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Focused Ultrasound Thalamotomy and Other Interventions for Medication-Refractory Essential Tremor: An Indirect Comparison of Short-Term Impact on Health-Related Quality of Life

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ABSTRACT

Background: Up to 50% of essential tremor patients are refractory to medication and require alternative treatment to achieve tremor relief. This study aimed to identify and analyze evidence supporting the use of the emerging magnetic resonance-guided focused ultrasound (MRgFUS) compared to alternative stimulatory and ablative interventions for the treatment of medication-refractory essential tremor: radiofrequency thalamotomy, unilateral deep brain stimulation (DBS), and stereotactic radiosurgery. **Methods:** A systematic literature review was conducted to identify clinical, health-related quality of life (HRQoL), and economic evidence for each intervention. Because of the lack of comparative evidence captured, a feasibility assessment was performed to determine possible comparisons between interventions, and newly established matching-adjusted indirect comparison and simulated treatment comparison techniques were used to conduct a comparison between unilateral DBS aggregate data and MRgFUS individual patient data. **Results:** The systematic literature review identified 1,559 records, and screening yielded 46 relevant articles. The captured studies

demonstrated that radiofrequency thalamotomy, DBS, stereotactic radiosurgery, and MRgFUS all exhibit clinical efficacy, with variation in onset and duration of tremor relief, and are each associated with a unique safety profile. The matching-adjusted indirect comparison and simulated treatment comparison results demonstrated no evidence of a difference in efficacy (measured by Clinical Rating Scale for Tremor Total) and HRQoL (measured by Clinical Rating Scale for Tremor Part C) outcomes between MRgFUS and unilateral DBS in the short term (≤ 12 months). **Conclusions:** This study provides preliminary evidence that MRgFUS could elicit similar short-term tremor- and HRQoL-related benefits to DBS, the current standard of care, and allowed for the first robust statistical comparison between these interventions.

Keywords: deep brain stimulation, essential tremor, focused ultrasound, indirect comparison.

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Introduction

Essential tremor (ET) is a chronic, progressive neurologic disease, characterized primarily by rhythmic and oscillatory tremor of the upper limbs [1]. It is one of the most common movement disorders, with an estimated global prevalence of approximately 0.4% [2]. The disease imposes a substantial burden on patients as a result of both physical and psychosocial disability, leading to reduced health-related quality of life (HRQoL) [3–6]. ET further imposes an overall societal burden because of patients' lost earnings, combined with elevated health care resource use [7–9].

Pharmacologic treatments are recommended by the American Academy of Neurology as first-line treatment for ET symptoms

[10,11]. However, it is estimated that 30% to 50% of ET patients will not experience any therapeutic effect [10,12] or will suffer from side effects [13]. The availability of alternative treatments is thus of high importance to medication-refractory patients.

Ablative and stimulatory interventions, which target regions of the thalamus believed to be involved in the pathophysiology of ET, include radiofrequency thalamotomy (RfT), deep brain stimulation (DBS), the current standard-of-care for medication-refractory ET [14]), and stereotactic radiosurgery (SRS) [15–17]. These involve surgical intervention, implantation of stimulatory hardware, or ionizing radiation to achieve their treatment effect [18–20]. Lastly, magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging technology for treatment of

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Table 1 – Criteria used to assess eligibility of abstracts and full texts.

| Criteria | Requirement for inclusion |
|----------------------|---|
| Population | Adult patients with medication-refractory ET |
| Intervention | MRgFUS, unilateral DBS, RfT, or SRS |
| Comparator | Any or none |
| Outcomes | Efficacy (including CRST Total score and the Part A and B subscores [22,23]), AEs, HRQoL (including CRST Part C subscore and QUEST [24]), costs |
| Design | Interventional clinical trials, including RCTs and nonrandomized designs, observational studies, economic evaluations, and SLRs, meta-analyses or HTA reviews (for hand-searching only) |
| Other considerations | English language, journal articles published after 1990 |

AE, adverse event; CRST, Clinical Rating Scale for Tremor; DBS, deep brain stimulation; ET, essential tremor; HRQoL, health-related quality of life; HTA, health technology assessment; MRgFUS, magnetic resonance-guided focused ultrasound; QUEST, Quality of Life in Essential Tremor Questionnaire; RCT, randomized controlled trial; RfT, radiofrequency thalamotomy; SLR, systematic literature review; SRS, stereotactic radiosurgery.

medication-refractory ET and involves the use of focused ultrasound with real-time feedback and monitoring. MRgFUS does not involve open brain surgery techniques such as craniotomy and allows precise ablation of the thalamic target without the need for general anesthesia [17,21].

