NHS England Evidence Review:

Unilateral thalamic Gamma Knife Stereotactic Radiosurgery (SRS) for medication refractory essential tremor

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Unilateral thalamic Gamma Knife Stereotactic Radiosurgery (SRS) for medication refractory essential tremor

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1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of unilateral thalamic gamma knife stereotactic radiosurgery (SRS) compared to current standard care in patients with medication refractory essential tremor (ET) who are either not suitable for deep brain stimulation (DBS) or for whom previous DBS treatment has failed. Patients are considered medication refractory (resistant) once two or more trials of appropriate medical therapy have failed. Essential tremor includes familial essential tremor, non-familial essential tremor, and benign essential tremor. Tremor may be unilateral or bilateral. Tremor related to Parkinson's disease is not relevant to this review.

Unilateral thalamic gamma knife SRS, also referred to as stereotactic radiosurgery, stereotactic surgery, or gamma knife thalamotomy, is a radiosurgical technique to treat tremor. Dosing ranges from 60 to 150Gy, with lower dosing given at the edge of target, and higher dosing at the centre of the target, given as a single fraction.

First-line treatment for medication refractory ET is deep brain stimulation, a surgical procedure that involves electrodes being inserted into a specific area of the brain. This is the preferred intervention in patients who have a bilateral tremor. Whilst it is an effective procedure, it is invasive, and the main risks are bleeding within the skull, stroke and infection. It also involves hardware being left within the brain, so regular follow up is needed to check batteries. Current standard care (with no unilateral thalamic gamma knife stereotactic radiosurgery) for people who are not suitable for DBS, or for whom DBS has previously failed, involves conservative management, which can include occupational therapy and physiotherapy, and unilateral transcranial MRI-guided focussed ultrasound thalamotomy. This can also be defined as brain focused ultrasound or high intensity focussed ultrasound.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with gamma knife SRS more than others, as well as the treatment dose of gamma knife SRS in the population of interest.

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2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of unilateral thalamic gamma knife stereotactic radiosurgery (GK SRS) compared to current standard care in patients with medication refractory essential tremor (ET) who are either not suitable for deep brain stimulation (DBS) or for whom previous DBS treatment has failed. The searches for evidence published since January 2013 were conducted on 7 December 2023 and identified 87 references; an additional reference was identified from the included systematic review. The 88[1] titles and abstracts were screened, and 22 full text papers were obtained and assessed for relevance.

Eight papers were identified for inclusion, one systematic review with network meta-analysis (NMA), five case series[2] (four with pre- and post-treatment data, one with change from baseline only), and two cost analyses. The NMA only included non-comparative studies: three case series of 62 people treated with unilateral GK SRS and 15 case series of 464 people who underwent focussed ultrasound thalamotomy (FUS-T), included here as the comparator MRgFUS (magnetic resonance-guided focussed ultrasound). The NMA was part of a wider systematic review that also included 11 non-comparative studies for analysis of safety. The five case series ranged in size from 27 to 73 people with ET. Three of the case series reported outcomes at 12 months and one had a mean follow-up of 28 months. One case series reported follow-up from four to six months with a median time to last follow up of 28 months and a longer follow-up for a small subset of patients at over three years. One case series took place in Japan, one case series was conducted in the USA, and the other three case series were evaluated by teams in Marseille, France.

In terms of clinical effectiveness:

- **Quality of life (critical outcome).** One case series provided very low certainty non-comparative evidence that, compared with pre-treatment Quality of life in Essential Tremor (QUEST) scores, there is a *statistically significant* improvement in quality of life for people with medication-refractory ET at 12 months following unilateral GK SRS.

- **Improvement in tremor severity scale (critical outcome).** One NMA provided very low certainty evidence that the improvement seen in Fahn-Tolosa-Marin Tremor Rating Scale (FTM TRS) A+B scores following GK SRS was 1.31 points (95% confidence interval -2.96 to 5.99) less that the improvement seen following MRgFUS, with a 73% probability that MRgFUS was the more efficacious treatment. Four case series provided very low certainty non-comparative evidence of *statistically significant* improvements from baseline in tremor, writing, drawing, and drinking scores, and the remaining case series reported the percentage of overall improvement without reporting statistical significance. Median follow-up times ranged from 12 to 54 months. At 12 months, *statistically significant* improvements from baseline FTM TRS tremor score of between 57% and 68% were reported for people with medication refractory ET (and *statistically significant* improvements from baseline FTM TRS tremor score of between 54% and 63% were reported for people with either ET or PD). A *statistically significant* improvement of 56% from baseline FTM TRS tremor score was reported at 28 months.

[1] Including one study identified from a systematic review

[2] Three were retrospective case series, one was a prospective case series, and it was not possible to determine whether the fifth was conducted prospectively or retrospectively.

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Improvements in FTM TRS tremor score at a median of 28 months[3] were in the region of 1.25 points (where the scale's possible score range from 0 to 4), with improvements in tremor being experienced by 93% of people. At the longest follow-up (> 3 years), 29% had complete resolution of tremor, 43% had an excellent outcome, and 29% had a good outcome for tremor control.

- **Activities of daily living (ADL) (critical outcome).** Two case series provided very low certainty evidence of an improvement in ADL (on the Bain questionnaire) at approximately 12 months after unilateral GK SRS. A *statistically significant* improvement from baseline of approximately 24 points was reported by one study, and another study reported an improvement of 72%.

- **Symptom recurrence (important outcome).** One case series provided very low certainty non-comparative evidence that the rate of symptom recurrence was approximately 10% at a median of 28 months follow-up and approximately 11% at a longer follow-up of 54 months.

- **Intraoperative pain (important outcome).** No evidence was identified for this outcome.

- **Length of hospital stay (important outcome).** No evidence was identified for this outcome.

In terms of safety:

- One systematic review (11 studies, 449 people; no comparative analysis) and two retrospective case series reported very low certainty evidence for adverse events at between one year and 152 months following unilateral GK SRS. Pooled data from 11 studies found that, at between 11 and 52 months follow-up, the most commonly reported adverse effects were motor weakness (3%) and dysarthria (2%). In the two case series, the overall rate of adverse effects ranged from 0 at 12 months to 22% at 28 months, with the most commonly reported adverse effects being lip numbness (11%), finger numbness (11%), dysarthria (7%) and complete hemiparesis (7%).

In terms of cost effectiveness:

- One study examined the cost of GK SRS compared with DBS[4] from a US perspective, with costs reported in 2016 USD. The study included costs for people with medication-refractory tremor, but this was not specified to be ET. The total cost of GK SRS was $10,811.77 per patient.

- One study examined the cost effectiveness of GK SRS compared with MRgFUS for people with ET. The study used a US provider perspective and reported costs in 2016 US dollars. Effectiveness, based on one-year data and measured by the amount of mean± standard deviation (SD) utility added, was statistically significantly higher for MRgFUS (0.194±0.005) than for GK SRS: (0.116±0.00; p<0.001 for difference). The base case result showed that MRgFUS ($20,593±$1402) is more costly than GK SRS ($20,013±$1036; p=0.654 for difference) but more effective. The authors concluded that

[3] The length of follow-up at the time of reporting post-GK SRS outcomes in the Niranjan et al 2017 paper is ambiguous. The text states that clinical and imaging follow-up was collected 4 to 6 months post-GK SRS, and that median time to last follow-up was 28 months (range 6 to 152).
[4] DBS results not reported here, as not within scope.

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MRgFUS is cost-effective for tremor compared with GK SRS but noted that if the effectiveness of MRgFUS were found to be less than initially measured (or the cost greater), GK SRS may be the more cost-effective procedure. The study authors estimated the cost of MRgFUS based on the cost of GK SRS with some additional reimbursement for the MRI scan and intraoperative mapping, and they acknowledge that this may be an underestimate of the actual cost.

In terms of subgroups:

- One case series reported data for one person with ET who had previously undergone DBS. This person's tremor score had improved by 45.7% at 12 months follow-up and their ADL score had improved by 66.7%. Although this study reported results for a single patient who had had previous DBS, it did not suggest that people with previous DBS might benefit from GK SRS more than the wider population of interest. The improvement in this patient was less that that reported for the overall cohort, where the overall tremor score improvement was 63.4% and the ADL improvement was 72.2%.
- The same case series of 50 people with either ET (n=36) or PD (n=14) reported data for the subgroup of people with an improvement in ADL of at least 50%. At 12 months, those patients whose ADL scores improved by at least 50% had a median improvement in ADL of 96%, compared with a median of no improvement in people with < 50% improvement. People with ≥50% improvement in ADL had a median improvement in global tremor score of 65%. The median improvement in global tremor score was not reported for those with ADL improvement of less than 50%. Although this study analysed improved versus non-improved patients, it is unclear what the clinical characteristics of these patients are and therefore it is not possible to identify a subgroup of patients that may benefit from GK-SRS from this data.

In terms of dosage:

- A maximum dose of 130 Gy was delivered in four case series, and one case series describes giving a median central dose of 140 Gy (range 130 to 150). The systematic review with NMA does not describe the doses used in the included studies.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The evidence was of very low certainty for all reported outcomes, mainly due to the lack of comparative data (other than the indirect comparison for tremor reduction). The NMA was limited by the inclusion of only non-comparative studies and lack of any direct evidence within the network, together with a considerable level of heterogeneity and decreased transitivity. Selection bias may have affected the non-comparative studies, mainly due to unclear information about consecutive/complete enrolment of eligible patients, exclusion of particular patients by two studies, and a mixed population of a majority of ET patients and a minority of PD patients in one study.

The majority of studies provided both pre-treatment and post-treatment data, with an assessment of change from baseline. Two studies provided more limited outcome data, with one retrospective case series only making a statement about the overall percentage improvement in FTM TRS, and one prospective case series providing the percentage

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improvement in tremor scores with a p-value for change from baseline, but the percentage improvement in ADL without any p-value for the change. In one prospective case series, an independent movement disorders neurologist assessed the FTM TRS by viewing videos before and at one year after unilateral GK SRS in a randomised, blinded manner. Where other studies used self-reported tools, there is the possibility of reporting bias.

There are a number of limitations of the two economic evaluations included in this report. Both studies were undertaken from the US perspective and used Medicare costs, so may not be generalisable to the UK. One study only reported costs with no consideration of treatment effects, and was for medication refractory tremor in general, not specifically ET, so may be of limited value in determining the cost effectiveness of GK SRS for people in the UK with medication refractory ET. The only study to have developed a cost-effectiveness model appears to have used a short time horizon of one year (the timescale for the effectiveness data), so may not capture any longer-term benefits of reduced tremor. In addition, the cost-effectiveness study only reported the costs and effectiveness of the two modelled treatments separately, with no ICER or cost per QALY reported for the comparison between GK SRS and MRgFUS. The study authors also acknowledged a likely underestimate of the true cost of MRgFUS, which could reduce its apparent cost-effectiveness.

Conclusion

The studies identified for this review provide very low certainty evidence that GK SRS resulted in a statistically significant improvement in quality of life, tremor scores and ADL for people with medication resistant ET who are not suitable for DBS or for whom DBS treatment has failed. The studies did not report whether changes were clinically meaningful for patients. No results for intraoperative pain and length of hospital stay were identified for inclusion. The indirect evidence comparing GK SRS to MRgFUS was limited and of very low certainty and should be treated with caution. It is uncertain to what extent the 2016 US based cost effectiveness outcomes are generalisable to the NHS in England in 2024.

Due to these limitations, it was not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of GK SRS compared to MRgFUS in people with medication refractory ET.

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3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people with medication refractory essential tremor, what is the clinical effectiveness of gamma knife SRS compared with current standard care?
2. In people with medication refractory essential tremor, what is the safety of gamma knife SRS compared with current standard care?
3. In people with medication refractory essential tremor, what is the cost-effectiveness of gamma knife SRS compared with current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from gamma knife SRS more than the wider population of interest?
5. From the evidence selected, what was the treatment dose of gamma knife SRS in the population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 7 December 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

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4. Summary of included studies

Eight papers were identified for inclusion (Bolton et al 2022, Horisawa et al 2023, Kondapavulur 2023, McClelland et al 2017, Niranjan et al 2017, Ravikumar et al 2017, Tuleasca et al 2018, Witjas et al 2015).

One paper was a systematic review with network meta-analysis (Kondapavulur et al 2023), one reported pre- and post-treatment data from a case series used for an imaging study (Bolton et al 2022), two were retrospective case series with analysis of pre- and post-treatment data (Horisawa et al 2023, Niranjan et al 2017), one was a prospective case series with pre- and post-treatment data (Witjas et al 2015), one was a retrospective case series that reported improvement from baseline only as part of an imaging study (Tuleasca et al 2018), and two reported cost-effectiveness data from a US perspective (McClelland et al 2017, Ravikumar et al 2017).

The systematic review and meta-analysis by Kondapavulur et al 2023 included tremor scores in an indirect comparison of GK SRS (3 studies) versus focussed ultrasound thalamotomy (FUS-T) (15 studies). One of these studies (Bolton et al 2022) is also included in this review, for the outcomes of quality of life (QoL) and activities of daily living (ADL) that were not reported by the systematic review. Kondapavulur et al 2023 used a wider group of 11 case series for a pooled summary of adverse events, including two studies that are included in this review for other outcomes (Niranjan et al 2017, Witjas et al 2015). The adverse event aggregates are reported here as noncomparative data as Kondapavulur et al 2023 did not report a formal indirect comparison between GK SRS and FUS-T for this outcome, only reporting the pooled aggregates for each type of study separately.

