog was long enough to observe impacts of the intervention. Seven participants achieved a reduction in seizure frequency of 50% or more near the end of follow-up. On average, seizure frequency reduced with 34% after one year with the seizure dog. HRQoL scores were estimated to increase with 14% over the same period. The other quality of life instruments, reflecting subjective health perception, epilepsy-specific quality of life and well-being, showed smaller improvements, with scores increasing by 1%, 1% and 5% in one year, respectively. Seizure dogs were not found to impact seizure severity. Six out of 25 participants discontinued their seizure dog trajectory during the trial, in some instances before the placement of the dog. This suggests that the intervention is not a suitable solution for all individuals.

Building on the trial data, in Chapter 6 a microsimulation model was developed to explore the cost-effectiveness of seizure dogs. This analysis adopted a societal perspective, in which both health care-related costs and broader societal costs, such as lost work hours and time spent on informal caregiving, are accounted for. The time horizon was set to 10 years, capturing the average duration of the seizure dog partnership. The intervention was modelled to reach its maximum potential two years after the start of the effect, after which the outcomes remain stable. The model demonstrated considerable improvements in HRQoL scores for both PSREs and their primary informal caregivers after receiving a seizure dog. The analysis further highlighted that an important share of the intervention costs is offset by savings. Approximately half of these savings occur in the health care sector, and the

other half results from a reduced need for informal care. As such, it was established that seizure dogs are a cost-effective addition to usual care for adults with severe refractory epilepsy in the Netherlands. The uncertainty surrounding cost parameters and assumptions on the extrapolation of the intervention effect broadened the range of incremental cost-effectiveness ratios. Nevertheless, the conclusion regarding cost-effectiveness remained consistent across all explored scenarios and was confirmed in 91% of the probabilistic sensitivity analysis iterations.

The qualitative study presented in Chapter 7 described the experiences and perspectives of 17 EPISODE participants and their caregivers at the end of trial follow-up. The interview study highlighted the complex impacts of severe refractory epilepsy on the lives of participants and their support networks, revealing how seizure dogs can bring both benefits and challenges in this context. The seizure dog was described to take on various roles, including that of a first responder, emotional support companion, seizure predictor, spotlight for public attention, and a responsibility. Perceived benefits of the seizure dog touched upon various aspects of daily life. Participants noted improvements in emotional well-being, they felt a sense of security and general upliftment. They felt the seizure dog enhanced their personal capabilities and autonomy, which helped them pursue their ambitions. For their social functioning, participants experienced greater confidence and better relationships with their informal caregivers. It was also noted that the seizure dogs presence has resulted in a lower seizure frequency. The presence of the seizure dog was felt to reduce the need for the informal caregiver's supervisory role. This led to a spillover of benefits to family members, who experienced a notable sense of relief and a better sense of independence, even as they remained ready to respond to the occurrence of a seizure. Challenges were also encountered, such as integrating care and training responsibilities in a daily routine, unwanted attention from strangers, and the visibility of epilepsy due to the seizure dog's presence. The extent to which benefits were felt and challenges were burdensome varied significantly between participants. Whereas some deemed the intervention life-altering, others were disappointed as their expectations about the seizure dog's response and alert capabilities were not met.

The Chapters of this thesis illustrated the multifaceted potential of seizure dogs for a severely burdened population. It demonstrated seizure dogs reduce seizure frequency and enhance the quality of life of persons with severe refractory epilepsy and their informal caregivers, and that it very likely concerns a cost-effective complement to usual care in the Netherlands. Yet, not all adults with severe refractory epilepsy benefit equally, as evidenced by considerable variation in outcomes, mixed experiences, and a significant rate of discontinuation of seizure dog trajectories. These insights assist stakeholders with balancing the considerations of clinical effectiveness, cost-effectiveness, and broader impacts when appraising the potential of seizure dogs.

Additionally, the EPISODE study serves as an illustrative case study of the application of established methods for economic evaluations to non-pharmacological interventions and episodic conditions.

