Outcome report

Resource centre Health Technology Assessment, AIIMS Jodhpur

Evaluation of Phase-2 in Drug-Resistant Epilepsy: Health Technology Assessment Perspective

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Proposal presented in TAC meeting

Background:

Epilepsy is a disease of the brain, which is categorized not only by a lasting tendency to cause seizures, but also by its neurologic, cognitive, psychological, societal, and economic consequences (1). It is characterized by recurrent seizures with brief episodes of involuntary movement that may involve a part of the partial body or the entire body and are sometimes accompanied by loss of consciousness and control of bowel or bladder function (2). It is one of the chronic non-communicable diseases which come across in routine neurologic practices and affect approximately 6.5 crore people worldwide (3). While for a majority of people with epilepsy (PWE), the seizures get controlled with anti-epileptic drugs (AED), nearly 30% of PWE are drug-resistant (4). People with drug-resistant epilepsy (DRE) are at an increased risk for early death, disabilities and a variety of psychosocial problems (5). People of LMIC are ill-equipped to tackle the enormous medical, psychosocial, and economic challenges posed by DRE (6). DRE is associated with developmental delay in infants and young children along with severe disability, morbidity and mortality. It can be either medically or surgically treatable with appropriate therapy. Epilepsy is also a neurological disorder regularly seen in the paediatric population and one-fifth of them do not respond to drugs considered as DRE. (7) Children and adolescents with DRE are at increased risk for poor long-term intellectual and psychosocial outcomes, along with a poor health-related quality of life. Effective management of epilepsy is especially important in children, as uncontrolled seizures may have detrimental effects on normal functional neurodevelopment and subsequent quality of life. (8) Epilepsy in children has an incidence rate of approximately 45 per 100,000 children per year with the greatest incidence in the first year of life. (9) About 20% of children with epilepsy will have chances to get DRE as a failure of adequate trials of 2 tolerated and appropriately chosen anti-epileptic drugs (AEDs), whether as monotherapy or in combination. The economic burden of epilepsy is greatest in patients with DRE and found that 20-25% of children and adults with DRE accounted for approximately 38% of annual direct and 86% of indirect medical costs of epilepsy. (10)

Epilepsy in the Indian context

India carries a massive burden of epilepsy and about one crore PWE, including thirty lacs with DRE and ten lacs potential candidates for epilepsy surgery (ES). (11). The prevalence of epilepsy in India is higher in the rural population (1.9%) as compared with the urban population (0.6%) and the overall prevalence is 0.56 to 1% . (3).

Treatment strategy and option for epilepsy

The treatment goals for epilepsy are no seizures without any side effects, and time to control, but these goals are too often unmet. Comprehensive epilepsy management must go beyond seizure control and include the prevention of comorbidities to improve the quality of life (5). Using the right diagnosis and monotherapy with the first line of anti-epileptic drugs, the majority of cases achieve cure or control of their epilepsy, however, some of them do not (12). Unfortunately, there is an enormous primary and secondary treatment gap in medical management along with limitations of the Indian health care system i.e. limited resources, facilities, etc (11)(13). Similarly, many eligible patients will not avail the advantage of epilepsy surgery because of illiteracy, ignorance and the wrongly perceived risks, costs and complications of epilepsy surgery (11)(13). The main treatment options for DRE is surgery, which includes diagnostic phases- Phase 1: Non- invasive pre-surgical evaluation (high-resolution MRI, video scalp EEG, PET scan, SPECT, MEG and detailed neuropsychological assessment) and Phase 2: Invasive pre-surgical evaluation (Intracranial EEG). Epilepsy surgery represents a valuable treatment option for DRE patients. Epilepsy surgery aims to control seizures by resection of the epileptogenic tissue while avoiding neuropsychological and other neurological deficits by sparing essential brain areas (14). When data is insufficient or non-concordant to specify a strategy, diagnostic intracranial electrodes may be considered to further clarify the situation (Phase 2). The clinical profile and outcomes of the patient influence the need for Phase 1 study v/s progressive to phase 2. Noninvasive approaches (Phase 1) are crucial for localization of the epileptogenic zone. However they may fail in particular situation, for which invasive procedures (Pase 2) are useful in pinpointing the seizure focus the resection of which will lead to possible seizure freedom.(15)

The economic aspect of epilepsy management

Epilepsy is a cost-intensive disorder and the total annual cost per person amounted to ₹ 13,755 reported in India. The total economic burden of epilepsy in India was found to be ₹ 68.75 billion as per 2001 data, which constituted 0.5 % of the total GNP of India (16).