The papers described the interventions using different terminology. Bolton et al 2022 referred to left ventral intermediate nucleus (VIM) GK SRS; Horisawa et al 2023, Niranjan et al 2017 and Witjas et al 2015 described the intervention as GK thalamotomy; Kondapavulur et al 2023 referred to stereotactic radiosurgery thalamotomy; McClelland et al 2017 used the term GK SRS VIM; Ravikumar et al 2017 called the intervention SRS (but the studies from which the clinical information was taken did specify GK SRS) and Tuleasca et al 2018 refer to the intervention as left unilateral VIM radiosurgery. In this report, terminology has been standardised to GK SRS for all studies.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Bolton et al 2022 Case series Single centre in Marseille, France	34 patients with medication-refractory right-dominant ET • Mean±SD age, years: 70.6±9.12 (range 49 to 83) • Mean±SD symptom duration, months: 35.53±18.28 (range 5 to 61) No subgroups reported	**Intervention** Unilateral GK SRS, with 4 mm isocentre and maximum dose of 130 Gy **Comparison** None	**Critical outcomes** • Quality of life (QUEST) at baseline and 12 months • Improvement in tremor severity scale[a] (HEAD) at baseline and 12 months **Important outcomes** • ADL at baseline and 12 months
Horisawa et al 2023	27 patients with ET[b] • Mean±SD age, years: 78.1±4.2 (range 74 to 81)	**Intervention**	**Critical outcomes** • Improvement in tremor severity scale (FTM-CRS

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Study	Population	Intervention and comparison	Outcomes reported
Retrospective case series Single centre in Japan	• Disease duration, years: 20 (range 10 to 30) No subgroups reported	Unilateral GK SRS with 4 mm isocentre and maximum dose of 130 Gy **Comparison** None	(tremor, writing, spiral drawing subscales) at mean follow-up of 28.3±17.6 months **Important outcomes** • Safety: adverse events at mean follow-up of 28.3±17.6 months
Kondapavulur et al 2023 SR with NMA (3 GK SRS studies for NMA of efficacy, 11 studies for pooled AE) Study locations not reported	526 medication-refractory ET patients in 18 studies Efficacy • GK SRS: 3 studies, pooled n=62 • FUS-T: 15 studies, pooled n=464 Adverse events analysis • 11 GK SRS studies (pooled n=449)[c] GK SRS (n=62) • Age, years: mean 71.1 • Disease duration, years: mean 33.6 • Follow-up time, months. Mean±SD: 14.1 FUS-T (n=464) • 152 (29.2%) female • Age, years: mean 63.3 • Disease duration, years: mean 59.5 • Follow-up time, months. Mean: 10.3 No subgroups reported	**Intervention** Unilateral GK SRS: no further details reported **Comparison** FUS-T: no further details reported	**Critical outcomes** • Improvement in tremor severity scale (FTM-TRS at baseline and 12 months **Important outcomes** • Safety: adverse events at 11 to 152 months follow-up
McClelland et al 2017 Cost analysis, US perspective	Treatment of medication-refractory tremor, not specifically ET. GK SRS costs derived from 2016 Medicare fee schedule. No subgroups reported	**Intervention** GK SRS: no further details reported **Comparison** DBS VIM (not within scope for this review)	**Important outcomes** • Cost effectiveness (reported as cost data only)
Niranjan et al 2017 Retrospective case series Single centre, Pittsburgh, USA	73 patients with medication-refractory ET • Age, years: mean: 77 (range 43 to 92) • Disease duration, years mean: 15 (range 2 to 70) No subgroups reported	**Intervention** Unilateral GK SRS with 4-mm isocentre and dose of 140 Gy (range 130 to 150) **Comparison** None	Median time to last follow-up[d]: 28 months (range 6 to 152), with additional long-term follow-up for 28/73 patients at > 3 years (Clinical and imaging follow-up was collected 4 to 6 months post-GK SRS.) **Critical outcomes** • Improvement in tremor severity scale, FTM-TRS (tremor, writing, drawing, drinking subscales).

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Study	Population	Intervention and comparison	Outcomes reported
			Important outcomes • Symptom recurrence • Safety[e]
Ravikumar et al 2017 Cost effectiveness (decision analysis model), US perspective	32 studies of 958 patients with medication-refractory ET with unilateral tremor GK SRS: 5 studies (n=260) MRgFUS: 4 studies (n=83) DBS: 23 (n=615) (not included here) Mean age[f] • GK SRS: 74.1±2.0 • MRgFUS: NR Mean follow-up time • GK SRS: 22.4±13.6 • MRgFUS: 7.3±5.6 No subgroups reported	**Intervention** GK SRS: no further details reported **Comparison** MRgFUS: no further details reported	**Important outcomes** • Cost effectiveness (measured as additional cost and utility, but no cost per QALY calculated).
Tuleasca et al 2018 Retrospective case series, single centre, Marseille, France	52 patients with medication-refractory right-sided ET Age, years, mean±SD: 71.6±6.9 No subgroups reported	**Intervention** Unilateral GK SRS; 4 mm isocentre and a maximum dose of 130 Gy **Comparison** None	**Critical outcomes** • Improvement in tremor severity scale (FTM-TRS at 1 year) **Important outcomes** • Safety (side effects) at 1 year
Witjas et al 2015 Prospective case series, single centre, Marseille, France	50 patients with medication-refractory ET (n=36) or Parkinsonian tremor (n=14) • Age, years, mean 75.5 (range 60 to 91) • Disease duration, years, mean: 22.4 (range 4 to 74) Subgroups • IP: ≥50% improvement in ADL vs NIP: <50% improvement in ADL • Patients with previous DBS	**Intervention** Unilateral GK SRS; 4 mm isocentre and a maximum dose of 130 Gy **Comparison** None	**Critical outcomes** • Improvement in tremor severity scale (FTM-TRS at 1 year: global score, upper limb score, rest, posture, intention, drinking[g], pouring, drawing and writing) **Important outcomes** • ADL[h] at 1 year • Safety[i]

Abbreviations
ADL: activities of daily living; AE: adverse events; DBS: deep brain stimulation; ET: essential tremor; FTM CRS: Fahn-Tolosa-Marin Clinical Rating Scale; FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale; FUS-T: focussed ultrasound thalamotomy; GK SRS: gamma knife stereotactic radiosurgery; Gy: gray; HEAD: Tremor Research Group Essential Tremor Rating Assessment; min: minute; mm: millimetre; MRgFUS: magnetic resonance-guided focused ultrasound; N: number; NMA: network meta-analysis; NR: not reported; QALY: quality adjusted life year; QUEST: quality of life in essential tremor; SD: standard deviation; VIM: ventral intermediate nucleus

Footnotes
[a] FTM-TRS is also reported by Bolton et al 2022 at baseline and 12 months, but is not reported separately here as the result is included in the Kondapavulur et al 2023 NMA.
[b] Horisawa et al 2023 do not state clearly that people were medication refractory, but this is implied within the text: "Many patients with ET do not respond to medical therapy and require surgical treatment".
[c] There was no direct evidence for GK SRS vs FUS-T. Indirect evidence for efficacy was included in the NMA, but Kondapavulur et al 2023 did not undertake a formal indirect comparison for AE and only reported data for individual studies, none of which compared FUS-T vs GK SRS data. Therefore, only AE from the GK SRS studies are reported here.

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Study	Population	Intervention and comparison	Outcomes reported
[d] The length of follow-up at the time of reporting post-GK SRS outcomes in the Niranjan et al 2017 paper is ambiguous. The text states that clinical and imaging follow-up was collected 4 to 6 months post-GK SRS, and that median time to last follow-up was 28 months (range 6 to 152). [e] Niranjan et al 2017: AE are included within the Kondapavulur et al 2023 SR so are not reported separately in this review. [f] Ravikumar et al 2017: it is not clear what the ± figures are in the published paper. Assumed to be SD. [g] Witjas et al 2015 used the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale for the item 'drinking from a cup'. [h] ADL assessed using the Bain 25-item self-questionnaire, scored from 1 (able to do the activity without difficulty) to 4 (cannot do the activity). [i] Witjas et al 2015: AE are included within Kondapavulur et al 2023 SR so not reported separately in this review.			

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5. Results

In people with medication refractory essential tremor, what is the clinical effectiveness and safety of unilateral thalamic Gamma Knife Stereotactic Radiosurgery (SRS) compared with current standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Quality of life **Certainty of evidence:** Very low	Quality of life is important to patients as it provides an indication of an individual's general health and their self-perceived well-being. Measurement of quality of life can help inform patient-centred decision making. In total, one case series presented non-comparative results for quality of life at 12 months after unilateral GK SRS for people with medication-refractory ET. **At approximately 12 months follow-up** • One case series[5] (Bolton et al 2022) reported a *statistically significant* improvement from baseline in quality of life for 34 people with medication-refractory ET who underwent unilateral GK SRS. The mean±SD (range) QUEST score[6] improved from 45.46±16.4 (12 to 80) before radiosurgery to 23.16±16.57 (1 to 57) at 12 months after GK SRS; a change of -24.79±13.21 (-47 to -2); p<0.0001 **(VERY LOW)** **One study provided very low certainty non-comparative evidence that there is a *statistically significant* improvement from baseline in quality of life for people with medication-refractory ET at 12 months following unilateral GK SRS.**
Improvement in tremor severity scale **Certainty of evidence:** Very low	This is important to patients because an improvement in their tremor suggests that treatment has been successful, and their symptoms will be improved. In total, one NMA reported a formal indirect comparison (and non-comparative data from a SR), and 5 case series[7] reported non-comparative results for improvements in tremor severity scale (using the FTM TRS[8]) for people with medication-refractory ET who underwent unilateral GK SRS. One case series also reported the HEAD[9] assessment. Across the studies, follow-up ranged from 12 months to 54 months in the longest study. **At approximately 12 months follow-up** • One NMA (Kondapavulur et al 2023) reported that the weighted mean difference in the absolute reduction in FTM TRS A+B scores between MRgFUS and GK SRS was 1.31 (95% CI -2.96 to 5.99). This was calculated as an indirect comparison between the pooled aggregate of 3 GK SRS studies' (n=62) mean reduction in A+B scores (-10.26, 95% CI[10] -14.21 to -5.96) and the pooled aggregate of 15 MRgFUS studies' (n=464) mean reduction in A+B scores (-11.57 (95% CI -13.3 to -9.93). The NMA results indicated a 72.8%

[5] It is not clear from the text whether this was a prospective or retrospective case series.
[6] QUEST scores range from 0 to 100, with benefit indicated by a lower score.
[7] Three retrospective case series, one prospective case series and one case series where it was not clear from the text whether this was a prospective or retrospective case series.
[8] FTM TRS is a 21-item scale, of which 9 items relate to tremor and three to drawing (A, B, C). Each item's score has a possible range of 0 to 4.
[9] Bolton et al 2022 describe the HEAD score as an assessment of head tremor on the Tremor Research Group Essential Tremor Rating Assessment. Possible scores range from 0 to 3, with benefit indicated by a lower score.
[10] Although Figure 2 in Kondapavulur et al 2023 appears to report credible intervals rather than confidence intervals, the main text of the paper describes confidence intervals, which would be consistent with their frequentist approach rather than a Bayesian analysis, so the data have been reported here as confidence intervals.

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Outcome	Evidence statement
	probability that MRgFUS is the more efficacious treatment for tremor reduction, compared with GK SRS. **(VERY LOW)** • The systematic review that underpinned the NMA (Kondapavulur et al 2023) also reported the pooled scores at baseline and 12-month follow-up for the GK SRS and MRgFUS studies separately (with no formal indirect comparison). The pooled mean FTM TRS A+B score (mean±SD) at baseline was 20.2±5.6 in the 3 GK SRS studies (n=62), improving to 9.0±8.7 at an average of 14.1 months follow-up. This represented an absolute tremor reduction of -11.41 (95% CI -17.39 to -5.44; I^2=84%) and a relative tremor reduction of 56.5%. In the 15 pooled MRgFUS studies (n=464), the baseline score of 18.3±5.2 improved to 7.3±5.7 at approximately 10.3 months follow-up. This represented an absolute tremor reduction of -11.13 (95% CI -12.74 to -9.52; I^2=79%) and a relative tremor reduction of 60.8%. **(VERY LOW)** • One case series (Tuleasca et al 2018) reported the percentage of overall improvement in FTM TRS at 12 months for 52 people with medication-refractory ET treated with unilateral GK SRS. The mean±SD (range) improvement was 67.8%±32.9% (range 0 to 100%). **(VERY LOW)** • One case series (Witjas et al 2015) reported that: ○ the median (IQR) FTM TRS global tremor score (unblinded assessment) improved *statistically significantly* from baseline by 63.40% (38.3 to 90.6); p<0.0001 between baseline and 12 months for 50 people (36 with ET and 14 with PD). **(VERY LOW)** ○ the median (IQR) FTM TRS upper limb tremor score (blinded assessment) improved *statistically significantly* from baseline by 54.2% (36.2 to 79.2); p<0.0001 between baseline and 12 months for 50 people (36 with ET and 14 with PD). **(VERY LOW)** • One case series (Bolton et al 2022) reported a *statistically significant* average improvement from baseline in HEAD score for 34 people with medication-refractory ET 12 months after unilateral GK SRS. The mean±SD (range) pre-treatment scores of 1±0.85 (0 to 2) improved to 0.56±0.75 (0 to 3), representing an average change of -0.39±0.83 (-2 to 1); p=0.035. **(VERY LOW)** **At approximately 28 months follow-up** • One case series (Horisawa et al 2023) reported subscales of the FTM CRS at a mean±SD follow-up of 28.3±17.6 months for 27 people with ET[11]: ○ a *statistically significant* improvement from baseline in FTM tremor score from 3.4±0.6 before treatment to 1.5±1.2 after unilateral GK SRS (55.9% improvement; p<0.001). **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM writing score from 3.3±1.0 before treatment to 1.4±1.1 after unilateral GK SRS (57.6% improvement; p<0.001). **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM spiral drawing score from 3.2±0.8 before treatment to 1.6±1.3 after unilateral GK SRS (50% improvement; p<0.001). **(VERY LOW)** • One case series (Niranjan et al 2017, n=73/91)[12] reported: ○ a *statistically significant* improvement from baseline in FTM TRS tremor score with a mean±SD score of 3.19±0.74 pre-treatment improving to 1.23±1.01; p<0.0001. **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM TRS writing score with a mean±SD score of 2.97±0.75 pre-treatment improving to 1.25±1.09; p<0.0001. **(VERY LOW)**

[11] Horisawa et al 2023 did not state clearly that people were medication refractory, but this was implied in the text.
[12] The length of follow-up in the Niranjan et al 2017 paper is ambiguous. The text states that clinical and imaging follow follow-up was collected 4 to 6 months post-GK SRS, but also mentions that median time to last follow-up was 28 months (range 6 to 152).