Samenvatting

Voor een kleine groep mensen met epilepsie blijven epileptische aanvallen regelmatig voorkomen, ondanks beschikbare behandelingen. Deze mensen hebben ernstige refractaire (d.w.z., moeilijk behandelbare) epilepsie. Epilepsiehonden zijn in beeld gekomen als een manier om in te spelen op zowel de risico's rondom epileptische aanvallen als emotionele uitdagingen die deze groep mensen ervaart. Epilepsiehonden krijgen een speciale training om de unieke kenmerken van de epileptische aanvallen van hun baasje te leren herkennen, en daar passend op te reageren. Het doel van de inzet van epilepsiehonden is om veiligheid en emotionele steun te bieden tijdens en rondom deze epileptische aanvallen. Anekdotische verhalen en verkennende studies wijzen erop dat epilepsiehonden de kwaliteit van leven van mensen met epilepsie kunnen helpen verbeteren en de frequentie van epileptische aanvallen verminderen. Echter, er is geen degelijk, wetenschappelijk bewijs beschikbaar ten aanzien van de voordelen van epilepsiehonden en dit vormt een barrière voor hun toelating tot vergoede zorg. Dit proefschrift, gebaseerd op de EPISODE (EPIlepsy SuppOrt Dog Evaluation) studie, had als doel een uitgebreide evaluatie uit te voeren van het potentieel van epilepsiehonden als een ondersteunende zorgvorm voor volwassenen met ernstige refractaire epilepsie. De hoofdstukken van dit proefschrift beschrijven de resultaten van onderzoeken naar de ziektelast van volwassenen met ernstig refractaire epilepsie, en de klinische effectiviteit, kosteneffectiviteit en bredere effecten van epilepsiehonden.

Het protocol van de EPISODE-studie werd uitgebreid beschreven in Hoofdstuk 2. De studie was ontworpen als een stepped wedge studie, een variant van gerandomiseerde gecontroleerde studies. Alle deelnemers zijn tegelijk aan het onderzoek begonnen, en kregen in eerste instantie de zorg die ze gebruikelijk kregen. Tijdens de onderzoeksperiode van drie jaar, kregen deelnemers één voor één een epilepsiehond naast de gebruikelijke zorg. De volgorde hiervan was willekeurig bepaald (gerandomiseerd). De voornaamste focus van de studie was het bepalen van de klinische effectiviteit van epilepsiehonden in het verminderen van epileptische aanvallen. Gegevens over de frequentie van epileptische aanvallen werden verzameld met behulp van aanvalsdagboeken. Daarnaast werden er elke drie maanden via vragenlijsten gegevens verzameld over de ernst van epileptische aanvallen, kwaliteit van leven, gebruik van gezondheidszorg en mantelzorg, en werk. Om ervoor te zorgen dat de onderzoeksbevindingen de impact van het getrainde gedrag van de epilepsiehond weergeven, en niet de impact van gewoon het hebben van een hond, werd in de berekeningen een vertraging in de start van de interventie-effecten aangenomen. Er werd verondersteld dat de effecten beginnen nadat de hond basisvaardigheden onder de knie heeft, en de hond en de deelnemer tijd hebben

gehad om aan elkaar te wennen. Daarnaast werd aangenomen dat de effecten toenemen naarmate de tijd met de epilepsiehond toeneemt. De studie startte op 1 juni 2019 met 25 deelnemers.

In Hoofdstuk 3 werden gegevens die in het eerste jaar van de EPISODE-studie verzameld werden gebruikt om inzicht te geven in de uitdagingen van het meten van gezondheidgerelateerde kwaliteit van leven bij episodisch aandoeningen. De analyse toonde aan dat deelnemers vaak de driemaandelijkse vragenlijsten invulden op dagen dat ze geen epileptische aanvallen hadden, of wanneer ze voor hun doen weinig epileptische aanvallen hadden. Dit patroon geeft aan dat de EQ-5D, het instrument dat werd gebruikt voor het meten van gezondheidgerelateerde kwaliteit van leven, de gemiddelde gezondheidstoestand van deelnemers mogelijk niet nauwkeurig weergeeft. Het instrument richt zich namelijk op de dag dat de vragenlijst wordt ingevuld (d.w.z., reflecterend op "uw gezondheid vandaag"). Bovendien lieten de analyses zien dat een lagere aanvalsfrequentie op de dag van invullen samenhangt met een betere gezondheidgerelateerde kwaliteit van leven. Deze bevindingen geven aan dat het gebruik van de EQ-5D zou kunnen leiden tot een onderschatting van de gezondheidsimpact die gepaard gaat met episodische aandoeningen, en daarmee ook van de voordelen van interventies die op deze populaties gericht zijn.

