QUality of life and Economic evaluation after neuroSTimulation for Epilepsy (QUESTE) in adolescents and adults with drug-resistant epilepsy: protocol for a multicentre, prospective observational cohort study in The Netherlands

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ABSTRACT

Introduction Epilepsy is one of the most common chronic neurological disorders. Antiepileptic medication (ASM) is the first choice of treatment, however, 30% of epilepsy patients are drug-resistant. For these patients, neuromodulation can be an option, especially when epilepsy surgery is not possible or did not lead to seizure freedom. Epilepsy is associated with reduced quality of life (QoL), which heavily depends on seizure control. The most recent Cochrane reviews have shown that vagus nerve stimulation and deep brain stimulation of the anterior nucleus of the thalamus, lead to a responder rate OR of, respectively, 1.93 and 1.20. The question arises if neuromodulation for drug-resistant epilepsy (DRE) will be more cost-effective than sole treatment with ASM. The current study aims to determine the change in QoL after neuromodulation. Secondarily, we aim to study the cost-effectiveness of these treatments.

Methods and analysis This prospective cohort study aims at including 100 patients aged 16 or above who will be referred for neuromodulation, from January 2021 to January 2026. After informed consent, QoL and other relevant parameters will be assessed at baseline, 6 months, 1, 2 and 5 years after surgery. Data on seizure frequency will be derived from patient charts. We expect that DRE patients will report better QoL after neuromodulation. Even if they would still report seizures, the treatment can be seen as useful. This is especially true when patients can participate in society again to a greater extent than before treatment.

Ethics and dissemination The board of directors of participating centres all gave permission for this study to commence. The medical ethics committees decided that this study does not fall under the Medical Research Involving Human Subjects Act (WMO). The findings of this study will be presented at (inter)national conferences and in peer-reviewed journals.

Trial registration number NL9033.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The three hospitals that treat drug-resistant epilepsy patients with deep brain stimulation and carry out a large part of vagus nerve stimulator implantations in The Netherlands all participate in this study.
⇒ The 6-month and 1-year, 2-year and 5-year follow-up will give both a short-term and long-term insight in the effect of neuromodulation on quality of life of drug-resistant epilepsy patients.
⇒ Because the number of patients in The Netherlands undergoing vagus nerve stimulation is much larger than the number of patients undergoing deep brain stimulation, comparing the outcomes of both methods will be difficult.

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders. An epileptic seizure is an unpredictable episodic event which is caused by excessive paroxysmal electrical discharging of brain cells. Treatment of first choice for epilepsy consists of antiepileptic medication (ASM). However, approximately 30% of patients with epilepsy are drug-resistant or suffer from too many drug-related side effects. Drug-resistant epilepsy (DRE) is defined as failure of adequate trials of two tolerated, appropriately chosen and used
ASM schedules. If a patient has DRE and is open to surgical treatment, a multidisciplinary team will review if the patient is eligible for epilepsy surgery, a curative invasive treatment option in which resection or disconnection of the so-called epileptogenic zone aims to provide seizure freedom. If a patient chooses not to undergo epilepsy surgery or if epilepsy surgery is not an option or did not lead to seizure freedom, neuromodulation, either vagus nerve stimulation (VNS) or deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS, referred to as ‘DBS’ in the rest of the article), can be considered in The Netherlands.6

Because ANT-DBS is the only type of DBS for epilepsy covered by health insurance in The Netherlands, we did not include patients with other types of DBS for epilepsy, such as centromedian thalamic nucleus DBS (CM-DBS). Both neuromodulation methods work by electrical stimulation. This can be either through one implanted bipolar electrode to the cervical part of the left vagus nerve (VNS) or through two implanted depth electrodes placed in the left and right ANT-DBS. Both systems are powered by a subcutaneously placed pulse generator with a battery.