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Outcome	Evidence statement
	○ a *statistically significant* improvement from baseline in FTM TRS drawing score with a mean±SD score of 3.16±0.67 pre-treatment improving to 1.26±1.12; p<0.0001. **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM TRS drinking score with a mean±SD score of 3.14±0.67 pre-treatment improving to 1.36±1.21; p<0.0001. **(VERY LOW)** • One case series (Niranjan et al 2017, n=73) also reported a summary of the improvements in FTM TRS score: ○ 68 (93.2%) experienced improvement in at least 1 FTM score ○ 57 (72.2%) improved in all 4 FTM scores ○ 3 (3.7%) improved in 3 FTM scores ○ 6 (7.6%) improved in 2 FTM scores ○ 2 (2.5) improved in 1 FTM score ○ 11 (13.8%) did not improve in any FTM score ○ 68 (93.2%) experienced improvement in tremor ○ 67 (91.8%) noted functional improvement (writing, drawing, drinking from a cup) for the treated arm, of whom: ▪ 25 (34.2%) had excellent functional improvement (a reduction of ≥3 levels or a score of 0) ▪ 59 (80.8%) had good or better (a reduction of 1 to <3 levels) ▪ 67 (91.8%) had satisfactory or better improvement (<1 level) ○ 18 (24.7%) experienced tremor arrest or complete recovery of function, with median time to tremor arrest of 4 months (range 2 weeks to 12 months). **(VERY LOW)** **At approximately 54 months follow-up** • One case series (Niranjan et al 2017) had longer-term follow-up for a subset of 28/91 patients followed up for > 3 years (median 54 months, range 37 to 152) and reported: ○ a *statistically significant* improvement from baseline in FTM TRS tremor score with a mean score[13] of 3.1 pre-treatment improving to 1.0 at approximately 54 months; p<0.01. **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM TRS writing score with a mean score of 2.85 pre-treatment improving to 0.96 at approximately 54 months; p<0.001. **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM TRS drawing score with a mean score of 2.96 pre-treatment improving to 0.79 at approximately 54 months; p<0.001. **(VERY LOW)** ○ a *statistically significant* improvement from baseline in FTM TRS drinking score with a mean score of 3.11 pre-treatment improving to 1.04 at approximately 54 months; p<0.001. **(VERY LOW)** • One case series (Niranjan et al 2017) also reported a summary of the improvements in FTM TRS score for a subset of 28/91 patients followed up for > 3 years (median 54 months, range 37 to 152): ○ 2/28 (28.57%) had complete resolution of tremor ○ 12/28 (42.8%) had an excellent outcome for tremor (tremor score of 1) ○ 8/28 (28.57%) had good outcome tremor control (tremor score of 2). **(VERY LOW)** **One NMA provided very low certainty evidence that the improvement seen in FTM TRS A+B scores for people with ET who underwent GK SRS was 1.31 points (95% CI -2.96 to 5.99) less that the improvement seen for people with ET who underwent MRgFUS, with a 73% probability that MRgFUS was the more efficacious treatment.** **Four studies also provided very low certainty non-comparative evidence that people with medication refractory ET who underwent unilateral GK SRS experienced *statistically significant* improvements from baseline in tremor, writing, drawing, and drinking scores, and one other study reported the percentage of overall improvement without reporting statistical significance.**

[13] Niranjan et al 2017 did not present SD for the long-term data.

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Outcome	Evidence statement
	Follow-up times ranged from 12 to 54 months. At 12 months, *statistically significant* improvements from baseline in tremor of between 57% and 68% were reported for people with medication refractory ET (and *statistically significant* improvements from baseline of 54% to 63% in a study of people with either ET or PD). A *statistically significant* improvement from baseline of 56% was reported at 28 months. Improvements in tremor at a median of 28 months were in the region of 1.25 points (where the scale's possible score range from 0 to 4), with improvements in tremor being experienced by 93% of people. At the longest follow-up (> 3 years), 29% had complete resolution of tremor, 43% had an excellent outcome, and 29% had a good outcome for tremor control.
Activities of daily living **Certainty of evidence:** Very low	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. In total, two case series[14] reported activities of daily living at approximately 12 months after unilateral GK SRS radiosurgery for people with medication-resistant ET. Both studies used the Bain questionnaire[15] to assess activities of daily living. **At approximately 12 months follow-up** • One case series (Bolton et al 2022) reported a *statistically significant* improvement from baseline in Bain score at 12 months after unilateral GK SRS for 34 people with medication-refractory ET. The mean±SD (range) pre-treatment scores of 29.59±11.39 (13 to 49) reduced to 6.03±11.26 (0 to 41), representing an average change (improvement) of -23.56±12.35 points (-48 to 2); p<0.0001. **(VERY LOW)** • One case series (Witjas et al 2015) reported that the mean[16] improvement in Bain score from baseline to 12 months follow-up was 72.2% (range 0% to 100%) but reported no statistical tests or any further data. This study included 50 people, 36 with ET and 14 with PD. **(VERY LOW)** **These studies provided very low certainty evidence of an improvement in activities of daily living for people with medication-refractory ET at approximately 12 months after unilateral GK SRS. A *statistically significant* improvement from baseline of approximately 24 points on the Bain questionnaire was reported by one study, and another study reported an improvement of 72% on the Bain questionnaire scores but did not report on statistical significance.**
Important outcomes	
Symptom recurrence **Certainty of evidence:** Very low	This is important to patients as the aim of treatment would be to reduce their essential tremor symptom burden and avoid further interventions of treatments. In total, one retrospective case series presented non-comparative results for symptom recurrence at a median time of 28 months after unilateral GK SRS for 73[17] people with medication-refractory ET, and longer follow-up of three or more years for 28 people with medication-refractory ET. **At approximately 28 months follow-up** • One case series (Niranjan et al 2017) reported that 7 (9.6%) of 73 patients had symptom recurrence within a median of 28-months follow-up. **(VERY LOW)**

[14] One prospective case series and one case series where it was not clear from the text whether this was a prospective or retrospective case series.
[15] The Bain self-reported questionnaire has 25 items, and each is scored from 1 (able to do the activity without difficulty) to 4 (cannot do the activity); benefit is indicated by a lower score.
[16] Although the Methods text in Witjas et al 2015 states that results are median (IQR), the result "72.2% (0% to 100%)" is stated to be the mean improvement.
[17] Niranjan et al 2015 analysed data from 73 people who had at least 6 months follow-up out of a total of 91 treated people.

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Outcome	Evidence statement
	At approximately 54 months follow-up • One case series (Niranjan et al 2017) reported that 3 (10.7%) of 28 patients followed-up for more than three years had symptom recurrence within a median of 54-months follow-up. **(VERY LOW)** **One study provided very low certainty non-comparative evidence that the rate of symptom recurrence after unilateral GK SRS for people with medication-refractory ET was approximately 10% at a median of 28 months follow-up and approximately 11% at a longer follow-up of 54 months.**
Intraoperative pain **Certainty of evidence:** Not applicable	This is important for patients as if a procedure is more likely to be comfortable and pain-free, they may take this into consideration when making autonomous decisions about their treatment. **No evidence was identified for this outcome.**
Length of hospital stay **Certainty of evidence:** **Not applicable**	This is important to patients as a shorter hospital admission or stay will have a less disruptive impact on their lives. **No evidence was identified for this outcome.**
Safety	

Adverse effects
Certainty of evidence:
Very low
	These outcomes are important to patients because they will impact on their treatment choices and recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.
	In total, one systematic review and two retrospective case series reported adverse events experienced by people with medication-refractory ET at between one year and 152 months following unilateral GK SRS.
	At 12 months follow-up
	• One case series (Tuleasca et al 2018) reported that 0 of 52 patients with ET experienced any side effects within a year of unilateral GK SRS. **(VERY LOW)**
	At approximately 28 months follow-up
	• One case series (Horisawa et al 2023) reported that 21 of 27 people with ET[18] (77.8%) had no adverse events at a mean±SD follow-up of 28.3±17.6 months, and that 6 (22.2%) had at least one adverse event (some patients had >1). The following were reported:
	  ○ Dysarthria: 2 (7.4%)
	  ○ Dysphagia: 1 (3.7%)
	  ○ Lip numbness: 3 (11.1%)
	  ○ Finger numbness: 3 (11.1%)
	  ○ Complete hemiparesis: 2 (7.4%)
	  ○ Foot weakness: 1 (3.7%)
	  ○ Death: 1 (3.7%). **(VERY LOW)**
	At approximately 11 to 152 months follow-up
	• One systematic review (Kondapavulur et al 2023) reported pooled adverse event data from 11 GK SRS studies (n=449) but did not present any statistical analysis[19]:
	  ○ Imbalance/gait disturbance: 0 (0%)
	  ○ Sensory disturbance: 5 (1.1%)
	  ○ Dysmetria: 0 (0%)

[18] Horisawa et al 2023 did not state clearly that people were medication refractory, but this was implied in the text.
[19] There was no direct evidence for GK SRS vs FUS-T. Indirect evidence for efficacy was included in the NMA, but Kondapavulur et al 2023 did not undertake a formal indirect comparison for AE and only reported data for individual studies, none of which compared FUS-T vs GK SRS data.

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Outcome	Evidence statement
	○ Dysgeusia: 0 (0%) ○ Motor weakness: 12 (2.7%) ○ Dysarthria: 11 (2.4%) ○ Other: 3 (0.7%). **(VERY LOW)** **These studies provide very low certainty non-comparative evidence that the overall rate of adverse effects ranged from 0 at 12 months to 22% at 28 months. The most commonly reported adverse effects among people with ET who had unilateral GK SRS included lip numbness (11%), finger numbness (11%), dysarthria (7%) and complete hemiparesis (7%). Pooled data from 11 studies found that, at between 11- and 152-months follow-up, the most commonly reported adverse effects were motor weakness (2.7%) and dysarthria (2.4%)**
Abbreviations ADL: activities of daily living; CI: confidence interval; ET: essential tremor; FTM CRS: Fahn-Tolosa-Marin Clinical Rating Scale; FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale; GK SRS: gamma knife stereotactic radiosurgery; HEAD: Tremor Research Group Essential Tremor Rating Assessment; IQR: interquartile range; MRgFUS: magnetic resonance-guided focused ultrasound; NMA: network meta-analysis; PD: Parkinson's disease; QUEST: quality of life in essential tremor	

In people with medication refractory essential tremor, what is the cost effectiveness of gamma knife SRS compared with current standard care?

Outcome	Evidence statement
Cost of GK SRS in 2016 USD	One study (McClelland et al 2017) examined the cost of GK SRS compared with DBS[20] from a US perspective, with costs reported in 2016 USD. The study included costs for people with medication-refractory tremor, but this was not specified to be ET. The study did not include any effectiveness data, and costs were based on 2016 Medicare Ambulatory Payment Classification costs for GK SRS and the RVU code, multiplied by a conversion factor of $37.942[21] per RVU to obtain the neurosurgeon cost for VIM radiosurgery. • The total cost of GK SRS was $10,811.77 per patient
Cost-effectiveness of GK SRS	One study (Ravikumar et al 2017) examined the cost effectiveness of GK SRS compared with MRgFUS for people with ET. The study used a US provider perspective and reported costs in 2016 USD. The time period of the model is based on one-year effectiveness data. • Effectiveness[22], mean±SD GK SRS: 0.116±0.003 MRgFUS: 0.194±0.005 Difference: p<0.001 • Cost (2016 USD) GK SRS: $20,013±$1036 MRgFUS: $20,593±$1402 Difference: p=0.654 The base case result showed that MRgFUS is more costly than GK SRS but more effective. The authors concluded that MRgFUS is cost-effective for tremor compared with GK SRS but noted that if the effectiveness of MRgFUS were found to be less than initially measured (or the cost greater), GK SRS may be the more cost-effective procedure. The authors estimated the cost of MRgFUS based on the cost of GK SRS with some additional reimbursement for the MRI scan and

[20] DBS results not reported here, as not within scope.
[21] The conversion factor used by McClelland et al 2017 was taken from their earlier publication on Parkinson's Disease.
[22] Ravikumar et al 2017: Effectiveness measured by amount of utility added by the procedure. The higher the number, the more effective. It is not clear what the ± figures are in the published paper. Assumed to be standard deviations.

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Outcome	Evidence statement
	intraoperative mapping. They acknowledge that this may be an underestimate of the actual cost. **Cost effectiveness is an important outcome for decision makers, although it may not be a priority to individual patients. Limitations of the two economic evaluations included here are that the US perspective may not be generalisable to the UK, one study only reported costs with no indication of cost-effectiveness (i.e. no consideration of treatment effects), and the short time horizon used by the only study to have developed a cost-effectiveness model. In addition, the cost-effectiveness study only reported the costs and effectiveness of the two modelled treatments separately, with no ICER or cost per QALY reported for the comparison between GK SRS and MRgFUS, although these were reported for the comparison between DBS and GK SRS.**
Abbreviations DBS: deep brain stimulation; ET: essential tremor; GK SRS: gamma knife stereotactic radiosurgery; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; RVU: relative value unit; SD; standard deviation; USD: United States dollars; VIM: ventral intermediate nucleus	

From the evidence selected, are there any subgroups of patients that may benefit from gamma knife SRS more than the wider population of interest?

Subgroup	Evidence statement
People with previous DBS	One case series (Witjas et al 2015) reported subgroup results for one person with ET[23] who underwent unilateral GK SRS having previously been treated with DBS, with a follow-up time of 12 months. • For the person with previous DBS, tremor score had improved by 45.7% at 12 months. • For the person with previous DBS, ADL score improved by 66.7% at 12 months. **Although Witjas et al 2015 reported results for a single patient who had had previous DBS, they do not suggest that people with previous DBS might benefit from GK SRS more than the wider population of interest. The improvement in this patient was less that that reported for the overall cohort, where the overall tremor score improvement was 63.4% and the ADL improvement was 72.2%.**
Improved patients (with ≥50% improvement in ADL) vs non-improved patients (<50% improvement in ADL)	One case series (Witjas et al 2015) divided patients with ET or PD[24] into 'improved' or 'non-improved' based on their ADL score (50% or more improvement vs <50% improvement, respectively). Improved patients (n=38) • Median (IQR) ADL improvement at 12 months: 96.4% (87.5% to 100%) • Median (IQR) global tremor score at baseline: 17 (14 to 22) • Median (IQR) global tremor score improvement at 12 months: 64.9% (50% to 86%) Non-improved patients (n=12) • Median (IQR) ADL improvement: 0% (5.9% to 15.2%)[25] • Median (IQR) global tremor score at baseline: 21 (14.8 to 25) • Median (IQR) global tremor score improvement: NR

[23] Witjas et al 2015 report previous DBS separately for people with ET and people with PD, so only the ET results are reported here.
[24] Witjas et al 2015 did not report results separately for the 36 patients with ET but did note that "Neither the tremor etiology (PD or ET) nor the tremor score severity influenced the outcome".
[25] Witjas et al 205 describe this as "12 were nonimproved (median ADL improvement 0% [5.9%–15.2%])." From elsewhere in the text, the range in brackets is assumed to be the IQR, but it is not clear why this does not include the median value of 0%.

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Subgroup	Evidence statement
	Although Witjas et al 2015 analysed improved vs non-improved patients, it is unclear what the clinical characteristics of these patients are and therefore it is not possible to identify a subgroup of patients that may benefit from GK-SRS from this data.
Abbreviations ADL: activities of daily living; DBS: deep brain stimulation; ET: essential tremor; GK SRS: gamma knife stereotactic radiosurgery; IQR: interquartile range; n=number; NR: not reported		

From the evidence selected, what was the treatment dose of gamma knife SRS in the population of interest?