De ziektelast van de deelnemers van de EPISODE-studie werd in Hoofdstuk 4 onderzocht. De gegevens die in het eerste jaar van de EPISODE-studie verzameld werden, vóórdat deelnemers een officiële epilepsiehond hadden, lieten een aanzienlijke impact van de ziekte zien. Deelnemers hadden doorgaans meerdere keren per week epileptische aanvallen, met meerdere aanvallen op een dag. Een kleine meerderheid van de deelnemers had naast epilepsie ook andere gezondheidsproblemen. Slechts een kwart van de deelnemers had een betaalde baan. De gezondheidgerelateerde kwaliteit van leven score was aanzienlijk lager (namelijk 24%) dan voor personen zonder epilepsie in Nederland in dezelfde leeftijdsklasse. Epilepsie-specifieke kwaliteit van leven scores waren lager dan in de literatuur beschreven voor andere personen met epilepsie. De maatschappelijke kosten van ernstige refractaire epilepsie bedroegen circa €40.000 per persoon per jaar. Dit betrof onder andere uitgaven aan bijna wekelijkse bezoeken aan een gezondheidszorginstelling, en dagelijks drieënhalf uur aan mantelzorg.

In Hoofdstuk 5 werden de resultaten van de studie met betrekking tot de klinische effectiviteit van epilepsiehonden beschreven. Voor 20 van de 25 deelnemers werden er lang genoeg gegevens verzameld om de effecten van de epilepsiehond te evalueren. Bij zeven deelnemers was de hoeveelheid epileptische aanvallen met 50% of meer afgenomen tegen het einde van de onderzoeksperiode. Gemiddeld hadden de deelnemers 34% minder aanvallen dan voorheen na een jaar met een

epilepsiehond. Hun gezondheidgerelateerde kwaliteit van leven verbeterde met 14% over dezelfde periode. De andere kwaliteit van leven instrumenten, die subjectieve gezondheid, epilepsie-specifieke kwaliteit van leven en welzijn meten, lieten kleinere verbeteringen zien. Deze scores stegen respectievelijk met 1%, 1% en 5% na een jaar met de epilepsiehond. De ernst van de epileptische aanvallen veranderde niet door de epilepsiehond. Tijdens het onderzoek was bij zes van de 25 deelnemers (24%) het traject met de epilepsiehond stopgezet, soms al voordat ze de hond hadden gekregen. Dit geeft aan dat de interventie niet voor iedereen een passende oplossing is.

In Hoofdstuk 6 is gebruik gemaakt van gegevens uit de studie om een model te ontwikkelen waarmee de kosteneffectiviteit van epilepsiehonden onderzocht is. Deze analyse nam een maatschappelijk perspectief aan, waarbij niet alleen is gekeken naar de kosten van de zorg, maar ook naar bredere kosten, zoals verloren werkuren en de tijd die mensen besteden aan het verzorgen van hun naasten. Met het model werden kosten en effecten geschat over een periode (tijdshorizon) van 10 jaar, wat overeenkomt met de gemiddelde tijd dat de epilepsiehond werkzaam is. Het model ging ervan uit dat het twee jaar duurt totdat de maximale impact van de epilepsiehond is bereikt, waarna de uitkomsten stabiel blijven. Uitkomsten van het model lieten zien dat mensen met ernstig refractaire epilepsie, evenals hun belangrijkste mantelzorgers, aanzienlijke verbeteringen in hun kwaliteit van leven ervaren na ontvangst van een epilepsiehond. Bovendien liet de analyse zien dat de kosten van de interventie grotendeels werden gecompenseerd door besparingen. Ongeveer de helft van deze besparingen vindt plaats in de gezondheidszorgsector, en de andere helft is het gevolg van een verminderde behoefte aan mantelzorg. Het onderzoek toonde aan dat epilepsiehonden een kosteneffectieve toevoeging zijn op gebruikelijke zorg voor volwassenen met ernstige refractaire epilepsie in Nederland. Onzekerheid rond de kosten en rond de aannames over het moment waarop de maximale impact van de epilepsiehond bereikt is zorgden voor een brede reikwijdte van kosteneffectiviteitsratio's. Desalniettemin bleef de conclusie met betrekking tot kosteneffectiviteit overeind in alle verkende scenario's, en werd deze bevestigd in 91% van de simulaties in de probabilistische gevoeligheidsanalyse.