Epilepsy is associated with reduced quality of life (QoL), which heavily depends on seizure control.7 Previous studies have shown that neuromodulation in epilepsy increases QoL. A Mexican study with 35 patients reported an increase of 12.7 points on the Qolie-31-P questionnaire after follow-up of at least 1 year.8 A clinically relevant increase in QoL 1 and 2 years after implantation was also described in a small Turkish sample of seven DRE patients treated with VNS.9 A Cochrane review from 2022 reported that VNS leads to small QoL increases, however, they only included studies with a maximum follow-up of 20 weeks.10 DBS also leads to a clinically relevant increase in QoL both 1 and 5 years after implantation. A previous American study on the long-term effects of ANT-DBS in a similar patient population described a mean improvement in Qolie-31 score after 1 year and 5 years of 5.0 (95% CI 3.0 to 6.5) and 6.1 (95% CI 4.0 to 8.0) points, respectively. After 1 year, 46% achieved an improvement of 5 points; after 5 years this was 48%.11 A Cochrane review from 2017 states that DBS does not have a clinically meaningful effect on QoL, however, they only included studies with a follow-up of up to 3 months.13

Dutch QoL studies on neuromodulation in adult DRE patients are still lacking. QoL is highly region-specific for a number of reasons, including cultural reasons and the way in which the healthcare system is organised. Therefore, it is important to perform similar studies within The Netherlands.

An international controlled study from 1994 shows that VNS leads to a mean seizure frequency reduction of 30.9%. A more than 50% frequency reduction (the so-called responder rate) was seen in 38.7% of the patients.14 After 16–18 months, the mean frequency reduction increased to 52%.15

A systematic review from 2020 shows that VNS for DRE leads to a responder rate of 26%–40% after 1 year and 60%–70% after 5 years.16 However, the studies used for this systematic review are mostly non-controlled studies with low to moderate quality evidence. A Mexican study with 35 participants reported a 55.65% median frequency reduction after a follow-up of at least 1 year.1 A small Dutch long-term follow-up study shows that VNS for DRE leads to an average seizure frequency reduction of 25% after 2 years and 43% after 5 years. Of the 19 included patients, 33% were classified as responders after 2 years. After 5 years 38% of the 9 patients who were still participating were considered responders.17 A Cochrane review from 2022 shows an OR of 1.93 (95% CI 1.1 to 3.4) for the responder rate across all included studies.10

The largest long-term efficacy trial on DBS for DRE, the SANTE-trial conducted in the USA, shows that DBS leads to a median seizure reduction of 56% after 2 years and 69% after 5 years. The responder rate was, respectively, 69% and 68% after 2 and 5 years,11 which was confirmed in a smaller German sample.18 A systematic review from 2017 confirmed these results.19 A Cochrane review from the same year shows an OR of 1.20 (95% CI 0.52 to 2.80) for the responder rate of ANT-DBS. The authors state that there is a need for more large and well-designed randomised studies to further research the effect of DBS on people with DRE.13

Both VNS and DBS are expensive treatment options. The expected lifetime costs in The Netherlands are, respectively, €156,871 and €187,791, for VNS and DBS, compared with €64,670, for treatment with ASM.20 VNS and DBS do usually not lead to complete seizure freedom. As a result of the high lifetime costs, the question arises if neuromodulation for DRE is cost-effective. According to a study conducted in The Netherlands, both treatment options are potentially cost-effective for the treatment of DRE, based on gain in quality-adjusted life-years (QALYs).20 According to the National Institute for Health and Care Excellence, one QALY is equal to 1 year of life in perfect health.21

In The Netherlands, VNS is offered in several specialised hospitals, including the three participating centres in this study. Together, they implant a large part of VNS systems in the country. Patients with DRE can only be treated with DBS-implantation surgery in the centres participating in this study.