Outcome	Evidence statement
Treatment dose of GK SRS	In four case series, a maximum dose of 130 Gy was delivered (Bolton et al 2022, Horisawa et al 2023, Tuleasca et al 2018, Witjas et al 2015). The case series by Niranjan et al 2017 describes giving a median central dose of 140 Gy (range 130 to 150). The systematic review and NMA by Kondapavulur et al 2023 does not describe the doses used in the included studies.
Abbreviations GK SRS: gamma knife stereotactic radio surgery; Gy: gray; NMA: network meta-analysis	

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6. Discussion

This evidence review considered the clinical effectiveness and safety of unilateral GK SRS compared to current standard care in patients with medication refractory ET who are either not suitable for DBS or for whom previous DBS treatment has failed. The critical outcomes of interest were quality of life, improvement in tremor severity scale, and ADL. Important outcomes were symptom recurrence, intraoperative pain, length of hospital stay and safety. Evidence on cost effectiveness was also sought.

Limited comparative evidence was available from one NMA for the outcome of improvement in tremor severity scale at 12 months follow-up, based on a formal indirect comparison between three GK SRS case series (62 patients) and 15 MRgFUS case series (464 patients). Non-comparative evidence was available from five case series, ranging in size from 27 to 73 people with ET. One study reported pre- and post-treatment data from a case series used for an imaging study, two were retrospective case series with analysis of pre- and post-treatment data, one was a prospective case series with pre- and post-treatment data, and one was a retrospective case series that reported improvement from baseline only as part of an imaging study. Three of the case series reported outcomes at 12 months, one had a mean follow-up of 28 months, and the follow-up time in one case series was ambiguous, interpreted as from four to six months post GK SRS with a median time to last follow up of 28 months, and a longer follow-up for a small subset of patients at over three years. Three of the case series mentioned that improvements in tremor were generally seen within approximately five months, so all of the studies were long enough to capture evidence for this outcome, with related impacts on quality of life and ADL likely to be closely related to this time frame given the close relationship between improvements in ADL and improvements in tremor calculated in one of the case series. In addition, two cost analyses were identified, neither of which had a UK/NHS perspective.

The mean ages of patients in the included studies were between 70 and 78 years old, with an overall age range of 43 to 92 across the studies. Disease duration varied considerably, with one case series reporting a mean duration of 36 months, and others reporting mean durations of between 15 and 34 years. All studies specified that patients were medication refractory with the exception of one case series, where this was implied in the text. All studies reported unilateral GK SRS, although terminology varied between studies.

One case series took place in Japan, one case series was conducted in the USA, and the other three case series were evaluated by teams in Marseille, France. The study dates were not specified for one case series (Tuleasca et al 2018), so it is possible that there may have been some overlap in inclusion of patients assessed by Witjas et al 2015, who were treated at the same hospital between 2004 and 2010. The systematic review with NMA did not specify the locations of the included studies. Both cost evaluation studies took place in the USA. The extent to which the clinical and cost effectiveness evidence is generalisable to the UK/NHS setting is therefore not certain.

Only one case series (34 patients) reported the critical outcome of quality of life, using the QUEST tool, at approximately 12 months follow-up. Comparative evidence was available from one NMA for the outcome of improvement in tremor severity scale at approximately 12 months follow-up. Pooled tremor scores from the systematic review on which the NMA was based were also included in this review to provide wider context for the NMA results. In addition, five case series provided non-comparative data for this outcome, with follow-up at 12 months in three of the case series, and at a median of 28 months in two case series (with three-year data for a small number of participants in one of these). All studies used the FTM tool to measure tremor improvement, with two case series reporting scores for writing, drawing and drinking in addition

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to the tremor subscore. Non-comparative evidence for the critical outcome of ADL was available from two case series, both of which reported the Bain score at 12 months follow-up. Although the pre- and post-treatment data for all three critical outcomes were assessed statistically by at least one study in each case, with statistically significant p-values (compared with baseline) being reported, none of the studies defined the minimum clinically important difference. Therefore, it is not clear whether the magnitude of improvement reported by the studies represents a meaningful level of improvement for individual patients.

In terms of important outcomes, symptom recurrence was reported by one retrospective case series at a median time of 28 months after GK SRS, with a longer follow-up of approximately 54 months available for around one-third of the original patients. No evidence was identified for the important outcomes of intraoperative pain or length of hospital stay. For the important outcome of safety, non-comparative evidence was available in the form of an aggregate of adverse event data at approximately 11 to 152 months from 11 SRS GK studies pooled in one systematic review. This aggregate included two studies included for other outcomes in this review (Niranjan et al 2017 and Witjas et al 2015), so their adverse event data were not included separately. Additional non-comparative evidence on safety was available from two case series reporting at 12 months and 28 months, respectively.

The certainty of evidence for all critical and important outcomes was very low when assessed using modified GRADE.

The NMA was underpinned by a systematic review that only included non-comparative studies of either GK SRS or MRgFUS, which were the only two interventions in the network. Consequently, some critical appraisal items in the modified PRISMA for NMA could not be assessed (for example, the level of agreement between direct and indirect evidence in the treatment network; exploration of the geometry of the treatment network). The NMA authors stated that they assessed transitivity[26] by examining characteristics of included studies in terms of age, sex, disease duration and follow-up times, with differences between the studies leading to decreased transitivity for comparison in the NMA. This is also apparent in the considerable heterogeneity in both the GK SRS pooled results and the MRgFUS pooled results, which had I^2 values over 75%, which limits confidence in the findings. In terms of the studies included in the systematic review, the NMA authors stated that 16 of the 18 included studies did not explicitly address confounding factors, four of the studies were at risk of selection bias, and two studies were at risk of attrition bias. By restricting inclusion to studies that reported total unilateral FTM TRS scores and excluding those that only reported subscores or percentage changes, the NMA authors included only a small number of studies for each intervention. Pooled adverse events could not be included in an indirect comparison, so were only presented as aggregates for GK SRS studies.

In addition to the non-comparative nature of the case series study design, there were a number of conduct or reporting factors which increased the uncertainty of the results. One case series did not describe the study's inclusion criteria, and it was not possible to ascertain whether this was a prospective or retrospective study. Another study's inclusion criteria did not state that patients were medication refractory. In some cases, the studies did not describe whether there was consecutive or complete inclusion of eligible patients. One case series excluded 13% of otherwise eligible patients from the study because they either had no follow-up appointment or had less than six months of follow-up. Another case series excluded 18% of patients because of loss to follow-up in seven cases, hospitalisation for concomitant disease in three patients, and

[26] The transitivity assumption is that the comparative effectiveness of treatments A versus B can be derived from comparisons of treatments A versus C and B versus C. In order for this assumption to hold, there should be low heterogeneity among studies of the same treatment.

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refusal of final video assessment by one patient[27]. This case series also included a mixture of 36 patients with ET and 14 with PD and only presented baseline demographic characteristics and outcomes for the whole cohort, not specifically those people with ET who were of relevance to this review, which may limit the generalisability of findings from that study.

The majority of studies provided both pre-treatment and post-treatment data, with an assessment of change from baseline. Two studies provided more limited outcome data, with one retrospective case series only making a statement about the overall percentage improvement in FTM TRS, and one prospective case series providing the percentage improvement in tremor scores with a p value for change from baseline, but the percentage improvement in ADL without any p-value for the change. However, an advantage of the prospective case series was that an independent movement disorders neurologist assessed the FTM TRS by viewing videos before and at one year after unilateral GK SRS in a randomised, blinded manner. Where other studies used self-reported tools, there is the possibility of reporting bias.

There are a number of limitations of the two economic evaluations included in this report. Both studies were undertaken from the US perspective and used 2016 Medicare costs, so may not be generalisable to the UK. One study only reported costs with no consideration of treatment effects, and was for medication refractory tremor in general, not specifically ET, so is of limited value in determining the cost effectiveness of GK SRS for people in the UK with medication refractory ET. The only study to have developed a cost-effectiveness model appears to have used a short time horizon of one year (the timescale for the effectiveness data), so may not capture the longer-term benefits of reduced tremor. In addition, the cost-effectiveness study only reported the costs and effectiveness of the two modelled treatments separately, with no ICER or cost per QALY reported for the comparison between GK SRS and MRgFUS, although these were reported for the comparison between DBS and GK SRS. The authors of the cost-effectiveness study also noted that the Medicare reimbursement value for MRgFUS had not yet been established, so they estimated this based on the cost of the SRS procedure plus the MRI scan and intraoperative mapping. They acknowledge that, given the longer procedural time and expertise required for MRgFUS, it is likely that the actual reimbursement of MRgFUS will be greater than for SRS, i.e. the costs may be underestimated. This will have an impact on the confidence that can be placed in the outcome from this economic evaluation.

Limited evidence was available about subgroups of patients who may benefit more from GK SRS. Only one study reported results for people who had previously undergone DBS, with only one person with ET meeting this description. The same study also divided patients into ‘improved’ and ‘non-improved’ groups based on whether their ADL scores had improved by at least 50% and assessed the level of tremor improvement between groups. The study did not identify patients who might benefit from GK SRS more than the wider population with ET.

[27] Witjas et al 2015 note that partial follow-up data is available for some of these patients. The supplementary data are only accessible via the journal’s website, and it has not been possible to access these for the current review.

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7. Conclusion

This review included one systematic review and NMA of non-randomised studies and five case series which provided very low certainty evidence for the critical and important outcomes following unilateral GK SRS for the treatment of medication refractory ET. Two economic evaluations were also identified.

None of the studies were conducted in the UK. All of the studies reported at 12 months or longer follow-up, and the five case series included between 27 and 73 people. The NMA included three GK SRS studies (with 62 people) and 15 MRgFUS studies (with 464 people).

One study reported a statistically significant improvement from baseline in quality of life during the 12 months after GK SRS. Very low certainty evidence was available from an indirect comparison between GK SRS and MRgFUS in the NMA. A similar improvement in tremor was reported for both treatments, with a between-treatment difference in FTM TRS A+B scores of 1.31 points (95% CI -2.96 to 5.99). The NMA indicated a 72.8% probability that MRgFUS is the more efficacious treatment for tremor reduction, compared with GK SRS. Five studies reported that GK SRS improved patients tremor scores (including the subscales of tremor, writing, drawing and drinking in some studies), with statistically significant improvements from baseline seen in four of the studies. Two studies reported improvements from baseline ADL following GK SRS, described as statistically significant by one of the studies. None of the studies reported the MCID, so it is not clear whether the changes represent clinically meaningful improvements.

One study reported a recurrence rate of approximately 10% of patients at 28 months follow-up. No evidence was identified for the important outcomes of intraoperative pain or length of hospital stay. The overall rate of adverse effects ranged from none at 12 months to 22% at 28 months.

The evidence was of very low certainty for all reported outcomes, mainly due to the lack of comparative data (other than the indirect comparison for tremor reduction). The NMA was limited by the inclusion of only non-comparative studies and lack of any direct evidence within the network, together with a considerable level of heterogeneity and decreased transitivity. Selection bias may have affected the non-comparative studies, mainly due to unclear information about consecutive/complete enrolment of eligible patients, exclusion of particular patients by two studies, and a mixed population of a majority of ET patients and a minority of PD patients in one study.

Two cost analyses provided estimates of the cost of treatment from a US perspective, with one of these also reporting costs and effectiveness compared with MRgFUS, but not presenting the ICER or QALY estimates. The cost-effectiveness study concluded that MRgFUS is cost-effective for tremor compared with GK SRS but noted that if the effectiveness of MRgFUS were found to be less than initially measured (or the cost greater, as they acknowledge may be the case due to its likely underestimated reimbursement cost), GK SRS may be the more cost-effective procedure.

There was limited evidence regarding subgroups of people with ET who may benefit more from GK SRS than the general population of interest. One study reported outcomes for one person who had previously had DBS, and also compared subgroups of people categorised according to their level of ADL improvement. The study did not identify patients who might benefit from GK SRS more than the wider population with ET. In terms of treatment dose, a maximum dose of 130 Gy was delivered in four studies and a median dose of 140 Gy was reported by one study.

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The studies identified for this review provide very low certainty evidence that GK SRS may improve quality of life, tremor scores and ADL for people with medication resistant ET. However, the studies did not report whether changes were clinically meaningful for patients and did not report the important outcomes of intraoperative pain and length of hospital stay which may also be important measures of success for people considering this treatment. The indirect evidence comparing GK SRS to MRgFUS was limited and of very low certainty and should be treated with caution. It is uncertain to what extent the cost effectiveness outcomes are generalisable to the NHS in England.

Due to these limitations, it was not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of GK SRS compared to MRgFUS in people with medication refractory ET.

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Appendix A PICO document

The review questions for this evidence review are:

1. In people with medication refractory essential tremor, what is the clinical effectiveness of gamma knife SRS compared with current standard care?
2. In people with medication refractory essential tremor, what is the safety of gamma knife SRS compared with current standard care?
3. In people with medication refractory essential tremor, what is the cost-effectiveness of gamma knife SRS compared with current standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from gamma knife SRS more than the wider population of interest?
5. From the evidence selected, what was the treatment dose of gamma knife SRS in the population of interest?

P – Population and Indication	People with medication-refractory (resistant) essential tremor who are either not suitable for Deep Brain Stimulation (DBS) or for whom previous DBS treatment has failed. [Patients are considered mediation refractory (resistant) once two or more trials of appropriate medical therapy have failed. Essential tremor includes familial essential tremor, non-familial essential tremor, and benign essential tremor. Tremor may be unilateral or bilateral. Tremor related to Parkinson's disease is not relevant to this review]. [Patients may not be suitable for DBS for many reasons, including comorbidities, pacemaker devices in situ, anticoagulation therapy, frailty, or previous cerebral infarcts]. [Patients may have already received a surgical intervention to treat their tremor, such as DBS or previous surgical thalamotomy]. Subgroups: - Varying levels of severity (for example: mild, moderate and severe tremor based on Clinical Rating Score for Tremor) - Patients who have previously had DBS. - Those with the inherited variety, familial essential tremor
I – Intervention	Unilateral thalamic Gamma Knife Stereotactic Radiosurgery (SRS) [This can also be referred to as stereotactic radiosurgery, stereotactic surgery, or gamma knife thalamotomy]. [Dosing ranges from 60 – 150Gy, with lower dosing given at the edge of target, and higher dosing at the centre of the target, given as a single fraction].