The availability of comparative clinical evidence between interventions is essential to help health care decision makers understand which treatments offer the greatest value to patients and payers. A systematic literature review (SLR) and subsequent feasibility assessment and indirect comparison, using recently established population-adjusted statistical methodology, were therefore performed to identify and analyze evidence for the use of MRgFUS and comparator interventions (RfT, unilateral DBS, SRS) for treatment of medication-refractory ET patients.

Methods

Systematic Literature Review

Identification and selection of studies

An SLR was performed to identify clinical, HRQoL, and economic evidence associated with the use of MRgFUS and its most relevant comparators (RfT, unilateral DBS, and SRS) in the treatment of medication-refractory ET, according to a predefined protocol. MEDLINE, Embase and The Cochrane Library databases were searched from inception to November 3, 2016. Key conference proceedings published after 2014 were searched, in addition to hand-searches of reference lists of relevant SLR and health technology assessments identified in the electronic searches. Additional horizon scanning searches through the Google and Google Scholar platforms were carried out to identify relevant published literature not captured by the electronic database or hand-searches. Publication titles and abstracts and subsequent potentially relevant full texts were assessed for eligibility by two independent reviewers according to the criteria outlined in Table 1 [22–24]. For full details of the search terms and eligibility criteria used in this study, please see Appendix 1 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2018.03.015>.

Data extraction and quality assessment

For each study that met the eligibility criteria, data relating to study design, methodology, baseline patient characteristics, and outcomes of interest were extracted and verified by an independent reviewer. Individual patient data (IPD) from MRgFUS-treated patients from the MRgFUS versus sham randomized controlled trial (RCT) [25] were obtained from InSightec Ltd. [26]. The quality of each study ultimately included was assessed using an adapted version of the Downs and Black checklist [27], and total quality

scores were calculated, where each item denoted “Yes” (indicative of a reduced risk of bias) was assigned 1 point; those with “No”, “Unclear” or “NA” were assigned 0 points. The Clinical Rating Scale for Tremor (CRST) and Quality of Life in Essential Tremor (QUEST) were selected as efficacy and/or HRQoL outcomes of interest in the SLR, as they are widely used tremor-specific rating scales (see Appendix Table 3 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2018.03.015>) [22–24,28].

Indirect Comparison

Feasibility assessment

An assessment was first performed to determine the feasibility of conducting a network meta-analysis in line with the standard methodology recommended by the National Institute for Health and Care Excellence (NICE) [29] to make a comparison between MRgFUS, unilateral DBS, RfT, and SRS. In anticipation of capturing limited RCT data in the SLR, other options such as indirect treatment comparison (ITC) using Bucher's method [30] or methods that permit inclusion of single-arm trials, such as matching-adjusted indirect comparison (MAIC) [31,32] and simulated treatment comparison (STC) [33], were also explored. The feasibility of conducting a comparison was assessed for several outcomes of interest: CRST Total score; Part A, Part B, and Part C subscores; and QUEST. The feasibility of conducting a comparison for safety outcomes was not formally assessed owing to a lack of consistent definitions of adverse events (AEs) or standard reporting of safety measures between studies. Studies included in the SLR were assessed according to the criteria listed in Table 2.

Assessment of heterogeneity

Heterogeneity was assessed between the IPD of MRgFUS-treated patients in the pivotal RCT and the aggregate data for the alternative interventions from studies meeting the feasibility assessment criteria. The assessment was conducted in terms of patient characteristics deemed to be clinically relevant and having the potential to influence the outcomes of the analysis: age, disease duration, and baseline score were assessed for each outcome of interest. The former two characteristics are known predictive factors for increased tremor severity [34], with baseline scores for outcomes of interest also representative of disease severity at baseline. The characteristics were chosen for the analysis after consultation with clinicians from the list of all patient characteristics reported in the pivotal RCT. Unreported characteristics were not assessed because they could not be adjusted for in the analysis. Differences in study design were also reviewed to assess the potential for unobserved bias.

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