Sir David Haslam
NICE Chair
National Institute for Health and Care Excellence
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20th August 2018

Dear Sir Haslam

Re: nusinersen NICE technology appraisal for Spinal Muscular Atrophy

We are writing to you as clinicians involved in the care and translational research of children with a devastating neuromuscular disease, spinal muscular atrophy (SMA), to express our strong dissatisfaction with the recent decision of NICE technology appraisal committee not to recommend nusinersen for reimbursement in England.

We are extremely concerned about the lengthy process for the NHSE and NICE appraisal of nusinersen; by the lack of clarity of the appropriate path for NICE to adopt for the appraisal of nusinersen, and for the implications of these choices for the well-being and clinical outcomes of our SMA patients.

In addition, we are writing to convey the pressing ethical issues that we face as physicians working on the ground with this rare, devastating and fatal condition for which now an effective therapeutic approach is available. This drug is available in most of our neighbouring countries, but not in the UK (outside the sponsor initiated Expanded Access Program for a subgroup of children with SMA1, who receive the drug freely from Biogen).

Nusinersen has clearly demonstrated a very robust therapeutic effect with highly significant positive results on the functional outcome of affected SMA children, their health and survival. Following well conducted studies in which some of the UK centres took part (Lancet 2016, PMID: 27939059; NEJM 2017 PMID: 29091570; NEJM 2018, PMID: 29443664) this drug was approved by FDA in December 2016, less than 4 months from the study end; and by EMA shortly after.

Severely affected children with SMA1 (who never acquire sitting position and who typically die at a mean age of 9 months of life) now have the prospect of a therapy that – especially if initiated close to the onset of disease- can very substantially reduce the respiratory comorbidities and deaths; allows a proportion of affected children the ability to acquire the sitting position; to stand, and to participate to life by speaking, as they, for the first time can move sufficient air to generate speech. Neither we as expert clinicians, nor the peer reviewed excellent publication track record, nor FDA or EMA has any doubt that nusinersen is an effective therapeutic intervention for SMA. It is also clear however that delaying the initiation of treatment in this severe neurodegenerative disease leads to worse outcome. In particular, once an affected child has lost motor neurons and becomes paralysed, it is unlikely that they will be able to regain motor or respiratory function this again with treatment.

Nevertheless, the path for nusinersen assessment by NHSE and NICE in England followed an extraordinary convoluted and lengthy path which we summarise below.

Expanded Access Program. The double blind placebo controlled clinical trial of nusinersen was interrupted by the Sponsor in August 2016, as the result of predefined improvement in survival and motor milestones achievement in the SMA1 children, and this made it unethical to continue the blinded study. The Sponsor agreed in September 2016 to make the drug

nusinersen available free of charge in most countries via an EAP, provided there was a possible path for future drug adoption in the selected countries.

We are disappointed to report that England was one of the last countries to enable the EAP to be initiated (August 2017). At that time the EAP had been running in 23 other countries-17 from Europe- and the investigators and clinicians were reporting data on feasibility and efficacy on their EAP treated population. This led dozen of patients and their families to go abroad to get access to the EAP (for example to France; Austria, Germany); this contrasted with the instructions that NHSE provided to the individual trusts when they made enquiries about starting the programme, clearly stating that there would be no reimbursement of the patients assessment and hospital visits.

This delay of ~ 10 months put England as one of the last countries worldwide to have had access to nusinersen, with detrimental impact on the clinical outcomes of the SMA1 patient population in this country, unless families were able and prepared to travel abroad to access therapy – with all the potential risks of travelling with a very sick child.

Nusinersen NICE appraisal

The next lengthy step has been for NHSE and NICE to provide the Sponsor with a path for having the drug appraised in England. The initial scoping took place in January 2017 but it took a year (January 2018) i.e. 12 months after FDA approval and 7 months after EMA approval, to make a decision which appraisal route it should take. By that time, the dug was already commercially available in several EU countries and in the US.