Gap analysis

Epilepsy is a major neurologic disorder with major social impact. Surgery is a valuable option for patients, who doesn't respond to antiepileptic drugs. The treatment via surgery option has the following concerns:

- Social impact, and costs of the disease
- Clinical results, efficacy, and safety of surgery
- Quality of life after surgery
- Economic impact and productivity regained after surgery

Epilepsy is associated with an extensive economic burden that is inversely proportional to the degree of seizure control. Evidence from reported studies showed that the association of surgery and medical treatment has a fourfold higher success rate in terms of seizure freedom than medical treatment alone (17). According to a recent survey, till 2016, approximately 7143 epilepsy surgeries have been performed across 38 centres in India and currently, 734 epilepsy surgeries are carried out every year in India (18).

Challenges and opportunities for epilepsy management

The ultimate goal to make epilepsy treatment available for all the ten million people and reduce the financial and human cost of epilepsy is feasible only by a concerted effort by the government as well as non-governmental agencies and by educating patients, the general public, and medical communities. If we succeed in taking care of people with drug-resistant epilepsy, by rational usage of anti-epileptic medication, surgery, and alternate methods including lifestyle changes, there will be a substantial decrease in the overall burden of the disease in India (11).

Policy Statement

Evaluation of drug-resistant epilepsy (DRE) Phase 2

Aim

To assess the cost-effectiveness of drug-resistant epilepsy (DRE) Phase 2 patients followed by treatment

Potential objectives:

- To assess the cost of treatment of DRE via Phase 1 and Phase 2 followed by surgery.

- To assess the incremental cost-effectiveness ratio in terms of cost per QALY gained and cost per seizure control.

PICOT

Population:

Patients with drug-resistant epilepsy

Intervention:

Phase 1+ Phase 2 of DRE patient followed by surgery

Comparator:

- Surgery after Phase 1 evaluation
- Best medical treatment after phase 1 evaluation

Outcomes to be measured

Primary Outcome: Incremental cost-effectiveness ratio in terms of cost per QALY gained.

Secondary outcome: Assessment of cost in comparison to other methods (cost saved/ cost incurred) after Phase 1 and Phase 1+Phase 2 followed by surgery.
Impact of epilepsy surgery and Phase 1 and Phase 2 in DRE patients in terms of QALY gained and seizure control.

Time Horizon for the intervention/ parameter:

Lifetime horizon for the patient with DRE

Methodology
Study Setting

A Health Technology Assessment of cost-effectiveness of management of drug-resistant epilepsy (DRE) patients via Phase 1 and Phase 2 followed by epilepsy surgery based on secondary data in the Indian context

Perspective

A Health system, as well as abridged societal perspective will be taken into account as per the HTAIn reference case.

Search for input model parameters

Parameters about the study will be derived from published literature through systematic searches/targeted reviews as and where required. A literature review will be done in various online search engines like Pubmed, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database for systematic reviews, Meta-analysis, randomized clinical trials (RCTs), observational studies and CEA registry for economic evaluations using the MESH specific terms. The search strategy will be developed using appropriate Boolean terms, MEDLINE via PubMed strategy and will be adapted as per the specific norms of each separate electronic database. Data will be collected by searching these keywords: "surgery", "Phase 2 epilepsy" and "drug-resistant epilepsy".

The following input parameters will be searched for using the above-mentioned search methods:

1. **Demographic and epidemiological data**
   - Incidence and prevalence of DRE
   - DRE Mortality rate
   - Complications related to the treatment of DRE

2. **Clinical effectiveness**

   The search for the clinical effectiveness of the intervention strategy in terms of the following assessments will be conducted:
   - Proportion of responders
     - Responders to medicines
     - Responders to surgery
   - Change in seizure severity and frequency
   - Change in the seizure-free interval, seizure duration, seizure pattern and functional capacity
   - Incidence, prevalence and severity of adverse events at different time points.

3. **Health-related quality of life**
   - QoL of DRE patient after phase 2 intracranial evaluation
   - QoL of DRE patient after surgery
   - QoL after Complications of surgery

* QoL after delayed treatment (surgical and medical)

Model

A Decision tree framework will be used to assess the incremental cost-effectiveness ratio in terms of cost per seizure control and cost per QALY gained. Probabilities, cost and utilities will be derived through available documents literature and interviews. Microsoft Excel will be used to construct the decision tree mathematically

Sensitivity analysis

Sensitivity analysis [One-way and Probabilistic sensitivity analysis (PSA)] will be undertaken to ascertain the robustness of the study to address the potential parameter, structural and model uncertainties. Probabilistic sensitivity analysis (PSA) will be done using Macros Visual basic applications (VBA) coding. Input parameters will be varied by limits from literature/ by pre-fixed 20%. Appropriate distributions will be assigned for PSA.

Budget Impact Analysis

Budget Impact Analysis will be carried out to assess the cost implications of the intervention strategy adopted for the government.