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C – Comparator(s)	Current standard care: 1. No unilateral thalamic gamma knife stereotactic radiosurgery, including conservative management. [Conservative management can include occupational therapy and physiotherapy]. [This can also be referred to as stereotactic radiosurgery, stereotactic surgery, or gamma knife thalamotomy]. 2. Unilateral transcranial MRI-guided focussed ultrasound thalamotomy [This can also be defined as brain focused ultrasounds or high intensity focussed ultrasound].
O – Outcomes	**<u>Clinical Effectiveness</u>** *Unless stated for the outcome, minimal clinically important differences (MCIDs) are unknown.* Outcomes measured at 6, 12 and 24 months are of particular interest. Improvements in tremor are generally seen over several weeks and months after the intervention. *<u>Critical to decision making</u>* • **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health and their self-perceived well-being. Measurement of quality of life can help inform patient-centred decision making.* [Quality of life can be measured using the Quality of Life in Essential Tremor questionnaire (QUEST score). Other terms used to, but not limited to, describe or indicate quality of life include patient-reported quality of life, health related quality of life, visual analogue scale, EQ-5D Health-related Quality of Life Questionnaire]. • **Improvement in tremor severity scale** *This is important to patients because an improvement in their tremor suggests that treatment has been successful, and their symptoms will be improved.* [This can be measured including, but not limited to the Fahn-Tolosa-Marin scale, the Essential Tremor Rating Assessment Scale, the Clinical Rating Scale for Tremor (CRST), Global Tremor Relief, clinical Global Impression Severity (CGI-S) and Improvement (CGI-I) scales]. • **Activities of daily living (ADLs)** *ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.* [ADLs can be measured using assessments such as, but not limited to: o Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) o ADLs assessment using a tool (e.g., Barthel Index (BI), Karnovsky performance score or Independence in Activities of Daily Living (ADL)

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	○ Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work and other activities)]. *Important to decision making:* • **Symptom recurrence** *This is important to patients as the aim of treatment would be to reduce their essential tremor symptom burden and avoid further interventions of treatments.* [This can be measured by the number of patients who require further neurosurgical procedures to treat their tremor or the number of patients who report a recurrence in their tremor]. • **Intraoperative pain** *This is important for patients as if a procedure is more likely to be comfortable and pain-free, they may take this into consideration when making autonomous decisions about their treatment.* [This can be measured by numerical rating scores, the McGill Pain Questionnaire, visual analogue scales, Subjective/self-reported assessment]. • **Length of hospital stay** *This is important to patients as a shorter hospital admission or stay will have a less disruptive impact on their lives.* [This can be measured by the number of days required in hospital post-procedure]. **Safety** *These outcomes are important to patients because they will impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* Complications that may be encountered in the literature may include, but are not limited to: ○ Intraoperative complications ○ Immediate complications post procedure ○ Dysarthria ○ Paraesthesia ○ Gait/balance disturbance ○ Intracranial haemorrhage ○ Stroke Adverse events that are short term (lasting <1 year) or long term (lasting >1 year) are of relevance. **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only

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Patients	Human studies only
Age	All ages
Date limits	2013 – 2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, preprints and guidelines
Study design	Case reports, resource utilisation studies

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Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2013 to 7 December 2023

Medline search

1	Essential Tremor/
2	tremor?.ti,kf. or ((essential or familial or hereditary) adj3 tremor?).ab.
3	1 or 2
4	Radiosurgery/
5	((stereotactic adj3 (radiotherap* or radiation therap*)) or srs or sabr or sabrt or sbrt or radiosurg*).ti,ab,kf.
6	(linac or cyberknife or cyber knife or gammaknife or gamma knife).ti,ab,kf.
7	4 or 5 or 6
8	3 and 7
9	limit 8 to (english language and yr="2013 -Current")
10	exp animals/ not humans/
11	9 not 10
12	limit 11 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")
13	(comment or editorial or letter or news or review).pt. or case report.ti.
14	11 not 13
15	12 or 14

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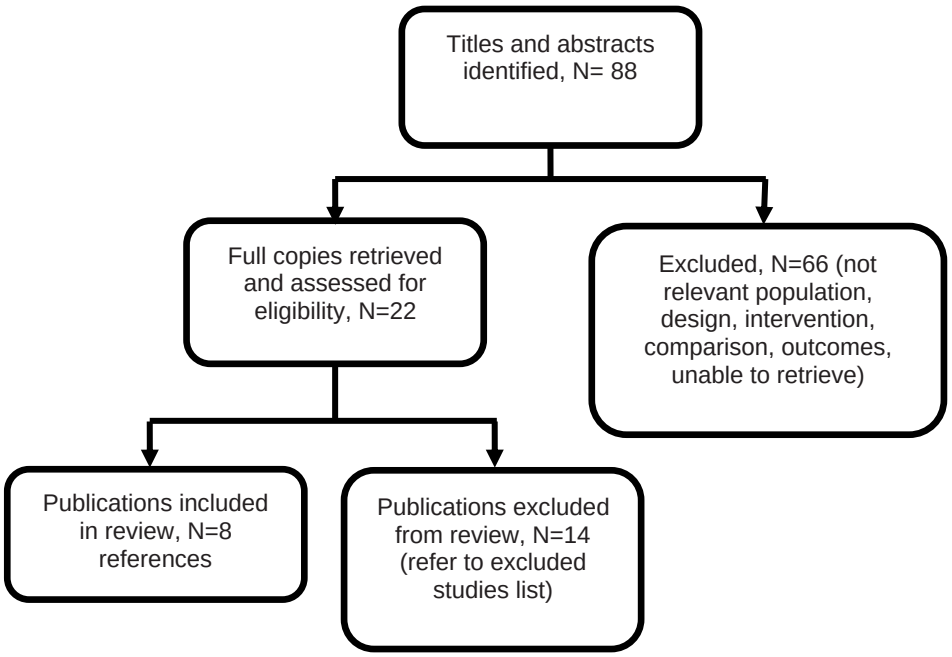
Appendix C Evidence selection

The literature searches identified 87 references, and one further reference was identified from its inclusion in a relevant systematic review. These were screened using their titles and abstracts and 22 references were obtained in full text and assessed for relevance. Of these, 8 references are included in the evidence summary. The remaining 14 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Kooshkabadi A, Lunsford LD, Tonetti D, Flickinger JC, Kondziolka D. Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era. J Neurosurg. 2013 Apr;118(4):713-8.	Excluded. There is a likely overlap between Kooshkabadi et al 2013 and Niranjan et al 2017. Kooshkabadi et al 2013 includes 48 patients with essential tremor (from a wider cohort of 86, with essential tremor, Parkinson disease or multiple sclerosis) who underwent gamma knife stereotactic radiosurgery (GK SRS) for tremor between 1996 and 2011 in Pittsburgh. Niranjan et al 2017 includes 73 ET patients treated with GK SRS in Pittsburgh between 1996 and 2015.
Niranjan A, Raju SS, Kooshkabadi A, Monaco E 3rd, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for essential tremor: Retrospective analysis of a 19-year experience. Mov Disord. 2017 May;32(5):769-777.	Included.
Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, Azulay JP, Régis J. A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology. 2015 Nov 3;85(18):1562-8.	Included.

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Appendix D Excluded studies table

Study reference	Reason for exclusion
Anonymous. A systematic review comparing focused ultrasound surgery with radiosurgery for essential tremor: Erratum. Neurosurgery. 2023;27:27.	Although this refers to the included Kondapavulur et al 2023 study, the error related to use of colour in the graphical abstract and has no relevance to the main publication.
Campbell AM, Glover J, Chiang VL, Gerrard J, Yu JB. Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: a systematic review of the literature. Radiotherapy & Oncology. 2015;114(3):296-301.	Superseded by more recent systematic reviews
Giammalva GR, Maugeri R, Umana GE, Paolini F, Bonosi L, Meccio F, et al. DBS, tcMRgFUS, and gamma knife radiosurgery for the treatment of essential tremor: a systematic review on techniques, indications, and current applications. Journal of Neurosurgical Sciences. 2022;66(6):476-84.	Qualitative summary with no statistical analysis or aggregate data. Superseded by more recent systematic review (Kondapavulur et al 2023) which considered the same papers for inclusion in the meta-analysis.
Gunawan K, Santoso F, Aman RA, Tandian D, Ichwan S, Nugroho SW. Gamma Knife Radiosurgery for Tremor Movement Disorder: A Systematic Review. Open Access Macedonian Journal of Medical Sciences. 2022;10:731-5.	No pooled analysis. Refer to individual studies
Khattab MH, Cmelak AJ, Sherry AD, Luo G, Wang L, Yu H, et al. Noninvasive Thalamotomy for Refractory Tremor by Frameless Radiosurgery. International Journal of Radiation Oncology, Biology, Physics. 2022;112(1):121-30.	Intervention out of scope.
Kooshkabadi A, Lunsford LD, Tonetti D, Flickinger JC, Kondziolka D. Gamma Knife thalamotomy for tremor in the magnetic resonance imaging era. J Neurosurg. 2013 Apr;118(4):713-8.	Excluded. There is a highly likely overlap between Kooshkabadi et al 2013 and Niranjan et al 2017. Kooshkabadi et al 2013 includes 48 patients with essential tremor (ET) (from a wider cohort of 86, with ET, Parkinson disease or multiple sclerosis) who underwent gamma knife stereotactic radiosurgery (GK SRS) for tremor between 1996 and 2011 in Pittsburgh. Niranjan et al 2017 includes 73 ET patients treated with GK SRS in Pittsburgh between 1996 and 2015.
Langford BE, Ridley CJA, Beale RC, Caseby SCL, Marsh WJ, Richard L. Focused Ultrasound Thalamotomy and Other Interventions for Medication-Refractory Essential Tremor: An Indirect Comparison of Short-Term Impact on Health-Related Quality of Life. Value in Health. 2018;21(10):1168-75.	No aggregate data presented for the 6 included gamma knife studies.
Martinez-Moreno NE, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, et al. Stereotactic radiosurgery for tremor: systematic review. Journal of Neurosurgery. 2018:1-12.	Superseded by more recent systematic review (Kondapavulur et al 2023) which considered the same papers for inclusion in the meta-analysis.
Middlebrooks EH, Popple RA, Greco E, Okromelidze L, Walker HC, Lakhani DA, et al. Connectomic Basis for Tremor Control in Stereotactic Radiosurgical Thalamotomy. Ajnr: American Journal of Neuroradiology. 2023;44(2):157-64.	Intervention out of scope.
Ochiai T. Gamma Knife Thalamotomy for a Medically Refractory Tremors: Longitudinal Evaluation of Clinical	Small case series (n=9 with ET).

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Study reference	Reason for exclusion
Effects and MRI Response Patterns. Acta Neurochirurgica - Supplement. 2021;128:127-32.	
Rohringer CR, Sewell IJ, Gandhi S, Isen J, Davidson B, McSweeney M, et al. Cognitive effects of unilateral thalamotomy for tremor: a meta-analysis. Brain Communications. 2022;4(6):fcac287.	Intervention out of scope for 7/8 studies included.
Schreglmann SR, Krauss JK, Chang JW, Bhatia KP, Kagi G. Functional lesional neurosurgery for tremor: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(7):717-26.	Superseded by more recent systematic review (Kondapavulur et al 2023) which considered the same papers for inclusion in the meta-analysis.
Tuleasca C, Najdenovska E, Regis J, Witjas T, Girard N, Champoudry J, et al. Clinical response to Vim's thalamic stereotactic radiosurgery for essential tremor is associated with distinctive functional connectivity patterns. Acta Neurochirurgica. 2018;160(3):611-24.	Small case series (n=17). Tremor scores included within Kondapavulur et al 2023. Larger studies report activities of daily living.
Tuleasca C, Witjas T, Najdenovska E, Verger A, Girard N, Champoudry J, et al. Assessing the clinical outcome of Vim radiosurgery with voxel-based morphometry: visual areas are linked with tremor arrest! Acta Neurochirurgica. 2017;159(11):2139-44.	Population appear to be incorporated within included Tuleasca et al 2018 paper, which has larger sample size.

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Appendix E Evidence table

For abbreviations see list after table.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Bolton TAW, Van De Ville D, Régis J, Witjas T, Girard N, Levivier M, Tuleasca C. Graph theoretical analysis of structural covariance reveals the relevance of visuospatial and attentional areas in essential tremor recovery after stereotactic radiosurgical thalamotomy. Front. Aging Neurosci. 2022;14:873605 **Study location** Centre Hospitalier Universitaire de la Timone in Marseille, France **Study type** Case series[28] with pre- and post-treatment analysis **Study aim** To use graph theoretical analysis to study structural covariance patterns in patients with ET before and after thalamotomy, as well as	**Inclusion criteria** Not reported. Patients were stated to have drug-resistant right-dominant ET. **Exclusion criteria** Not stated. Patients showed no other structural abnormalities on pretherapeutic MRI **Total sample size** N=34 **No. of participants in each treatment group** N/A **Baseline characteristics** • 17/34 (50%) female • Age, years mean±SD: 70.6±9.12 (range 49 to 83) • Symptom duration, months mean±SD:	**Intervention** GK SRS. The Leksell coordinate G frame was applied under local anaesthesia. After positioning the frame, patients underwent both stereotactic CT and MRI. Landmarks of interest, including the AC-PC, were identified on an MR scan. Uniform indirect targeting was performed using the Guiot diagram, placed 2.5mm above the AC-PC line, and 11 mm lateral to the wall of the third ventricle. A single 4 mm isocentre was used, and a maximum prescription dose of 130 Gy at the 100% isodose line was uniformly prescribed. **Comparator** None[29]	**Critical outcomes** **Quality of life** QUEST[30] N=34, mean±SD score, range • Pre-treatment: 45.46±16.4 (12 to 80) • 12 months: 23.16±16.57 (1 to 57) • Change from baseline: -24.79±13.21 (-47 to -2); p<0.0001 **Improvement in tremor severity scale** FTM-TRS: included within Kondapavulur et al 2023 SR, so not reported separately here. HEAD[31] N=34, mean±SD score, range • Pre-treatment: 1±0.85 (0 to 2) • 12 months: 0.56±0.75 (0 to 3) • Change from baseline: -0.39±0.83 (-2 to 1); p=0.035	This study was appraised using the JBI checklist for case series. 1. No 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** The study did not describe inclusion criteria for the study, or whether there was consecutive or complete inclusion. Patients gave individual consent and were followed up at an interval of one year for the imaging study, which was the focus of the paper.