De resultaten van het kwalitatieve onderzoek werden besproken in Hoofdstuk 7. In dit onderzoek werden 17 EPISODE deelnemers en hun mantelzorgers geïnterviewd aan het einde van de studie. Uit de interviews kwam naar voren dat ernstig refractaire epilepsie een complexe impact heeft op het leven van deelnemers en hun mantelzorgers, en dat epilepsiehonden zowel voordelen als uitdagingen kunnen brengen. De epilepsiehonden vervulden verschillende rollen, waaronder die van eerste hulpverlener, maatje voor emotionele steun, aanvalsvoorspeller, spotlight voor publieke aandacht en een verantwoordelijkheid. De voordelen van epilepsiehonden waren merkbaar in verschillende aspecten van het leven. Deelnemers benoemden

verbeteringen in hun emotioneel welzijn, zoals een gevoel van veiligheid en een betere stemming. Ze voelden zich ook capabeler en zelfstandiger door de epilepsiehond, wat hen in staat stelde om hun ambities na te streven. Op sociaal gebied ervoeren ze meer zelfvertrouwen en verbeterde relaties met hun mantelzorgers. Bovendien werd opgemerkt dat de aanwezigheid van de epilepsiehond voor minder aanvallen zorgde. Ook werd gevoeld dat de noodzaak van constant toezicht, bijvoorbeeld door een mantelzorger, afnam. Dit laatste leidde tot aanvullende voordelen voor gezinsleden, die zich gerustgesteld voelden en meer onafhankelijk konden zijn, ook al blijven ze klaar staan om te reageren als er een aanval plaatsvindt. Deelnemers ervoeren ook uitdagingen, zoals het inpassen van de zorg voor de hond en trainingstaken in het dagelijkse ritme, ongewenste aandacht van vreemden, en de zichtbaarheid van epilepsie door de epilepsiehond. De mate waarin voordelen werden gevoeld en uitdagingen als belastend werden ervaren, varieerde aanzienlijk tussen deelnemers. Sommigen beschouwden de interventie als levensveranderend, terwijl anderen teleurgesteld waren omdat verwachtingen over de reageer- en voorspelvaardigheden van de epilepsiehond niet werden waargemaakt.

De Hoofdstukken van dit proefschrift hebben het veelzijdige potentieel van epilepsiehonden voor een ernstig belaste populatie belicht. Ze toonden aan dat epilepsiehonden epileptische aanvallen verminderen en de kwaliteit van leven van volwassenen met ernstig refractaire epilepsie en hun mantelzorgers verbeteren, en dat ze zeer waarschijnlijk een kosteneffectieve aanvulling zijn op de gebruikelijke epilepsiezorg in Nederland. Toch profiteren niet alle volwassenen met ernstige refractaire epilepsie evenveel van de epilepsiehond, zoals blijkt uit grote variatie in uitkomsten, gemengde ervaringen en een hoog aantal stopzettingen van epilepsiehondentrajecten. Deze inzichten helpen belanghebbenden bij het afwegen van overwegingen van klinische effectiviteit, kosteneffectiviteit en bredere impact bij het beoordelen van het potentieel van epilepsiehonden. Daarnaast dient de EPISODE-studie als een voorbeeld casus voor de toepassing van gevestigde methoden voor economische evaluaties op niet-farmacologische interventies en episodische aandoeningen.

Portfolio

Publications

In this thesis

2020 **Wester V**, de Groot S, Kanters T, Wagner L, Ardesch J, Corro Ramos I, Enders-Slegers MJ, de Ruiter M, le Cessie S, Los J, Papageorgiou G, van Exel J, Versteegh M, on behalf of the EPISODE-team. Evaluating the Effectiveness and Cost-Effectiveness of Seizure Dogs in Persons With Medically Refractory Epilepsy in the Netherlands: Study Protocol for a Stepped Wedge Randomized Controlled Trial (EPISODE). Front Neurol. 2020;11:3.

2021 **Wester V**, de Groot S, Versteegh M, Kanters T, Wagner L, Ardesch J, Brouwer W, van Exel J; on behalf of the EPISODE-team. Good Days and Bad Days: Measuring Health-Related Quality of Life in People With Epilepsy. Value Health. 2021;24(10).

