NICE Highly Specialised Technology Assessment: Has Introduction of Willingness to Pay Thresholds Impeded Positive Guidance?

Buchanan V[1], Tahir W[1]

[1]Cogentia, Cambridge, UK

Contact the authors via cogentia.co.uk/contact

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BACKGROUND

- The Health Technology Assessment (HTA) process is well-suited to evaluating treatments that are expected to benefit large numbers, but concerns exist regarding their application to ultra-rare therapies, and whether standard HTA processes accurately reflect societal preferences for treating rare diseases[1]
- NICE introduced the highly specialised technology (HST) programme in 2015 to consider drugs for ultra-rare diseases, with lower evidence requirements than standard technology appraisals and without clear Willingness-to-pay (WTP) thresholds
- Discrete WTP thresholds were introduced to HST in April 2017. HST WTP thresholds vary on a sliding scale according to undiscounted QALY gains to the patient in their lifetime – ranging from £100,000 for therapies that deliver fewer than 10 QALYs to the patient, rising to £300,000 for treatments that deliver more than 30 additional QALYs to the patient[2]

OBJECTIVE

- This study examined whether introduction of discrete WTP thresholds has impacted the publication of positive HST guidance

METHODS

- HSTs that were in development or had published guidance were identified on the NICE website and divided into those with submission dates before and after the introduction of WTP thresholds
- HSTs that had not been through at least one committee meeting by December 2019, or had been terminated or withdrawn, were excluded from this study
- The time from first committee meeting to publication of final evaluation determination (FED) or 1st March 2020, whichever was earlier, was recorded
- Additionally, the study recorded whether FED outcomes were positive or negative, and whether guidance was actually published

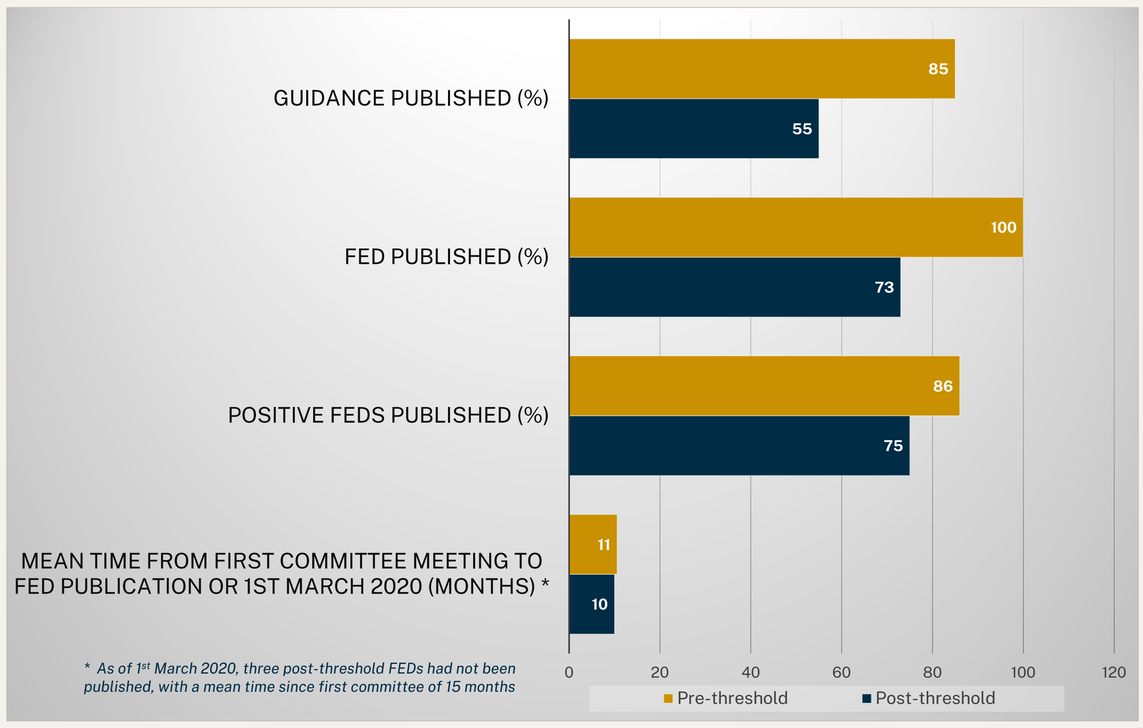
RESULTS

- The study identified 18 HSTs for inclusion (**Table 1**)
- Of the 18 included HSTs, 7 were submitted to NICE before the introduction of the WTP thresholds (i.e. pre-threshold), of which 6 (86%) had published guidance, all with a positive outcome
  - Only one pre-threshold HST had a negative FED and no guidance was published
- Eleven (out of the 18 identified HSTs) were submitted to NICE after the introduction of the WTP thresholds (i.e. post-threshold), of which 6 (55%) had published guidance, all with a positive outcome
  - Of the 5 post-threshold HSTs without published guidance, 2 of these had received FEDs (both with negative outcome) and 3 still had not received a FED by March 2020