[28] It is not clear from the text whether this was a prospective or retrospective case series.
[29] Healthy controls included by Bolton et al 2022 were only used for the comparison of imaging results, not for outcomes of interest to this review.
[30] QUEST scores range from 0 to 100, with benefit indicated by a lower score
[31] HEAD is the Tremor Research Group Essential Tremor Rating Assessment; scores range from 0 to 3

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
compared to age-matched healthy controls. **Study dates** September 2014 to April 2016	35.53±18.28 (range 5 to 61)		**Important outcomes** **ADL** Bain score N=34, mean±SD score, range • Pre-treatment: 29.59±11.39 (13 to 49) • 12 months: 6.03±11.26 (0 to 41) • Change from baseline: -23.56±12.35 (-48 to 2); p<0.0001	**Source of funding:** University of Lausanne
Horisawa S, Hayashi M, Tamura N, Kohara K, Nonaka T, Hanada T, et al. Gamma Knife Thalamotomy for Essential Tremor: A Retrospective Analysis. World Neurosurgery. 2023;175:e90-e6. **Study location** Japan **Study type** Retrospective case series with analysis of pre- and post-treatment data **Study aim** To investigate the effect of GK SRS for people with ET in terms of the long-term	**Inclusion criteria** Previous ET diagnosis by a neurologist or neurosurgeon who has specialised in movement disorders, the stereotactic target being the VIM nucleus of the thalamus, and bilateral hand tremors. Indications for GK SRS[32]: a high risk of RF or DBS surgery due to brain atrophy caused by an advanced age or antiplatelet/anticoagulant medication use. **Exclusion criteria**	**Intervention** Left-sided GK SRS[34] Under local anaesthesia, the Leksell stereotactic frame was fixed to the patient's skull. The treatment target was set from 11 to 12 mm lateral to the third ventricle wall, 2 to 3 mm dorsal to the AC-PC plane, and 5 to 7 mm anterior to the PC. A maximum dose of 130 Gy was delivered with a single 4-mm isocentre without beam blocking. The mean treatment dose rate was 2.1± 0.3 Gy/min (range: 1.662 to 3.054).	**Critical outcomes** **Improvement in tremor severity scale** Mean follow-up period 28.3±17.6[35] months FTM CRS, mean±SD Tremor • Preoperative: 3.4±0.6 • Postoperative: 1.5±1.2 • % improvement: 55.9%; p<0.001 Writing • Preoperative: 3.3±1.0 • Postoperative: 1.4±1.1 • % improvement: 57.6%; p<0.001 Spiral drawing • Preoperative: 3.2±0.8	This study was appraised using the JBI checklist for case series. 1. Unclear 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:**

[32] Horisawa et al 2023 do not state clearly that people were medication-refractory, but this is implied within the text: *"Many patients with ET do not respond to medical therapy and require surgical treatment."* The indications for GK SRS are assumed to refer to why they had GK SRS rather than DBS or other surgery.
[34] Horisawa et al 2023 described the intervention as gamma knife thalamotomy; referred to in this report as GK SRS for consistency.
[35] This is the value reported in the text of Horisawa et al 2023, which differs from that reported in their table 1 (32.5 ±19.4 (13-62)).

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
improvement of tremor and adverse events **Study dates** 2014 to November 2018	Loss to follow-up within 1 year after GK SRS and missing data regarding subjective evaluation scales; diagnosis of Parkinsons and other diseases. **Total sample size** N=27 **Baseline characteristics[33]** • 14/27 (51.9% male) • Disease duration, years: 20 (10 to 30) • Age, years mean±SD: 78.1±4.2 (range 74 to 81)	**Comparator** None. Pre- and post-treatment data assessed.	• Postoperative: 1.6±1.3 • % improvement: 50%; p<0.001 Tremor improvements started at 5.5 ± 4.2 months after GK SRS. **Important outcomes** **Safety: adverse events** Mean follow-up period 28.3±17.6 months • None: 21/27 (77.8%) • At least one AE: 6/27 (22.2%) Specific AE (some patients had >1 AE) • Dysarthria: 2/27 (7.4%) • Dysphagia: 1/27 (3.7%) • Lip numbness: 3/27 (11.1%) • Finger numbness: 3/27 (11.1%) • Complete hemiparesis: 2/27 (7.4%) • Foot weakness: 1/27 (3.7%) • Death: 1/27 (3.7%) Text states that the complication rate was 18.5%.	Inclusion criteria do not state that patients must be medication refractory, but this is strongly implied by general statements about requirement for surgery in refractory patients[36]. **Source of funding:** This study was supported by JSPS KAKENHI.
Kondapavulur S, Silva AB, Molinaro AM, Wang DD. A Systematic review comparing focused ultrasound surgery with radiosurgery for essential	**Inclusion criteria** ET patients receiving either unilateral GK SRS or FUS-T, with tremor severity scored on a	**Intervention** GK SRS **Comparator** FUS-T	**Critical outcomes** **Improvement in tremor severity scale** **FTM-TRS[39], pooled mean±SD**	This study was appraised using NICE's modified PRISMA for NMA checklist 1. Yes

[33] Horisawa et al 2023: there is some discrepancy between the baseline characteristics in Table 1 of the paper and those reported in the text. Those reported in the text are included here as they are more precise. It is not clear whether the numbers reported in brackets are the range or IQR.
[36] Horisawa et al 2023: *"Many patients with ET do not respond to medical therapy and require surgical treatment."*
[39] FTM-TRS is a 21-item scale, of which 9 items relate to tremor and three to drawing (A, B, C). Each item's score has a possible range of 0 to 4.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
tremor. Neurosurgery. 2023;93(3):524-38. **Study location** No information available[37] **Study type** Systematic review and network meta-analysis **Study aim** To examine the efficacy and adverse events of FUS-T vs GK SRS for treating medically refractory ET **Study dates** Search dates: from database inception to 6 October 2022	validated tremor scoring scale For inclusion in the NMA, total tremor score with SD was required. **Exclusion criteria** Non-English language studies, case reports or series with n<5, follow-up ≤3 months, mixed populations (e.g. ET and PD) where data for ET patients were not available separately. **Total sample size** Efficacy analysis 18 studies (n=526) **No. of participants in each treatment group** Efficacy GK SRS: 3 studies, pooled n=62 FUS-T: 15 studies, pooled n=464 Adverse events analysis	No further details are reported for the included studies' interventions.	GK SRS (3 studies, n=62) • Baseline: 20.2±5.6 • 14.1 months follow-up: 9.0±8.7 • Absolute tremor reduction: -11.41 (95% CI -17.39 to -5.44); I^2=84% • Relative tremor reduction: 56.5% FUS-T (15 studies, n=464)[40] • Baseline: 18.3±5.2 • 10.3 months follow-up:7.3±5.7 • Absolute tremor reduction: -11.13 (95% CI -12.74 to -9.52) I^2=79% • Relative tremor reduction: 60.8% **NMA of weighted mean difference in FTM-TRS A+B reduction** GK SRS (3 studies, n=62) • Absolute tremor reduction: -10.26 (95% CI[41] -14.21 to -5.96) FUS-T (15 studies, n=464) • Absolute tremor reduction: -11.57 (95% CI -13.3 to -9.93) FUS-T vs GK SRS weighted mean difference: 1.31 (95% CI -2.96 to 5.99); 72.8% probability that FUS-T is the more efficacious treatment for tremor reduction	2. Yes 3. Unclear 4. Yes 5. Unclear 6. n/a 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. n/a 13. Yes **Other comments:** There was no direct evidence for GK SRS vs FUS-T, and the NMA was based on non-comparative studies, so critical appraisal items relating to the treatment network and comparison of indirect and direct evidence are either unclear or n/a. There were no subgroup/sensitivity analyses and only a descriptive summary of analysis of failure rates was possible due to the limited number of studies included and

[37] Kondapavulur et al 2023 does not report the locations of the studies included in the NMA.
[40] MRgFUS results are included here to give context for the NMA only.
[41] Although Fig 2 in Kondapavulur 2023 appears to report credible intervals rather than confidence intervals, the main text of the paper describes confidence intervals, which would be consistent with their frequentist approach rather than a Bayesian analysis, so the data have been reported here as confidence intervals.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
	11 GK SRS studies (n=449) [38] **Baseline characteristics** GK SRS (n=62) • 31 (50%) female • Age, years: mean 71.1 • Disease duration, years: mean 33.6 Mean follow-up time, months: 14.1 FUS-T (n=464) • 152 (29.2%) female • Age, years: mean 63.3 • Disease duration, years: mean 59.5 • Mean follow-up time, months: 10.3		**Important outcomes** **Safety** Pooled results (n=11 studies, n=449) • Follow-up: range 11 to 152 months • Imbalance/gait disturbance: 0 (0%) • Sensory disturbance: 5 (1.1%) • Dysmetria: 0 (0%) • Dysgeusia: 0 (0%) • Motor weakness: 12 (2.7%) • Dysarthria: 11 (2.4%) • Other: 3 (0.7%)	heterogeneity in their reporting (item 12). The NMA used indirect methods to compare the efficacy of the two interventions, but there was no formal indirect comparison for adverse events. AE data were presented separately for each intervention, so have only been included here for GK SRS studies. **Source of funding:** The study did not receive any funding or financial support.
McClelland S, 3rd, Jaboin JJ. Treatment of the ventral intermediate nucleus for medically refractory tremor: A cost-analysis of stereotactic radiosurgery versus deep brain stimulation. Radiotherapy & Oncology. 2017;125(1):136-9. **Study location**	**Inclusion criteria** The study conducted a literature search to acquire estimated operating room time of unilateral VIM DBS[43]. **Exclusion criteria** NR **Total sample size**	**Intervention** GK SRS **Comparator** VIM DBS (not within scope for this review) The 2016 Medicare Ambulatory Payment Classification for GK SRS was added to the work RVU	**Important outcomes** **Cost effectiveness** For GK SRS, the total cost was $10,811.77 per patient	Appraisal with a checklist is not required for cost effectiveness studies **Other comments:** Analysis is of treatment for medically refractory tremor, not specifically ET. **Source of funding:**

[38] There was no direct evidence for GK SRS vs FUS-T. Indirect evidence for efficacy was included in the NMA, but Kondapavulur et al 2023 did not undertake a formal indirect comparison for AE and only reported data for individual studies, none of which compared FUS-T vs GK SRS data.
[43] The estimated radiation oncology cost of radiosurgical VIM thalamotomy (GK SRS or linear accelerator) was derived from the 2016 Medicare fee schedule, due to its relative resistance to geographic and hospital variations in billing.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
US perspective **Study type** Economic (cost) evaluation **Study aim** A cost comparison of unilateral DBS vs radiosurgery of the VIM[42] **Study dates** Costs were based on 2016 rates	N=57 in the only study to report OR time for DBS. **No. of participants in each treatment group** N/A **Baseline characteristics** NR	to determine the total cost of GK SRS. RVU codes were multiplied by a conversion factor of $37.942[44] per RVU to obtain the neurosurgeon cost for VIM radiosurgery.		No funding sources were used.
Niranjan A, Raju SS, Kooshkabadi A, Monaco E, 3rd, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for essential tremor: Retrospective analysis of a 19-year experience. Movement Disorders. 2017;32(5):769-77. **Study location** Pittsburgh, USA **Study type** Retrospective case series, with pre- and post-treatment comparison **Study aim**	**Inclusion criteria** Patients with medically refractory ET treated with GK SRS **Exclusion criteria** Patients with no follow-up or less than 6 months follow-up. **Total sample size** N=73, from a total of 91 people who received GK SRS **Baseline characteristics** • Mean (range) age, years: 77 (43 to 92)	**Intervention** GK SRS: Leksell model G stereotactic coordinate frame used; high-resolution MR images obtained. Target localised to the VIM nucleus of the thalamus by coordinates relative to the anterior commissure-posterior (AC-PC) line. The inferior border of the radiosurgery lesion using the 4-mm isocentre of the Leksell Gamma knife was projected to extend just inferior to the AC-PC line.	**Critical outcomes** **Improvement in tremor severity scale** **FTM scores, mean±SD** Length of follow-up[45] Median time to last follow-up was 28 months (range 6 to 152), and 12/73 had <12 months follow-up. (Clinical and imaging follow-up was collected 4 to 6 months post-GK SRS). **Tremor** • Pre-GK SRS: 3.19±0.74	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes

[42] McClelland et al 2017 do not state any clear objective for their paper, so this is an interpretation.
[44] The conversion factor used by McClelland et al 2017 was taken from their earlier publication on Parkinson's Disease.
[45] The length of follow-up at the time of reporting post-GK SRS outcomes in the Niranjan et al 2017 paper is ambiguous. The text states that clinical and imaging follow-up was collected 4 to 6 months post-GK SRS, and that median time to last follow-up was 28 months (range 6 to 152).

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
To retrospectively analyse the outcomes of GK SRS for patients suffering from medication-refractory ET. **Study dates** August 1996 to December 2015	• 45/73 (62%) male • Mean (range) duration of ET, years: 15 (2 to 70) • Treatment side: right GK SRS: 14/73 (19%), left GK SRS: 59/73 (81%) • 63% had at least one comorbid condition that led to selection of GK SRS	A median central dose of 140 Gy (range 130 to 150) was given in a single procedure. **Comparator** None. Patients' pre- and post-treatment data were compared.	• Post-GK SRS: 1.23±1.01; p< 0.0001 **Writing** • Pre-GK SRS: 2.97± 0.75 • Post-GK SRS: 1.25±1.09; p< 0.0001 **Drawing** • Pre-GK SRS: 3.16±0.67 • Post-GK SRS: 1.26±1.12; p< 0.0001 **Drinking** • Pre-GK SRS: 3.14±0.67 • Post-GK SRS: 1.36±1.21; p< 0.0001 **Post-GK SRS summary** • 68/73 (93.2%) experienced improvement in at least one FTM score • 57/73 (72.2%) improved in all 4 FTM scores • 3/73 (3.7%) improved in 3 FTM scores • 6/73 (7.6%) improved in 2 FTM scores • 2/73 (2.5) improved in 1 FTM score • 11/73 (13.8%) did not improve in any FTM scores. • 68/73 (93.2%) experienced improvement in tremor. • 67/73 (91.8%) noted functional improvement (writing, drawing, drinking from a cup) for the	**Other comments:** Limitations The study excluded 12 patients with no follow-up and 6 patients with < 6 months follow-up. **Source of funding:** Paper states 'Nothing to report' for financial disclosures.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
			treated arm, of whom 25 (34.2%) had excellent functional improvement (a reduction of ≥3 levels or a score of 0), 59 (80.8%) had good or better (a reduction of 1 to <3 levels) and 67 (91.8%) had satisfactory or better improvement (<1 level). • 18/73 (24.7%) experienced tremor arrest or complete recovery of function, with median time to tremor arrest of 4 months (range 2 weeks to 12 months). **Long-term follow-up (>3 years)** For n=28/73, median follow-up of 54 months (range 37 to 152) **Tremor** • Pre-GK SRS: 3.1 • Long-term follow-up: 1.0; p<0.001 **Writing** • Pre-GK SRS: 2.85 • Long-term follow-up: 0.96; p<0.001 **Drawing** • Pre-GK SRS: 2.96 • Long-term follow-up: 0.79; p<0.001 **Drinking** • Pre-GK SRS: 3.11 • Long-term follow-up: 1.04; p<0.001	