We have developed the QUESTE trial (QUality of life and Economic evaluation after neuroSTimulation in Epilepsy), aimed at prospectively evaluating disease-specific and generic QoL, before and after neuromodulation in patients with DRE. In addition, healthcare usage, productivity, credibility, expectations and satisfaction about the treatment are evaluated. Informal caregivers will be asked to evaluate how they experience providing informal care by preoperative and postoperative validated questionnaires. We will also aim to study the cost-effectiveness of neuromodulation for DRE.
Hypotheses

Hypothesis 1: patients with DRE will report a clinically relevant increase in disease specific (Qolie-31P scores) and generic QoL. (EuroQol 5-Dimension 5-Level, EQ-5D-5L scores) 6 months, 1, 2 and 5 years after neuromodulation compared with baseline.

Hypothesis 2: patients with DRE will report a significant reduction in seizure frequency and severity 6 months, 1, 2 and 5 years after neuromodulation compared with baseline.

Hypothesis 3: patients with DRE will report a significant decrease in healthcare use (imTA Medical Costs Questionnaire, iMCQ scores) 6 months, 1, 2 and 5 years after neuromodulation compared with baseline.

Hypothesis 4: patients with DRE will report a significant increase in productivity (iMTA Productivity Costs Questionnaire, iPPCQ scores) 6 months, 1, 2 and 5 years after neuromodulation compared with baseline.

Hypothesis 5: patients with DRE who will have their pulse-generators replaced when the battery is near end of service, will report a significantly larger QoL change than patients who will not have them replaced.

METHODS

Study design

The QUESTE-study is a multicentre, prospective, observational cohort study that will be conducted from January 2021 to January 2026. Three Dutch hospitals and their referral partners will include patients who will receive neuromodulation in one of the participating hospitals. Implantation surgery will take place in the Maastricht University Medical Centre+ (MUMC+), Amsterdam University Medical Centre (AUMC) and Medisch Spectrum Twente (MST). Neuromodulation aftercare and follow-up will take place in the Academic Centre of Epileptology location Kempenhaeghe (for the MUMC+), Stichting Epilepsie Instellingen Nederland (SEIN) location Zwolle for the MST and AUMC.

Participant criteria

Included are DRE patients aged 16 or older who will be referred for VNS or DBS for the first time in the MUMC+, AUMC and MST.

Excluded are patients who will not be able to understand the Dutch language and patients with a severe intellectual disability, because they will not be able to fill in the used questionnaires.

Selection of the sample

For this study, patients who will be referred as candidate for VNS or DBS for DRE between 1 January 2021 and 1 January 2026 will be invited to participate in the QUESTE-study. Participants will receive a patient information file and an informed consent form by post or email prior to the presurgery consultation with the neurosurgeon and nurse practitioner at the neurosurgery outpatient clinic. During this visit, patients will be asked to participate. If they have any further questions, they will be referred to the investigator or independent medical doctor. When the patient agrees, the signed consent form will be returned by post or handed in at the neurosurgery outpatient clinic. When their operation date is known, a database file will be created, and the first questionnaires will be sent out; in general, this will be 2–4 weeks before surgery.

Outcome measures

Primary outcome measure is the difference in disease specific QoL between the preoperative and postoperative measurements.

Secondary outcome measures are the preoperative and postoperative differences in terms of generic QoL (1) seizure frequency (2) and severity (3), usage of healthcare (4), productivity (5) and the burden on informal caregivers (6).

Quality of life

To measure QoL-related outcome measures of the study, the following questionnaires will be used:

- Qolie-31-P (Patient-Weighted Quality Of Life In Epilepsy inventory), this is a validated disease-specific questionnaire for measuring QoL in patients with epilepsy, able to determine small but clinically relevant differences in disease burden. The questionnaire consists of 31 questions aimed at the most important subdomains of QoL: overall QoL, seizures, emotional well-being, energy level, cognitive and social functioning, and medication side effects. For each domain, the level of distress a patient feels about their problems is asked for.

- EQ-5D-5L, this is a standardised and international validated measurement tool for measuring generic health status in five domains (mobility, self-care, daily activities, pain/discomfort and anxiety/depression). For the evaluation of QoL in a broader sense, it is recommended to measure generic QoL in addition to disease specific QoL. The outcomes of this questionnaire will also be used to calculate a utility for performing the economic evaluation later on.