HST timeframe

- For those HSTs with a FED, average time from first committee meeting to FED publication was 11 months pre-threshold HST versus 9 months for post-threshold HST
- For the 3 HSTs that were still awaiting a FED (all submitted post threshold), a mean time of 15 months (3–22 months) had elapsed from first committee meeting until March 2020

Figure 1 Comparison between pre- and post-threshold outcomes



* As of 1st March 2020, three post-threshold FEDs had not been published, with a mean time since first committee of 15 months

Table 1 Summary of highly specialised technologies

	HST ID	Name	Publication status	Date of first committee	Date of FED	FED outcome	Date of guidance
PRE-THRESHOLD							
1	HST1	Eculizumab for treating atypical haemolytic uraemic syndrome	Published	15/12/2013	25/12/2014	Positive	28/01/2015
2	HST2	Elosulfase alfa for treating mucopolysaccharidosis type Iva	Published	15/03/2015	23/11/2015	Positive	16/12/2015
3	HST3	Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene	Published	15/09/2015	15/05/2016	Positive	20/07/2016
4	HST4	Migalastat for treating Fabry disease	Published	15/09/2016	03/01/2017	Positive	22/02/2017
5	HST5	Eliglustat for treating type 1 Gaucher disease	Published	15/09/2016	31/05/2017	Positive	28/06/2017
6	HST6	Asfotase alfa for treating paediatric-onset hypophosphatasia	Published	21/10/2015	05/07/2017	Positive	02/08/2017
7	ID737	Lysosomal acid lipase deficiency - sebelipase alfa	In development	20/01/2016	13/02/2017	Negative	no guidance published
POST-THRESHOLD							
1	HST7	Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency	Published	28/09/2017	28/12/2018	Positive	07/02/2018
2	HST8	Burosumab for treating X-linked hypophosphataemia in children and young people	Published	23/05/2018	05/09/2018	Positive	10/10/2018
3	HST9	Inotersen for treating hereditary transthyretin amyloidosis	Published	14/11/2018	16/04/2019	Positive	22/05/2019
4	HST10	Patisiran for treating hereditary transthyretin amyloidosis	Published	14/11/2018	08/07/2019	Positive	14/08/2019
5	HST11	Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations	Published	25/07/2019	04/09/2019	Positive	09/10/2019
6	HST12	Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2	Published	17/01/2018	25/10/2019	Positive	27/11/2019
7	ID861	Metreleptin for treating lipodystrophy	In development	28/06/2018	06/06/2019	Negative	no guidance published
8	ID927	Afamelanotide for treating erythropoietic protoporphyria	In development	23/11/2017	22/05/2018	Negative	no guidance published
9	ID800	Velmanase alfa for treating alpha-mannosidosis	In development	25/04/2018	no FED	No FED	n/a
10	ID856	Human alpha1-proteinase inhibitor for treating emphysema	In development	23/08/2018	no FED	No FED	n/a
11	ID1326 *	Volanesorsen for treating familial chylomicronaemia syndrome	In development	28/11/2019	n/a	No FED	n/a

* *Following completion of this study, this HST was published as HST13, Publication date 21 October 2020, with a positive outcome*

CONCLUSIONS

- Compared with pre-threshold HSTs, a smaller proportion of post-threshold HSTs appear to be reaching FED within the same timeframe
- Furthermore, in contrast with NICE single technology appraisals (STAs), only positive FEDs appear to be converted into HST guidance
- With the caveat of small numbers, publication of NICE HST guidance appears to be reduced and positive guidance more challenging to achieve in the post-threshold era
- This study demonstrates that, whilst the HST process has been introduced to overcome some of the challenges presented to ultra-rare therapies, introduction of discrete WTP thresholds may have introduced a barrier
- The basic WTP threshold in HST is £100k/QALY, with higher thresholds possible at committee's discretion following convincing demonstration of significant QALY gains
- The prices required to meet this threshold may be unsustainable commercially in ultra-orphan indications, an issue highlighted by Berdud et al. (2020)[3], who estimated a threshold of around £900k as an appropriate cut off
- While it is appropriate to subject ultra-orphan medicines to cost-effectiveness assessments, NICE should consider whether a threshold that is only 3.5 to 5 times that of STAs may currently be prohibitively low for developers of ultra-orphan medications, which typically are prescribed to less than 100 patients in the UK
- Reduced or slower access will inevitably disadvantage those patients with ultra-rare diseases

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