

Online Resource 1: Delphi Panel Study

A Cost-utility Analysis of Add-on Cannabidiol Versus Usual Care Alone for the Treatment of Seizures Associated With Tuberous Sclerosis Complex in England and Wales

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Declarations

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Conflicts of interest

All authors met the ICMJE authorship criteria and had full access to the relevant data. Neither honoraria nor payments were made for authorship. Colin Burke and Emma Tyas are employees of Lumanity, Inc.; Catriona Crossan, Matthew Hemstock, and Dawn Lee were employees of Lumanity, Inc., when the study was conducted and are currently employed by Putnam, Source Health Economics, and the University of Exeter, respectively. Sally Bowditch is an employee of Jazz Pharmaceuticals, Inc., and holds stock / stock options in Jazz Pharmaceuticals, Inc.

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Delphi Panel Study

A two-round Delphi panel study was conducted to elicit information on the relationship between tuberous sclerosis complex (TSC) and TSC-associated neuropsychiatric disorders (TAND), and healthcare resource utilization (HCRU) [1,2]. In round one, 10 experts participated with consensus achieved at a predefined threshold of 70%; in round two, 9 experts were involved and the predefined threshold for consensus was >70% [1]. The Delphi method is well suited for this as it is a widely used, accredited, and accepted method for achieving convergence of opinions concerning real-world knowledge solicited from experts [3]. The strengths of the Delphi method include quasi-anonymity, which avoids dominance of one opinion, and iteration, thereby allowing individuals to change their opinions based on the information and explanations provided by other panelists in previous rounds [4]. It has been noted that qualitative expressions of expert judgment elicited by the Delphi method can be used to scope economic models, while quantitative expressions can contribute towards defining point estimates of parameters and characterizing uncertainty [3,5].

Delphi Panel Study – TAND

Questions were included on [1]:

- TAND profile – to identify relevant aspects of TAND
- Potential impact of reduction in seizures on TAND aspects and level of reduction required to impact progression of TAND
- Age at which treatment of seizures may be beneficial in reducing TAND

Key Aspects of TAND Identified by the Delphi Panel Study

As part of the first round of the Delphi study, respondents were asked to provide information on the main aspects of TAND [1]. The respondents identified six key TAND aspects for inclusion in the model analysis: delayed development, behavioral issues, intellectual disability, autism spectrum disorder, attention deficit hyperactivity disorder, and anxiety disorders (panic, phobia, separation anxiety disorder).

Seizure Reduction Required to Impact the Progression of TAND

During the second round of the Delphi study, there was consensus that all aspects of TAND would be impacted by a new treatment that reduces seizure frequency. During the first round, respondents were asked if a reduction in seizures would impact the development of TAND symptoms favorably. If they answered yes, they were asked a follow-up question to elicit the minimum percentage reduction in seizures required to impact favorably on the development of TAND symptoms. Based on the responses in the first round, respondents were then asked in the second round if they agreed with the average minimum figure. Although consensus was not achieved, 60% agreed a reduction of ~50% would be required for a favorable impact on TAND symptoms [1].

Age at Which It Is Beneficial to Treat to Impact the Progression of TAND

The Delphi panel asked the clinical experts to provide opinions on the age at which the treatment of seizures would be beneficial in reducing the progression of TAND [1]. The mean age returned as part of the first round of the Delphi panel was 4.3 years. As some of the respondents in the first round returned non-numerical responses, this was further explored in the second round, and age categories were provided (<2 years, ≥2–<5 years, ≥5–<12 years, ≥12 years). The respondents

were asked to respond to what age a patient would need to be treated for a benefit to be seen for each TAND aspect. The Delphi panel returned varying levels of responses regarding the age of onset at which the treatment of seizures may be beneficial to reduce the progression of TAND (Online Resource Table 1) [1]. The trend in responses suggests that earlier effective treatment provides a better long-term prognosis.

Online Resource Table 1 Age at which treatment of seizures would be beneficial in reducing or preventing TAND (Delphi panel response)

Aspect of TAND	Before what age should treatment commence? The number of panelists agreeing			
	<2 years	≥2–<5 years	≥5–<12 years	>12 years
Delayed development	9/9	6/9	3/9	3/9
Behavioral issues	9/9	8/9	5/9	4/9
Intellectual disability	9/9	6/9	3/9	1/9
ASD	9/9	4/9	1/9	1/9
ADHD	9/9	6/9	3/9	1/9
Anxiety disorders	9/9	8/9	5/9	3/9

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; TAND, tuberous sclerosis complex-related neuropsychiatric disorders.

Delphi Panel Study – HCRU

The Delphi panel aims included understanding HCRU for patients with TSC-associated epilepsy and estimating this as accurately as possible. Patients with TSC-associated epilepsy may have many other manifestations; however, for the purposes of the questionnaires, we noted to the experts that we were focusing on the HCRU associated with the management of their epilepsy only. Additionally, HCRU for patients with TSC-associated epilepsy may be affected by seizure type, seizure frequency, and the patients' age [2].

As such, the following definitions were provided:

- Patient seizure types: although there are other categories of seizure types, the Delphi panel focused on the two types relevant to the cost-effectiveness model – focal seizures with impairment of awareness and convulsive seizures (focal to bilateral generalized seizures; generalized tonic-clonic, tonic, clonic, and atonic seizures)
- Seizure frequency: HCRU was collected relating to the seizure frequency categories which were used in the model: no seizures (seizure free), ≤ 2 seizures, $>2-\leq 7$ seizures, or $>7-\leq 50$ seizures per week
- HCRU by the service being attended: based on patients attending a pediatric service or patients attending an adult service

Note that during the NICE appraisal of cannabidiol for TSC-associated epilepsy, it was deemed by the committee that the hospitalization rates obtained through the Delphi panel were overestimated. Consequently, the NICE committee approved a 50% decrease in the hospitalization rates, and this decrease was incorporated in the hospitalization rates utilized for this analysis [6].

Further details on the HCRU costs and model inputs are described in ESM3: Model Inputs and Costs.

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