Clinical efficacy

The seizure frequency will be measures using the International League Against Epilepsy (ILAE)-classification based on patient charts. Information on status epilepticus, emergency medication use, ER or hospital visits after a seizure, getting wounded during a seizure and urinary incontinence during a seizure, will be derived from the patient records. In addition, previous interventions (epilepsy surgery, prior neuromodulation), stimulation parameters, DBS-targets, surgical complications and stimulation-induced side effects will be derived from patient records. A 5-year measurement will be added to study the long-term effects of neuromodulation on DRE. The retention rate will be determined as well. The rate is the percentage of patients who will continue.
their treatment. If a patient is satisfied with the treatment, the stimulator will remain on and the patient will most likely choose to replace the battery when it becomes empty. If a patient is not satisfied with the treatment, it is most likely that the patient chooses to deactivate the stimulator, to have the stimulator removed or to not replace the battery when it is empty. Whether the patient chooses to continue the treatment is an indirect measurement of being satisfied with the treatment.28

Costing

To measure the economic evaluation-related outcome measures, the following questionnaires will be used:

iMCQ29: This is a generic validated measuring instrument for monitoring determinants of QoL and healthcare costs for the purpose of economic evaluation, designed in The Netherlands and based on the Dutch healthcare system. The iMCQ aims to be a standardised method to increase the comparability between studies. This questionnaire maps out the patients healthcare use.

iPCQ30: This is a generic validated measuring instrument for monitoring determinants of QoL and healthcare costs for the purpose of economic evaluation. The iPCQ aims to be a standardised method to increase the comparability between studies. This questionnaire maps out the patients work situation and workload.

Other outcomes

Before surgery, at baseline, questions about credibility and expectations, based on the Credibility/Expectancy Questionnaire will be added to the questionnaires (table 1).31

At follow-up, satisfaction with the results of the operation will be measured by the question: To what extent does the result of the operation correspond to your expectations?

Finally, the burden on the informal caregivers of the patient will be tracked using the iMTA Valuation of Informal Care Questionnaire (iVICQ).32 The goal of the iVICQ is to describe informal care and the effects on the informal caregivers. For this study, the so-called core-questionnaire will be used. This is a shorter version of the iVICQ, which will be sufficient for this secondary outcome measure.

The questionnaires above are all taken at baseline (2–4 weeks prior to surgery) and 6 months, 1, 2 and 5 years after surgery (figure 1).

Table 1 Questions on credibility and expectancy asked to the participants at baseline, based on the CEQ

<table>
<thead>
<tr>
<th>Credibility</th>
<th>Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>How logical does the therapy offered to you seem?</td>
<td>How much improvement in your symptoms do you think will occur?</td>
</tr>
<tr>
<td>How successful do you think this operation will be in reducing your number of seizures?</td>
<td>How much do you really feel that the operation will help you to reduce your seizures?</td>
</tr>
<tr>
<td>How confident would you be in recommending this treatment to a friend or relative?</td>
<td>How much improvement in your epilepsy symptoms do you really feel will occur?</td>
</tr>
</tbody>
</table>

CEQ, Credibility Questionnaire.

Figure 1 Flow diagram of the QUESTE-study. DBS, deep brain stimulation; EQ-5D-5L, EuroQol 5-Dimension 5-Level; iMCQ, iMTA Medical Costs Questionnaire; iPCQ, iMTA Productivity Costs Questionnaire; iVICQ, iMTA Valuation of Informal Care Questionnaire; Qolie-31P, Patient-Weighed Quality Of Life In Epilepsy; QUESTE, QUality of life and Economic evaluation after neuroSTimulation in Epilepsy; VNS, vagus nerve stimulation.

Blinding

There will be no blinding of study participants, participating doctors or researchers.