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Long-term summary • 2/28 (28.57%) had complete resolution of tremor • 12/28 (42.8%) had an excellent outcome for tremor (tremor score of 1) • 8/28 (28.57%) had good outcome tremor control (tremor score of 2) **Important outcomes** **Symptom recurrence** 7/73 (9.6%) had initial tremor relief that diminished over time, with median time to recurrence of tremor of 28 months (range 9 to 40). 3 of these patients had their tremor scores return to pre-GK SRS levels, and 4 maintained scores better than pre-GK SRS levels. Among the 28 patients with long-term follow-up, 3/28 (10.7%) had some recurrence of tremor at 9, 22 and 40 months, respectively. **Safety** Safety data are included within the Kondapavulur et al 2023 systematic review.	
Ravikumar VK, Parker JJ, Hornbeck TS, Santini VE, Pauly KB, Wintermark M, et al. Cost-effectiveness of focused ultrasound, radiosurgery, and DBS for	**Inclusion criteria** Studies that reported both pre- and postoperative part C scores of the TRS or CRST for MRgFUS, GK	**Intervention** SRS **Comparator** MRgFUS	**Important outcomes** **Cost effectiveness**	Appraisal with a checklist is not required for cost effectiveness studies **Other comments:**

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
essential tremor. Movement Disorders. 2017;32(8):1165-73. **Study location** US perspective **Study type** Decision analysis model **Study aim** To compare clinical outcomes and costs of MRgFUS, GK SRS and DBS for medically refractory ET. **Study dates** Reimbursement costs were calculated in 2016 US dollars. Literature search dates: October 1998 to June 2016	SRS or DBS. All included studies were for ET with unilateral tremor. **Exclusion criteria** Publications without original data, individual case reports, review articles, letters and editorials, technical reports without original outcome data. **Total sample size** 32 studies (n=958) **No. of participants in each treatment group** GK SRS: 5 studies (n=260) MRgFUS: 4 studies (n=83) DBS[46]: 23 (n=615) **Baseline characteristics** Mean age • GK SRS: 74.1±2.0[47] • MRgFUS: NR Rate of female patients • GK SRS: 0.44±0.12 • MRgFUS: 0.29± 0.21	**Model** The decision tree was populated using pooled mean utilities and probabilities as a result of each treatment type. A rollback analysis was subsequently implemented to calculate expected costs and utilities. Sensitivity analyses employed 2-dimensional Monte Carlo simulation (100 simulated trials of 100 patients in each treatment arm) and were carried out to identify the parameters that had the greatest impact on cost-effectiveness. Pooled complication rates from the literature search were used to populate the model's transition probabilities, and utilities associated with the complications were obtained from the literature. Published quality of life scores were mapped onto the utilities using published algorithms or extrapolation.	Effectiveness[48], mean±SD • GK SRS: 0.116±0.003 • MRgFUS: 0.194±0.005 • Difference: p<0.001 Cost (2016 US dollars) • GK SRS: $20,013±$1036 • MRgFUS: $20,593±$1402 • Difference: p=0.654 The base case result shows that MRgFUS is more costly than GK SRS but more effective. The authors conclude that MRgFUS is cost-effective for tremor compared with GK SRS but note that if the effectiveness of MRgFUS were found to be less than initially measured (or the cost greater), GK SRS may be the more cost-effective procedure.	Whilst the authors present an ICER for the comparison between unstaged DBS and GK SRS in the form of a cost per QALY, they do not present one for the comparison of GK SRS vs MRgFUS. The model's time horizon appears to use 1-year effectiveness data. The 1-year effectiveness of MRgFUS is mentioned as one of the parameters (alongside cost) that had the greatest impact on cost-effectiveness. It should be noted that the cost of MRgFUS was estimated based on the cost of GK SRS with some additional expenditure for the MRI scan and intraoperative mapping, so may be an underestimate of the actual cost. **Source of funding:** This study received Halpern Laboratory startup funding from the Department of Neurosurgery, Stanford University

[46] Ravikumar et al 2017: DBS arm not included in this review.
[47] Ravikumar et al 2017: it is not clear what the ± figures are in the published paper. Assumed to be standard deviations.
[48] Ravikumar et al 2017: Effectiveness measured by amount of utility added by the procedure. The higher the number, the more effective.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Mean follow-up time • GK SRS: 22.4±13.6 • MRgFUS: 7.3±5.6			
Tuleasca C, Witjas T, Van de Ville D, Najdenovska E, Verger A, Girard N, et al. Right Brodmann area 18 predicts tremor arrest after Vim radiosurgery: a voxel-based morphometry study. Acta Neurochirurgica. 2018;160(3):603-9. **Study location** Marseille, France **Study type** Retrospective case series **Study aim** To test the hypothesis that visual areas might play a role in tremor alleviation and/or arrest after GK SRS. **Study dates** Not stated	**Inclusion criteria** ET diagnosis confirmed by movement disorder neurologist from clinical history and examination; drug-resistance after adequate trials; age 18 to 80; medical contraindication for DBS or radiofrequency thalamotomy; VIM thalamic area apparent on pretherapeutic MRI. The indications for GK SRS rather than DBS were medical co-morbidities, drug-resistance, advanced age or patient's refusal. **Exclusion criteria** Previous contralateral VIM RS, history of stroke or epilepsy, Parkinson-plus syndrome suspected, brain tumours, prior stereotactic and/or radiosurgical procedures in the basal ganglia area. **Total sample size** N=52	**Intervention** GK SRS: Leksell coordinate G Frame application, under local anaesthesia, stereotactic CT and MRI, indirect targeting using Guiot's diagram (2.5 mm above the AC-PC line, 11 mm lateral to the wall of the third ventricle, and at a mean of 7.3 mm in front of the PC (3.8 to 9.8; SD 1.3). A unique 4 mm isocentre was used, and a maximal prescription dose of 130 Gy. **Comparator** None	**Critical outcomes** **Improvement in tremor severity scale** FTM TRS at 1 year Overall improvement, mean±SD: 67.8% (32.9%) (range 0 to 100%) 4/52 were considered clinical non-responders **Important outcomes** **Safety** At 1-year follow-up 0/52 experienced side effects.	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. No 8. No 9. Yes 10. Unclear **Other comments:** The focus of this paper was the correlation between anatomical site and tremor improvement, so reporting of clinical outcomes was limited. There was no information on whether there was consecutive or complete inclusion of participants. Clinical information such as duration of tremor was not reported. No data were reported for the FTM TRS beyond a statement about overall improvement, with no statistical

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics • 30/52 (57.7%) male • Age, years mean±SD: 71.6±6.9 (range 49 to 82)			analysis other than a standard deviation for the percentage. Study dates not clear, but possible that this includes the 2004 to 2010 cohort reported by Witjas 2015 (also treated at the Timone University Hospital in Marseille) **Source of funding:** Timone University Hospital, the Swiss National Science Foundation, the Centre d'Imagerie BioMédicale (CIBM) of the University of Lausanne (UNIL), the University of Geneva (UniGe), the Centre Hospitalier Universitaire Vaudois (CHUV) and the Leenaards and Jeantet Foundations. Support from the A*MIDEX project funded by the Investissements d'Avenir French Government program, managed by the French National Research Agency.
Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, et al. A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology. 2015;85(18):1562-8. **Study location** Marseille, France **Study type**	**Inclusion criteria** Patients ≥ 18 years old with medically refractory ET or parkinsonian tremor, with severe disabling tremor of one or both upper limbs, who could not undergo VIM DBS for any medical or surgical reasons, or who refused DBS. **Exclusion criteria**	**Intervention** Unilateral GK SRS. Leksell G frame applied under local anaesthesia, placed parallel to the orientation of the AC-PC line (AC and PC were defined on the MR ventriculography). The centre of the target was placed 2.5 mm above the AC-PC line, 11 mm lateral to the wall of the third ventricle, and at a mean of 7.3 mm in front of the PC.	**Critical outcomes** **Improvement in tremor severity scale[50]** From baseline to 12-month follow-up, median (IQR) improvement on FTM TRS. N=50 patients (36 with ET, 14 with PD) • Global tremor score improvement (unblinded	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. No

[50] Witjas et al 2015 only provide outcome data for the whole cohort (n=50), not specifically those with ET (n=36).

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
Prospective case series pre- and post-treatment assessments **Study aim** To evaluate the safety and efficacy of unilateral GK SRS for treatment of severe tremor with a prospective blinded assessment **Study dates** 2004 to 2010	< 18 years old, abnormal anatomy of thalamic area **Total sample size** 36/50 patients had ET (14 had PD) **Baseline characteristics[49]** • 32/50 (64%) male • Age, years 75.5 (range 60 to 91) • Disease duration, years: 22.4 (range 4 to 74)	A unique 4-mm isocentre was used. The prescription dose was 130 Gy (maximum dose) in all patients. **Comparator** None. Pre- and post-treatment analysis of same patients.	assessment): 63.40% (38.3 to 90.6); p<0.0001 • Upper limb tremor score improvement (blinded assessment): 54.2% (36.2 to 79.2); p<0.0001 • Blinded assessment of subscores for rest, posture, intention, drinking[51], pouring, drawing and writing all showed statistically significant improvements[52] (p<0.001) **FTM TRS for tremor severity of upper limbs** Improvement was seen at a median of 5.3 months (range 1 to 12 months) after radiosurgery. **Activities of daily living** Assessed by Bain 25-item self-questionnaire, scored from 1 (able to do the activity without difficulty) to 4 (cannot do the activity). Reported as median (range) N=50 patients (36 with ET, 14 with PD) Mean[53] improvement in ADL: 72.2% (0% to 100%)	7. No 8. No 9. Yes 10. U**nclear** **Other comments:** Demographics, clinical information and outcome data are only presented for the whole cohort (n=50), not separately for the majority (n=36) with ET. Data from the 14 people with PD are included within the results. 11 patients were excluded from the analysis[57] (7 lost to follow-up, 3 hospitalised for concomitant disease, 1 refused last video assessment). No baseline data are presented for outcomes, only percentage improvement. Whilst a p value is provided for FTM TRS, no p value is presented for ADL. An independent movement disorders neurologist assessed TRS by viewing videos before and at 1

[49] Witjas et al 2015 only provide baseline characteristics for the whole cohort (n=50), not specifically those with ET (n=36).
[51] Witjas et al 2015 used the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale for the item 'drinking from a cup'
[52] Mean and SEM for subscores are only presented graphically by Witjas et al 2015 so could not be included in this review.
[53] Although the Methods text in Witjas et al 2015 states that results are median (IQR), the result "72.2% (0% to 100%)" is stated to be the mean improvement.
[57] Witjas et al 2015 note that partial follow-up data is available for some of these patients. The supplementary data are only accessible via the journal's website, and it has not been possible to access these for the current review.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Subgroups Tremor score improvement was correlated with ADL improvement (p<0.0001) Definitions: IP: ≥50% improvement in ADL NIP: <50% improvement in ADL Results are median (IQR) IP (n=38) ADL improvement at 12 months: 96.4% (87.5% to 100%) Global tremor score at baseline: 17 (14 to 22) Global tremor score improvement at 12 months: 64.9% (50% to 86%) NIP (n=12) ADL improvement 0% (5.9% to 15.2%)[54] Global tremor score at baseline: 21 (14.8 to 25) Global tremor score improvement: NR "Neither the tremor etiology (PD or ET) nor the tremor score severity influenced the outcome"[55]. Patients with previous bilateral DBS N=1 with ET[56] • Tremor score improved by 45.7% after GK SRS (whereas	year after unilateral GK SRS in a randomised, blinded manner. **Source of funding:** No targeted funding reported.

[54] Witjas et al 2015 describe this as "12 were nonimproved (median ADL improvement 0% [5.9%–15.2%])." From elsewhere in the text, the range in brackets is assumed to be the IQR, but it is not clear why this does not include the median value of 0%.
[55] Witjas et al 2015 state that the outcome was not influenced by tremor aetiology but do not provide any data to compare ET and PD.
[56] Witjas et al 2015 report previous DBS separately for people with ET and people with PD, so only the ET results are reported here.

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Study details	Population	Interventions	Study outcomes	Appraisal and funding
			the post-DBS improvement had been 85%). • ADL improved by 66.7% after GK SRS **Important outcomes** Safety data are reported within the systematic review by Kondapavulur et al 2023.	

Abbreviations
AC-PC: anterior commissure–posterior commissure; ADL: activities of daily living; AE: adverse events; CI: confidence interval; CT: computed tomography; DBS: deep brain stimulation; ET: essential tremor; FTM CRS: Fahn-Tolosa-Marin Clinical Rating Scale; FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale; FUS-T: focussed ultrasound thalamotomy; GK SRS: gamma knife stereotactic radiosurgery; Gy: gray; HEAD: Tremor Research Group Essential Tremor Rating Assessment; IP: improved patients; IQR: interquartile range; JBI: Joanna Briggs Institute; min: minute; mm: millimetre; MR: magnetic resonance; MRgFUS: magnetic resonance-guided focused ultrasound; MRI: magnetic resonance imaging; N: number; N/A: not applicable; NICE: National Institute for Health and Care Excellence; NIP: nonimproved patients; NMA: network meta-analysis; NR: not reported; PD: Parkinson's disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; OR: operating room; QALY: quality adjusted life year; QUEST: quality of life in essential tremor; RF: radiofrequency; RVU: relative value unit; SD: standard deviation; SR: systematic review; VIM: ventral intermediate nucleus

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Appendix F Quality appraisal checklists

NICE-modified PRISMA-NMA checklist[58]

Did the study:

1. Describe the reasons for the evidence review in the context of what is already known, including why an NMA has been conducted.

2. Specify the study characteristics (for example, PICOs, length of follow-up) and report characteristics (for example, years considered, language, publication status) used to decide the eligibility of studies, giving the reasons for the characteristics used. Clearly describe eligible treatments included in the treatment network and note whether any have been clustered or merged into the same node (with justification).

3. Describe methods used to explore the geometry of the treatment network and potential biases related to it (for example, if there are important links in the network where the studies are at high-risk of bias). This should include how the evidence base has been graphically summarised for presentation, and what characteristics were compiled and used to describe the evidence base to readers.

4. State the principal summary measures (for example, risk ratio, difference in means). Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.

5. Describe the methods of handling data and combining results of studies for each NMA. This should include, but not be limited to:

    a) handling of multi-arm trials

    b) selection of variance structure

    c) selection of prior distributions in Bayesian analyses

    d) assessment of model fit.

6. Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address inconsistency when found.

7. Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:

    a) sensitivity or subgroup analyses

    b) meta-regression analyses

    c) alternative formulations of the treatment network

    d) use of alternative prior distributions for Bayesian analyses (if applicable).

[58] Developing NICE guidelines: the manual – appendices A to P. Last updated 21 December 2023

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8. Provide a network graph of the included studies to enable visualisation of the geometry of the treatment network.

9. Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomised patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure (for example, publication bias).

10. Present results of each meta-analysis done, including confidence/credible intervals. In larger networks, authors may focus on comparisons versus a particular comparator (for example, placebo or standard care). League tables and forest plots may be considered to summarise pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.

11. Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, P values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.

12. Give results of additional analyses, if done (for example, sensitivity or subgroup analyses, meta-regression analyses, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses).

