Highly Specialised Technologies (HST) criteria checklist

Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations

### Introduction

The NICE HST criteria checklist is to highlight where a technology meets/partially meets or does not meet the criteria for routing to the HST programme. Its purpose is to show the details of why a technology may not be appropriate for HST evaluation, but also where it has been identified as suitable. For more information, please see [section 7 of NICE health technology evaluation topic selection: the manual](https://www.nice.org.uk/process/pmg37/chapter/highly-specialised-technologies)

### Key – does the technology meet the criteria? Please use the colour key to advise if the technology meets the criteria

|  |  |
| --- | --- |
| Met | There is clear and strong evidence that this criterion is met |
| Not met | There is no evidence or limited evidence that the criterion is met.  There is some evidence, or the evidence available is unclear. |

### MA wording: \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* (expected MA wording only)

| **Number** | **Criterion** | **Description of how the technology meets the criteria** | **Does the technology meet the criteria?** |
| --- | --- | --- | --- |
|  | The disease is very rare defined by 1:50,000 in England | Amyotrophic lateral sclerosis (ALS) is the most common type of motor neurone disease (MND). Superoxide dismutase (SOD1) variants have been identified to cause around 15% of familial and 1% of sporadic ALS1.  Over 180 variants have been identified associated with SOD1 and the variants are distributed throughout the gene and protein. This differs to other genetic causes of ALS, where variants arise in specific functional domains of proteins. Some variants in SOD1 may also be coincidentally found in people with ALS but not cause their disease.2  The Topic Selection Oversight Panel (TSOP) understood that SOD1-ALS may present with certain symptoms such as lower motor neurone symptoms, without frontal temporal dementia and at younger age of onset, but TSOP agreed that these symptoms are not specific to ALS caused by SOD1 mutations alone as there is significant heterogeneity in clinical presentation and these symptoms are found in other causes of ALS too, so TSOP considered the disease prevalence to be related to ALS rather than the genetic subgroup of SOD1-ALS. 2 - 4  Prevalence estimates of ALS vary in the literature depending on how you define ALS (range 3-13:100,000) and there are geographical variations but prevalence is likely to be larger than 1:50,000:   * Prevalence data reported in NG42 ([Motor neurone disease: assessment and management](https://www.nice.org.uk/guidance/ng42), 2016)states that ~4000 people have MND of which 90% have ALS in England and Wales. This translates to 3:50,000. * Company highlighted that NG42 is not up to date: [recent meta analyses](https://pubmed.ncbi.nlm.nih.gov/34247168/) at consultation reported 2,700 patients in the UK with ALS, based on a median prevalence estimate of 4.03:100,000 (2:50,000) people   TSOP considered if flexibility could be applied for this criterion but agreed that although criteria 2 and 3 were clearly met, discretion had already been applied to criterion 4 with the agreement that there were no satisfactory treatment options for patients despite an approved Technology Appraisal in this disease area. TSOP also considered the vision of the HST programme and if there was substantial need to encourage research because there are challenges generating evidence robust enough to bring the product to market. Given that ALS is 2-3 times more common than other diseases normally considered for the HST programme it was not persuaded that flexibility could be applied. | Not met |
|  | Normally no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications | Tofersen would only be used in people with SOD1 mutations. The company provided prevalence figures from Brown et al:   * Around 2,700 people have ALS, at any time in the UK * Around 2,278 people have ALS in England (based on a population of population of 56,536,400) * Of these, 5-10% (114 – 228 people) have the familial type and 90-95% (2050 – 2164 people) have the sporadic type5, 6 * SOD1 gene mutations cause 14.8% of familial and 1.2% of sporadic ALS.7 * Total = 59 prevalent cases in England (0.1:50,000) * Highest estimates include 120 people with SOD1-ALS.   At the scoping workshop the stakeholders explained that there is not currently equitable access to genetic screening.  Only people meeting R58 “Adult Onset Neurodegenerative disorder” criteria are currently tested (people who are symptomatic and a) aged under 50 or b) with family history of ALS).  Post workshop, the testing criteria has been updated to capture a broader population within the criteria for ALS with or without frontotemporal dementia:  a) Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic or neuropathologic examination, AND  b) Evidence of upper motor neuron (UMN) degeneration by clinical examination, AND  c) Progressive course, AND  e) No evidence of other aetiology  It is unclear if the previous restrictions impacted the number of people eligible for treatment but clinicians at the scoping workshop did not expect a large increase in diagnoses following the expansion of testing.  Genetic testing for SOD1 mutations can take up to a year to receive, once diagnosed with an SOD1 mutation, tofersen would be used in combination with standard of care treatments. | Met |
|  | The very rare condition significantly shortens life or severely impairs its quality | The condition affects the brain and spinal cord and is associated with progressive degeneration of motor skills.8 Progression of the disease leads to increased muscle weakness and problems with communicating and breathing. Most people typically do not survive beyond 2-3 years of developing symptoms.9,10   * (<https://www.mndassociation.org/app/uploads/mnd-association-key-messages-infographic.pdf>) | Met |
|  | There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options. | * **Additional benefit of tofersen:** Tofersen does not present itself as curative treatment option. Initial results from pivotal trial (VALOR and OLE, primary outcome: change from baseline to week 28 in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)) showed tofersen did not statistically improve clinical end points and was associated with adverse events. However, the benefits of tofersen are being further evaluated in the extension phase11 * **Current treatment options:** There is an available treatment (Riluzole) recommended in NICE TA20 for people with ALS. Riluzole is not curative and extends median survival by 2-3 months only ([TA20 review papers](https://www.nice.org.uk/guidance/ta20/resources/appendix-a-static-list-review-paper2)).Given this, the TSOP panel considered whether riluzole could be classed as a satisfactory treatment option for ALS caused by SOD1 mutations. It noted that riluzole shows some benefit over standard care in clinical trials. It also noted feedback from stakeholders during the scoping workshop that riluzole is offered to all patients at diagnosis of ALS. However, it is not considered a very effective treatment option by clinicians. The TSOP panel considered that conditions with a NICE recommended treatment option normally would not meet this HST criterion. But, it agreed that, for the eligible population; ALS caused by SOD1 mutations, the poor survival benefit associated with riluzole meant that it could not be classed as a satisfactory treatment option. So, this criterion is met. | Met |