Conceptual framework of Decision tree for Drug Resistant Epilepsy
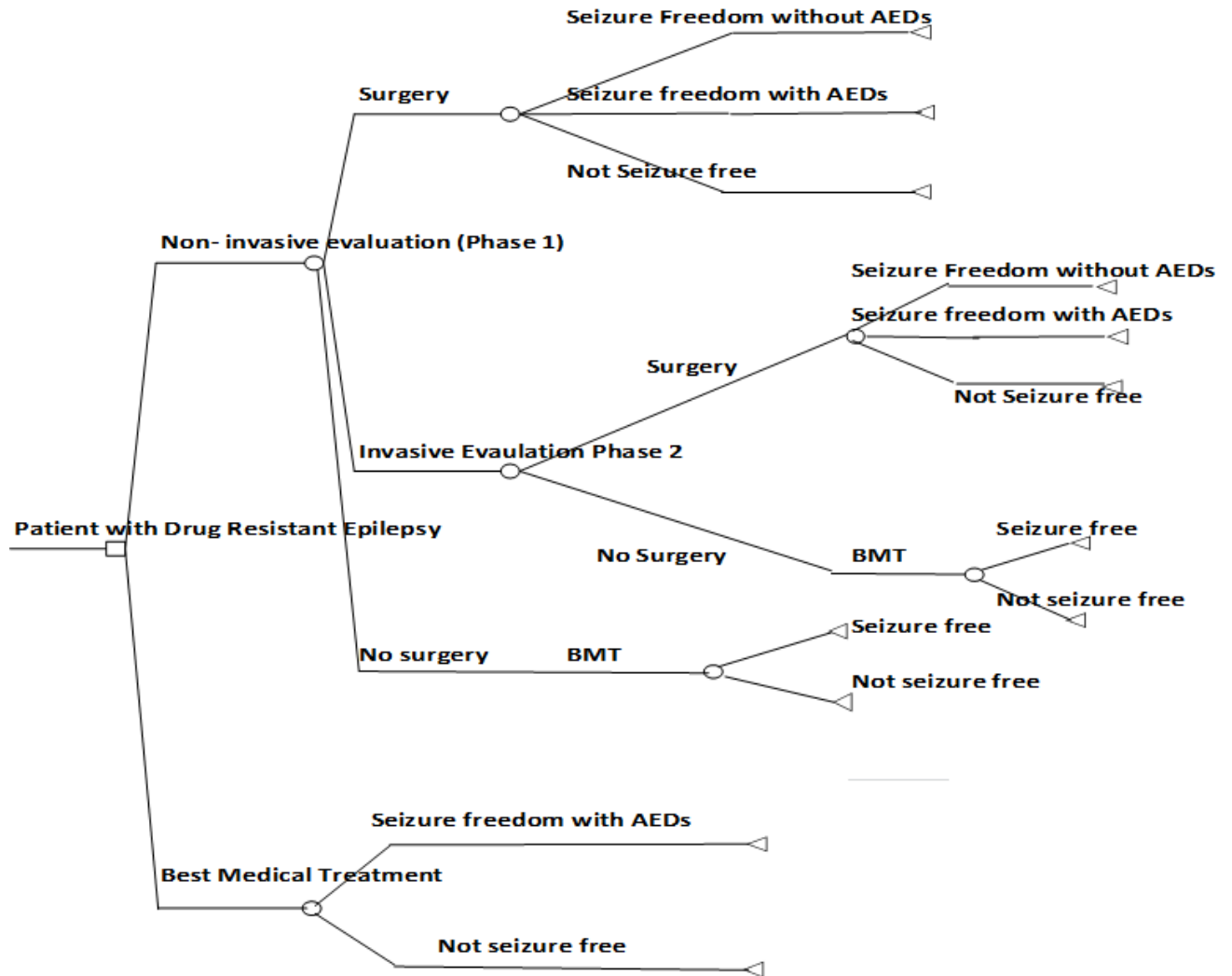
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Comment received: For Phase 2 effectiveness of epilepsy surgery data is necessary which is not available.

Closure report: A topic 'Evaluation and management of Phase 2 Drug resistant epilepsy-Health Technology Assessment Perspective' was given to AIIMS Jodhpur by NHA to conduct Health Technology Assessment. The proposal was presented in 32nd TAC meeting on December 20, 2022. As there is no secondary data available on clinical-effectiveness (Randomized controlled trials) of Phase 2 Drug Resistant Epilepsy (DRE) patients so Health Technology Assessment (HTA) for this study cannot be conducted as per the comments from TAC members. Although, we conducted a systematic review and meta-analysis (Evaluation of invasive intracranial Electroencephalography diagnosis and surgery in Drug-Resistant Epilepsy patients: A Systematic Review and Meta-analysis) using prospective studies of phase 2 DRE. The PROSPERO registration number for the systematic review is CRD42022361204 and the manuscript is under process.