13. Discuss limitations at study and outcome level (for example, risk of bias), and at review level (for example, incomplete retrieval of identified research, reporting bias). Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (for example, avoidance of certain comparisons).

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

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Appendix G GRADE profiles

For abbreviations and footnotes see end of tables

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	GK SRS	MRgFUS	Result		
Quality of life (1 case series)									
QUEST at 12 months (mean±SD score (range)). QUEST scores range from 0 to 100, with benefit indicated by a lower score.									
1 case series Bolton et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	34	None	• Pre-treatment: 45.46±16.4 (12 to 80) • 12 months: 23.16±16.57 (1 to 57) • Change from baseline: -24.79±13.21 (-47 to -2); p<0.0001	Critical	Very low
Improvement in tremor severity scale (1 NMA and 5 case series)									
HEAD, the Tremor Research Group Essential Tremor Rating Assessment at 12 months (mean±SD score (range)). HEAD score possible range 0 to 3; benefit indicated by lower score.									
1 case series Bolton et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	34	None	• Pre-treatment: 1±0.85 (0 to 2) • 12 months: 0.56±0.75 (0 to 3) • Change from baseline: -0.39±0.83 (-2 to 1); p=0.035	Critical	Very low
FTM-CRS: tremor score at mean±SD follow-up: 28.3±17.6 months (mean±SD score). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Horisawa et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	27	None	• Preoperative: 3.4±0.6 • Postoperative: 1.5±1.2 • % improvement: 55.9%; p<0.001	Critical	Very low
FTM-CRS: writing score at mean±SD follow-up: 28.3±17.6 months (mean±SD score). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Horisawa et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	27	None	• Preoperative: 3.3±1.0 • Postoperative: 1.4±1.1 • % improvement: 57.6%; p<0.001	Critical	Very low

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FTM-CRS: spiral drawing score at mean±SD follow-up: 28.3±17.6 months (mean±SD score). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Horisawa et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	27	None	• Preoperative: 3.2±0.8 • Postoperative: 1.6±1.3 • % improvement: 50%; p<0.001	Critical	Very low
FTM-TRS, A+B score absolute tremor reduction at 12 months, result from NMA indirect comparison; benefit indicated by lower score[A].									
1 SR with NMA Kondapavulur et al 2023	Serious limitations[4]	No serious indirectness	Very serious inconsistency[5]	Not calculable	62 (3 studies)	464 (15 studies)	• GK SRS: -10.26 (95% CI -14.21 to -5.96)[B] • MRgFUS: -11.57 (95% CI -13.3 to -9.93) • MRgFUS vs GK SRS weighted mean difference: 1.31 (95% CI -2.96 to 5.99) • 72.8% probability that MRgFUS is the more efficacious treatment for tremor reduction	Critical	Very low
FTM-TRS A+B score, mean±SD, pooled for studies with follow-up at approximately 12 months; benefit indicated by lower score.									
1 SR with NMA Kondapavulur et al 2023	Serious limitations[4]	Serious indirectness[6]	Very serious inconsistency[5]	Not calculable[C]	62 (3 studies)	464 (15 studies)	GK SRS • Baseline: 20.2±5.6 • At 14.1 months follow-up: 9.0±8.7 • Absolute tremor reduction: -11.41 (95% CI -17.39 to -5.44); I^2=84% • Relative tremor reduction: 56.5% MRgFUS • Baseline: 18.3±5.2 • At 10.3 months follow-up: 7.3±5.7 • Absolute tremor reduction: -11.13 (95% CI -12.74 to -9.52) I^2=79% • Relative tremor reduction: 60.8%	Critical	Very low
FTM TRS: tremor, post-GK SRS data collected from 4 to 6 months, median time to last follow-up 28 months (range 6 to 152)[D]. FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	73/91[E]	None	Pre-GK SRS: 3.19±0.74 Post-GK SRS: 1.23±1.01; p< 0.0001	Critical	Very low

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FTM TRS: tremor, long-term follow-up (> 3 years), median 54 months (range 37 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	28/91	None	Pre-GK SRS: 3.1 Long-term follow-up: 1.0; p<0.001	Critical	Very low
FTM TRS: writing, post-GK SRS data collected from 4 to 6 months, median time to last follow-up 28 months (range 6 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	73/91	None	Pre-GK SRS: 2.97± 0.75 Post-GK SRS: 1.25±1.09; p< 0.0001	Critical	Very low
FTM TRS: writing, long-term follow-up (> 3 years), median 54 months (range 37 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	28/91	None	Pre-GK SRS: 2.85 Long-term follow-up: 0.96; p<0.001	Critical	Very low
FTM TRS: drawing, post-GK SRS data collected from 4 to 6 months, median time to last follow-up 28 months (range 6 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	73/91	None	Pre-GK SRS: 3.16±0.67 Post-GK SRS: 1.26±1.12; p< 0.0001	Critical	Very low
FTM TRS: drawing, long-term follow-up (> 3 years), median 54 months (range 37 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	28/91	None	Pre-GK SRS: 2.96 Long-term follow-up: 0.79; p<0.001	Critical	Very low
FTM TRS: drinking, post-GK SRS data collected from 4 to 6 months, median time to last follow-up 28 months (range 6 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	73/91	None	Pre-GK SRS: 3.14±0.67 Post-GK SRS: 1.36±1.21; p< 0.0001	Critical	Very low
FTM TRS: drinking, long-term follow-up (> 3 years), median 54 months (range 37 to 152). FTM-TRS score possible range: 0 to 4; benefit indicated by lower score.									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	28/91	None	Pre-GK SRS: 3.11 Long-term follow-up: 1.04; p<0.001	Critical	Very low
FTM TRS: summary of improvement, post-GK SRS data collected from 4 to 6 months, median time to last follow-up 28 months (range 6 to 152)									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	73/91	None	• 68/73 (93.2%) experienced improvement in at least one FTM score • 57/73 (72.2%) improved in all 4 FTM scores • 3/73 (3.7%) improved in 3 FTM scores	Critical	Very low

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							• 6/73 (7.6%) improved in 2 FTM scores • 2/73 (2.5) improved in 1 FTM score • 11/73 (13.8%) did not improve in any FTM scores. • 68/73 (93.2%) experienced improvement in tremor. • 67/73 (91.8%) noted functional improvement (writing, drawing, drinking from a cup) for the treated arm, of whom 25 (34.2%) had excellent functional improvement (a reduction of ≥3 levels or a score of 0), 59 (80.8%) had good or better (a reduction of 1 to <3 levels) and 67 (91.8%) had satisfactory or better improvement (<1 level). • 18/73 (24.7%) experienced tremor arrest or complete recovery of function, with median time to tremor arrest of 4 months (range 2 weeks to 12 months).		
FTM TRS: summary of improvement, long-term follow-up (> 3 years), median 54 months (range 37 to 152).									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	28/91	None	• 2/28 (28.57%) had complete resolution of tremor • 12/28 (42.8%) had an excellent outcome for tremor (tremor score of 1) • 8/28 (28.57%) had good outcome tremor control (tremor score of 2)	Critical	Very low
FTM TRS: percentage overall improvement at one year follow-up (mean±SD score)									
1 case series Tuleasca et al 2018	Very serious limitations[8]	Serious indirectness[2]	Not applicable	Not calculable	52	None	67.8%±32.9% (range 0 to 100%)	Critical	Very low

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FTM TRS: global tremor score (unblinded assessment), percentage improvement from baseline to 12-month follow-up (median (IQR))									
1 case series Witjas et al 2015	Very serious limitations[9]	Serious indirectness[2]	Not applicable	Not calculable	50 (36 with ET, 14 with PD)	None	63.40% (38.3 to 90.6); p<0.0001	Critical	Very low
FTM TRS: upper limb tremor score (blinded assessment), percentage improvement from baseline to 12-month follow-up (median (IQR))									
1 case series Witjas et al 2015	Very serious limitations[9]	Serious indirectness[2]	Not applicable	Not calculable	50 (36 with ET, 14 with PD)	None	54.2% (36.2 to 79.2); p<0.0001	Critical	Very low
Activities of daily living (2 case series)									
Bain score at 12 months (mean±SD score (range)). 25-item self-questionnaire, each item's score possible range 1 to 4; benefit indicated by lower score.									
1 case series Bolton et al 2022	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	34	None	• Pre-treatment: 29.59±11.39 (13 to 49) • 12 months: 6.03±11.26 (0 to 41) • Change from baseline: -23.56±12.35 (-48 to 2); p<0.0001	Critical	Very low
Bain score: mean (range) percentage improvement from baseline **to 12-month follow-up (median (IQR))**									
1 case series Witjas et al 2015	Very serious limitations[9]	Serious indirectness[2]	Not applicable	Not calculable	50 (36 with ET, 14 with PD)	None	72.2% (0% to 100%)	Critical	Very low
Symptom recurrence (1 case series)									
Symptom recurrence, median time to last follow-up 28 months (range 6 to 152).									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	73/91	None	7 (9.6%)	Important	Very low
Symptom recurrence, long-term follow-up (> 3 years), median 54 months (range 37 to 152).									
1 case series Niranjan et al 2017	Serious limitations[7]	Serious indirectness[2]	Not applicable	Not calculable	28/91	None	3 (10.7%)	Important	Very low
Safety (1 NMA and 2 case series)									
Adverse events at mean±SD follow-up: 28.3±17.6 months									
1 case series Horisawa et al 2023	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	27	None	• None: 21(77.8%) • At least one AE: 6 (22.2%) Specific AE (some patients had >1) • Dysarthria: 2 (7.4%) • Dysphagia: 1 (3.7%)	Important	Very low

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							• Lip numbness: 3 (11.1%) • Finger numbness: 3 (11.1%) • Complete hemiparesis: 2 (7.4%) • Foot weakness: 1 (3.7%) • Death: 1 (3.7%)		
Adverse events, pooled results at 11 to 152 months follow-up									
1 SR Kondapavulur et al 2023	Serious limitations[10]	Serious indirectness[11]	Not applicable	Not calculable	449 (11 studies)	N/A[F]	• Imbalance/gait disturbance: 0 (0%) • Sensory disturbance: 5 (1.1%) • Dysmetria: 0 (0%) • Dysgeusia: 0 (0%) • Motor weakness: 12 (2.7%) • Dysarthria: 11 (2.4%) • Other: 3 (0.7%)	Important	Very low
Side effects one year follow-up									
1 case series Tuleasca et al 2018	Serious limitations[8]	Serious indirectness[2]	Not applicable	Not calculable	52	None	0 patients experienced side effects.	Important	Very low

Abbreviations
ADL: activities of daily living; AE: adverse events; CI: confidence interval; ET: essential tremor; FTM CRS: Fahn-Tolosa-Marin Clinical Rating Scale; FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale; GK SRS: gamma knife stereotactic radiosurgery; HEAD: Tremor Research Group Essential Tremor Rating Assessment; IQR: interquartile range; MRgFUS: magnetic resonance-guided focused ultrasound; NMA: network meta-analysis; PD: Parkinson's disease; QUEST: quality of life in essential tremor; SD: standard deviation; SR: systematic review

A It is not clear what the possible range of scores is for the FTM TRS A+B scores. The FTM TRS is a 21-item scale, of which 9 items relate to tremor and three to drawing (A, B, C). Each item's score has a possible range of 0 to 4.
B Although Figure 2 in Kondapavulur et al 2023 appears to report credible intervals rather than confidence intervals, the main text of the paper describes confidence intervals, which would be consistent with their frequentist approach rather than a Bayesian analysis, so the data have been reported here as confidence intervals.
C The results presented here relate to the separately pooled results for the GK SRS studies and MRgFUS studies, included to provide background to the NMA results; there is no direct or formal indirect comparison of the two groups' data other than the NMA, so imprecision is not calculable.
D The length of follow-up in the Niranjan et al 2017 paper is ambiguous. The text states that clinical and imaging follow-up was collected 4 to 6 months post-GK SRS, and that median time to last follow-up was 28 months (range 6 to 152).
E 18 pts were excluded as they either had no follow-up or < 6 months follow-up.
F AE for MRgFUS are presented within the SR but are from different studies and there was no formal indirect comparison for this outcome.

1 Risk of bias: serious limitations due to unclear reporting of study participants (in relation to lack of clear inclusion criteria, non-consecutive and/or incomplete inclusion)
2 Indirectness: serious indirectness due to lack of comparator group.
3 Risk of bias: serious limitations due to unclear reporting of study participants (in relation to lack of clear inclusion criteria: patients were not stated to be medication refractory, although this is implied.)
4 Risk of bias: serious limitations due to lack of direct evidence in the NMA precluding evaluation of agreement of direct and indirect evidence in the treatment network. In addition, only non-comparative data were included in the systematic review, and Kondapavulur et al 2023 assessed 16/18 included studies to be at risk from confounding, 4/18 to have a risk of selection bias, and 2/18 had likely attrition bias.
5 Inconsistency: very serious inconsistency due to considerable heterogeneity in study-level meta-analyses for the separate treatments (I^2=84% for GK SRS, I^2=79% for FUS-T) and lack of transitivity in the NMA.

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6 Indirectness: serious indirectness due to lack of comparator group. There was no direct evidence for GK SRS vs FUS-T, the data presented here are from separate studies and are included here to give context for the NMA results.
7 Risk of bias: serious limitations due to incomplete inclusion of participants: the study excluded 12 patients with no follow-up and 6 patients with <6 months follow-up.
8 Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion), limited reporting of clinical information of participants, and lack of detailed reporting of FTM-TRS scores.
9 Risk of bias: very serious limitations due to unclear reporting of study participants (outcomes and baseline data not presented separately for in-scope patients, although these formed the majority (36/50 with ET, 14/50 with PD).
10 Risk of bias: serious limitations; this outcome is based on the SR not the NMA. Only non-comparative data were included in the systematic review, and Kondapavulur et al 2023 assessed 16/18 included studies to be at risk from confounding, 4/18 to have a risk of selection bias, and that 2/18 had likely attrition bias.
11 Indirectness: serious indirectness due to lack of comparator group. There was no direct evidence for GK SRS vs FUS-T. Although formal indirect evidence for efficacy was included in the NMA, Kondapavulur et al 2023 did not undertake a formal indirect comparison for AE and only reported aggregate data for GK SRS studies and FUS-T studies separately; the FUS-T data has not been reported here as it was from different studies than the GK SRS data.

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Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Network meta-analysis	An analysis that compares 2 or more interventions using a combination of direct evidence (from studies that directly compare the interventions of interest) and indirect evidence (from studies that do not compare the interventions of interest directly).
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.

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Term	Definition
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Time horizon	The time period over which the main differences between interventions in effects and the use of resources in health and social care are expected to be experienced, taking into account the limitations of the supporting evidence.

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Term	Definition
Transitivity	The assumption that the trials in a network meta-analysis are similar, on average, in all important factors other than the intervention comparison being made.

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