1. Tang L, Ma Y, Liu X-l, Chen L, Fan D-s (2019). [Better survival in female SOD1-mutant patients with ALS: a study of SOD1-related natural history](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325854/). Translational Neurodegeneration. 8(1):2.
2. Opie-Martin, S., Iacoangeli, A., Topp, S.D. et al. (2022) The SOD1-mediated ALS phenotype shows a decoupling between age of symptom onset and disease duration. Nat Commun 13, 6901. <https://doi.org/10.1038/s41467-022-34620-y>
3. Millecamps, S., Salachas, F., Cazeneuve, C et al. (2010) [SOD1, ANG, VAPB, TARDBP, and FUS mutations in familial amyotrophic lateral sclerosis: genotype-phenotype correlations. J. Med. Genet, 47 (8).](https://unilim.hal.science/hal-00607332v1/file/MillecampsetalJMG2010-AcceptedManuscript.pdf)
4. Wicks, P,. Abrahams, S,. Papps, B. et al (2009) [SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis](https://pubmed.ncbi.nlm.nih.gov/19252762/). J Neurol, 256 (2) :234-41.
5. Gowland A et al. (2019) [Predicting the future of ALS: the impact of demographic change and potential new treatments on the prevalence of ALS in the United Kingdom, 2020-2116](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6567553/)
6. Sheffield MND Care and Research Centre (2015) [What is the difference between MND and ALS?](https://sheffieldmndcarecentre.group.shef.ac.uk/support/mnd-als/) Accessed September 2021.
7. Zou et al. (2017) [Genetic Epidemiology of Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis](https://pubmed.ncbi.nlm.nih.gov/28057713/). J Neurol Neurosurg Psychiatry. 88(7):540-549.
8. Amyotrophic Lateral Sclerosis Frontotemporal Degeneration. 20(3-4):264-274.
9. Talbot K (2009). [Motor neuron disease](https://pn.bmj.com/content/9/5/303). Practical Neurology. 9(5):303.
10. Simon NG et al. (2014) [Quantifying disease progression in amyotrophic lateral sclerosis](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4305209/). Ann Neurol. 76(5):643-657.
11. Timothy M. Miller et al. (2022) Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS. N Engl J Med; 387:1099-1110