Sample size calculation

The primary outcome measure will be the difference in Qolie-31P score between the preoperative and...
postoperative measurements. The minimum change on the Qolie-31-P that is also considered clinically relevant (Minimal Clinical Important Change, MCIC) in this patient group is 5.19 points.\textsuperscript{33}

We expect that in our patient group similar differences that have been found in previous research can be observed for both treatments. However, because much more patients will be referred for VNS compared with DBS, comparing the differences between those groups will be difficult. In order to measure an MCIC of 5.19 points or above baseline with a power of 80\%, a minimum of 34 patients need to be included. Considering a drop-out of 25\%, this would require a minimum of 43 patients. No power analysis is performed to carry out economic evaluations. The rule of thumb is that data from at least 100 patients is needed to carry out a reliable economic evaluation.

Annually, about 50 patients are indicated for VNS or ANT-DBS in The Netherlands. The majority of these patients are indicated to get a VNS implantation. A large part of VNS implantations and all ANT-DBS implantations, take place in the participating centres. Based on an inclusion period of 4 years, with a drop-out of 25\%, we expect to reach the number of 100 patients within this inclusion period. However, because ANT-DBS implantation is performed less often than VNS implantation, there will be more VNS than DBS inclusions.

\textbf{Data analysis plan}

Baseline characteristics will be described as mean with SD or as median and first and third quartiles for continuous variables, and as number and percentage for categorical variables. Incomplete data will be imputed if the percentage of patients missing at least one outcome is greater than 5\%. In that case, multiple imputation with full conditional specification will be used to impute the data. The number of imputations will be set equal to the percentage of incomplete patients.

Differences in mean disease-specific (Qolie-31-P) and generic (EQ-5D-5L) QoL as well as the burden on informal caregivers (iVICQ) and productivity (iPCQ) will be tested between follow-up and baseline using the paired samples t-test. In addition, we will use linear mixed-effects regression to model continuous outcomes over the entire follow-up time. The choice of covariance matrix for random effects and the way in which temporal correlation will be modelled will be determined using the Akaiake information criterion.

Seizure frequency based on the ILAE outcome classification will be described in absolute numbers and percentages and then dichotomised into 1 vs 2–6.\textsuperscript{34} The McNemar test will then be used to test whether the proportions differ between the presurgery and postsurgery measures. The association between change in QoL and seizure reduction will be tested using the independent samples t-test, by calculating the QoL change score for each patient and comparing the mean change score for those scoring ILAE 1 with those scoring ILAE 2–6.

\textbf{Patient and public involvement}

Patients were not involved in the study design.

We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing our report, which provides evidence-based recommendations for the minimum content of a clinical trial protocol.\textsuperscript{35}

\textbf{ETHICS AND DISSEMINATION}

The Board of Directors of MUMC\textsuperscript{+}, epilepsy centre Kempenhaeghe, AUMC, MST and SEIN all gave permission for this study to commence. The medical ethics committee of MUMC\textsuperscript{+} decided that this study does not fall under the Medical Research Involving Human Subjects Act (WMO, number: METC 2020-2439 A1). This decision was later adopted by the medical ethics committees of the other participating centres.

\textbf{DATA STATEMENT}

The pseudonymised research data will be stored in an online research database called Castor Electronic Data Capture (Castor EDC). A secured IBM SPSS Statistics (Version 28.0) document, with Castor patient number, without name and date of birth, will be stored on a computer secured by hospital software. These data will also be stored on an external hard drive in a locked cabinet in the hospital. Only the principal investigator and the executive investigator have access to the key of the code and thus to the traceable patient data. They will always follow the Dutch law for the protection of privacy and personal data, the Algemene Verordening Gegevensbescherming (AVG). All patients must sign informed consent forms. The findings of this study will be presented at (inter) national conferences and in peer-reviewed journals.

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\textsuperscript{5}Smeets JJAS, et al. BMJ Open 2023;13:e071575. doi:10.1136/bmjopen-2023-071575
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