In January 2018 NICE indicated that Nusinersen would be appraised via the single technology appraisal (STA) route used for regular commissioning services, not the highly specialised technologies (HST) route. This choice was apparently due to the fact that in England, contrary to most of the other countries, the definition of rare disease is different; and, in addition, the decision was made to assess nusinersen for all forms of SMA including those with onset in adult life. While from a genetic perspective this milder condition are allelic to the severe infantile or childhood onset forms of SMA, the impact on survival, function and health of these different forms is completely different.

As a result of this decision, the NICE evaluation used the STA's key measure of a therapy's effectiveness that is appropriate for more common diseases i.e. the QALY life improvement. This metric is however clearly inappropriate for devastating conditions affecting infants, of which there are approximately 60-100 with SMA every year in the entire UK, and indeed this metric has not been used in other similarly devastating early childhood diseases.

This inequality of assessment of devastating childhood conditions now leads to inequality of access to this life-saving drug for children with the severe forms of SMA. Even members of the NICE team have acknowledged - expressing their personal opinion - that the binary options of having either an appraisal mechanism for assessing rare devastating diseases on one hand, and another one for assessing milder and more common diseases, leaves no process for assessing drugs that have a role in situations like this one.

Our clear opinion, which we voiced also during public consultations of the drug and at All Parliamentary Party groups meetings at the House of Commons, is that to appraise a drug such as nusinersen using the regular commissioning route is inappropriate. We also feel that the complete lack of flexibility in the way NHSE and NICE appraise drugs for these groups of patients, fails to provide an effective mechanism to respond to the needs of subgroups of children with devastating conditions.

As indicated above, we are the physicians in the frontline who manage these patients and are currently and reluctantly needing to manage the frustration of families who are faced with accepting the deterioration and death of their children despite an effective treatment being available.

Cost of the drug. We are fully aware that one of the concerns, explicitly expressed by NHSE and NICE relates to the perceived or likely high drug cost of nusinersen. We completely agree that every effort should be made to ensure that the NHSE has access to reasonably priced drugs for our patients, and that these drugs must provide a clear benefit to patients.

We note however that successful negotiations have been held already in 20 countries where nusinersen is available to patients affected by early onset SMA (including Scotland), while the drug is anticipated to become available imminently in another 20 countries as a result of a clear path for approval.

While we support the efforts that NHSE and NICE put in ensuring that drug prices are proportionate and reasonable, we clearly see that in this country, the answer to the drug price has not been that of entering in frank negotiations with the company, but has been instead to put an infinite series of obstacles which are presented as a "process" that we find ourselves unable to support nor we think it is working in the interest of our patients.

In view of the risk for the health to our patients that this long series of delays are causing, we urge NHSE and NICE to identify processes that are fit for the purpose to provide the expected standards of care to the SMA patient in England. We note that as part of our GMC duties, our primary aim is to work to ensure best outcome for our patients. The situation regarding nusinersen creates an ethical dilemma for the treating physician, one that in other countries the respective health authorities have dealt with more effectively than here.

Repercussions of an effective path to appraise and adopt novel therapies for translational research in England. We finally wish to point out that while the research infrastructure of England, heavily supported via NIHR, is one of the most efficient in the world; the mechanism of assessment and potential adoption of novel drugs is antiquated and unfit for purpose of the 21st century. This has started to alienate industrial partners from considering this country as "the place" to perform experimental studies, with detrimental consequences for our research environment and eventually the health of our patients.

Yours sincerely

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Note: due to the summer holidays we have not been able to reach out to every single member of the SMA REACH network; and of the BMS. A list of the colleagues of these two networks who have had the time to respond and endorse this document can be found in the last page.

Also note that the views expressed in this letter are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health, nor of the respective NHS Trusts and Universities where we work.

CC:

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- *Dr Simon Stevens, CEO NHSE*
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As well as clinicians from across the country, signatories included SMA Support UK, The SMA Trust, Muscular Dystrophy UK and TreatSMA.