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submitted **van Hezik-Wester V**, de Groot S, van Exel J, van de Bovenkamp H, de Graaff B. One tail, two tales: a qualitative investigation into the experiences with seizure dogs among participants of the EPISODE study and their caregivers.

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2021 Cloosterman S, Wijnands I, Huygens S, **Wester V**, Lam K, Strijbis E, den Teuling B, Versteegh M. The Potential Impact of Digital Biomarkers in Multiple Sclerosis in The Netherlands: An Early Health Technology Assessment of MS Sherpa. Brain Sci. 2021;11(10).

2022 Klein PCG, Huygens S, Handels R, **Wester V**, Kanters T. Costs of Persons with Dementia Living in Nursing Homes in The Netherlands. J Alzheimers Dis. 2022;89(1).

2023 **van Hezik-Wester V**, Handels R, Wolfs C, Kanters T. Caregiver Burden and Quality of Life Across Alzheimer's Disease Severity Stages. Alzheimer Dis Assoc Disord. 2023;37(2).

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Other academic work

2018 **Wester V**, Wagner L, Ardesch J. Onderzoek naar de (kosten)effectiviteit van epilepsiehonden. Epilepsie, Periodiek voor Professionals. 2018;16(2)

2019 Waardebepaling, implementatie en bekostiging van voorspellende testen in Nederland. de Graaf G, de Groot S, **Wester V**, Vellekoop H, Versteegh M, Rutten-van-Mölkem, M. ZonMW. 2019.

2021 Wolff R, Penton H, Vellekoop H, **Wester V**, Abraham K, Klein P, et al. Crizanlizumab for preventing sickle cell crises in sickle cell disease: a Single Technology Assessment. National Institute for Health and Care Excellence (NICE). 2021. [ID1406]

2021 **Wester V**, Huygens S, Versteegh M. Vroege HTA naar de waarde van een beslissingsondersteunende AI-toepassing in multiple sclerose. Ministerie voor Volksgezondheid, Welzijn en Sport (VWS).

2021 Oordt A, **Wester V**, Eeuwijk J, Klein Kanters T, Bunge E, Uyl-de Groot C. Medical cannabis for treating various symptoms in Switzerland: Scoping Report. Federal Office of Public Health (FOPH).

2021 **Wester V**, Klein P, Kanters T, Oordt A, Eeuwijk J, Bunge E, Uyl-de Groot C. Medical cannabis for treating various symptoms in Switzerland: HTA Report. Federal Office of Public Health (FOPH).

Activities

Courses

2018 Survey Design and Effectiveness Research – Erasmus School of Health Policy & Management

2020 Multilevel Modelling 1: an introduction – Erasmus Graduate School of Social Sciences and the Humanities

2020 Communicating your research: lessons from Bitescience – Erasmus Graduate School of Social Sciences and the Humanities

2021 Data Analysis with R – Erasmus Graduate School of Social Sciences and the Humanities

2021 Using R for Decision Modelling in HTA – The Netherlands Institute for Health Sciences (NIHES)

2021 Science communication in Theory and Practice – University of Copenhagen

2022 Design & Analysis of Cluster Randomised Trials – London School of Hygiene & Tropical Medicine

Teaching

2019 Quantitative Research Methods, Bachelor Gezondheidswetenschappen, Beleid & Management Gezondheidszorg, Erasmus Universiteit Rotterdam

2019 Thesis, Bachelor Gezondheidswetenschappen, Beleid & Management Gezondheidszorg, Erasmus Universiteit Rotterdam

Conference presentations

2020	ISPOR Europe 2020, Milan – podium presentation
2022	ISPOR Europe 2022, Vienna – poster presentation

Invited presentations

2020	Vereniging Artsen Volksgezondheid – guest lecture
2023	Stichting Epilepsie Instellingen Nederland (SEIN) – research presentation
2023	Kempenhaeghe Academic Center for Epileptology – research presentation

Media communications

2020	De Ochtend Show to go – tv interview
2020	Algemeen Dagblad – interview for news paper
2024	Neurology Today – interview for journal

Miscellaneous

2017 - 2024	Researcher at the institute for Medical Technology Assessment (iMTA)
2023	Reviewer for *Journal of Alzheimer's Disease*

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