



A rare chance for reform

A new way forward for
evaluating medicines for
rare and ultra-rare diseases
in England

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Foreword from BIA



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Living with a rare or ultra-rare disease, many of which affect children, is tough. Particularly for families and carers. And still, despite incredible innovation from the life sciences sector, and successful regulatory incentives, the large majority of rare disorders lack licensed treatment options.

And what frustrates the community is that even when a successful therapy is developed and licensed, after many years of financial risk from companies supporting brave participants in clinical trials, people with rare diseases in England then still continue to suffer further limits and delays to the long hoped for treatments that can change and improve their lives, as well as those of their carers and families.

2020 shows that innovation can happen at pace. Covid 19 has transformed healthcare profoundly. NICE has had a once in a generation leadership change and is consulting on the Methods Review which has fostered a rethink on how we value medicines, patient care, and quality of life. But we need to continue discussions in areas adjacent to the specific scope of the review.

A straightforward, understandable and rapid process that respects and puts at its heart the needs of patients for rare diseases has significant benefits for the NHS and for the UK life science sector as it seeks to attract global investment.

We will need to enhance the framework for rare and ultra-rare diseases for the UK to continue to be an attractive primary launch market for these treatments in the post-Brexit era, else delays for NHS patients in England could get longer.

Fortunately, we currently have a government that recognises the excellence and importance of our sector, and is determined to increase investment into R&D. The new Innovative Medicines Fund can directly support this ambition. As the UK becomes a stand-alone market the posture and policies of the NHS on access will have a larger effect on global boardroom sentiment towards the UK and inform decision-making in terms of when and where to launch products, invest in R&D, manufacturing, operations and clinical trials.

The UK boasts an excellent research ecosystem which fosters incredible innovation in orphan and ultra-orphan medicines. In particular the UK's early investment in the understanding of genomics for rare disease makes it a great place to be able to both treat patients earlier in the disease pathway and then monitor for the longer term. Orphan medicines are forecast to comprise over 20 per cent of worldwide prescription medicine sales by 2024¹.

Many of the key growth companies in life science have a strong focus in rare disease. If we attract companies working in this area to the UK it will attract significant global R+D focus of this vital industry to anchor more activity here.

The BIA convened a group of its members interested in rare diseases to form the Rare Disease Industry Group, which has spearheaded this work. This report contains a package of recommendations that will go a long way to address these issues. Now more than ever do we need a rare and ultra-rare disease framework that works for patients, the sector, and the country.

¹ EvaluatePharma, Orphan Drug Report 2019, April 2019, available online via: <https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma%20Orphan%20Drug%20Report%202019.pdf>

Foreword from PwC



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We are pleased to be supporting BIA on this important piece of research and thank the companies, industry bodies, clinicians and patient associations who have contributed and helped make this work possible.

The impact of rare and ultra-rare diseases places a huge burden on patients, their families, carers and society. The nature of the diseases is often severe, and for most patients, there are no approved medicines. The pharmaceutical industry has made significant progress in developing new innovations to treat these diseases, but this innovation comes at a cost. It is largely through incentives such as the EU Orphan Regulation and conditional marketing authorisation, which accelerates access to the market, that industry can achieve meaningful returns on their investment.

However, due to the constraints of managing rising healthcare costs, access to new and innovative treatments is often restricted through the reimbursement appraisal process. Whilst obtaining value for money is an important consideration, the current process creates delays in access and risks undermining the regulatory effort to accelerate patient access to life saving medicines.

Early access to patients through rapid reimbursement is a real attraction for industry and how it prioritises investment and launches of new drugs. The pharmaceutical industry is a key pillar of the UK's Industrial Strategy. Post Brexit, with the end of transition period looming, it is vital that the UK maintains its status as an attractive early launch market, and a place where innovation can thrive.

The debate should consider the unique nature of orphan and ultra-orphan medicines and the uncertainty that exists when it comes to understanding their value. We hope that this research informs the debate by highlighting the challenges with the current process and the opportunities that exist to introduce mechanisms that will deliver better outcomes for patients, their communities, the NHS and industry.



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Executive summary

The NHS prides itself on its provision of gold-standard care for all patients and enjoys a reputation as one of the best healthcare systems in the world.

However, when it comes to medicines for rare and ultra-rare diseases (known as 'orphan' and 'ultra-orphan' medicines), there is scope to improve flexibility and create a more pragmatic system that takes into account the unique challenges presented by these diseases. The current appraisal process is not fit for purpose and does not offer incentives to innovation consistent with those of other advanced economies. In countries where those incentives exist, access to orphan medicines is often faster and more widespread. Despite the efforts of the

National Institute for Clinical Excellence (NICE) to enhance processes and improve patient access, many issues remain.

This paper outlines a new way forward. The framework it sets out will enable stakeholders to come together to value orphan and ultra-orphan medicines with the aim to increase patient access, ensuring they receive orphan and ultra-orphan medicines as quickly as possible, while continuing to offer value for money for the NHS. Rare and ultra-rare diseases place a heavy burden on patients, caregivers, families, society, and the NHS. We hope this framework will go some way to easing it.

We also recognise that system level change, including the way medicines are funded, as well as methodological changes, are needed to improve patient access to orphan and ultra-orphan medicines. Therefore, our recommendations within this report have been allocated against these two themes. Early access to medicines for patients and rapid reimbursement are fundamental to the way industry prioritises local investment and global launches. It is imperative that the UK does not continue a situation where access may be compromised due to the de-prioritisation of the UK as an early launch market for medicines for rare and ultra-rare diseases.

Recommendations that will require system level change

Accelerate access through a conditional access period: Introduce a fast initial evaluation that grants conditional access through a Managed Access Agreement, at a price consistent with other fast-adopting countries. The proposed Innovative Medicines Fund (IMF) would be the ideal vehicle to fund medicines within the Managed Access Agreement. This initial access should be followed by a more in-depth re-evaluation after a period agreed on a medicine by medicine basis, to improve the certainty and quality of data available for assessment. This process should be aligned with the existing accelerated regulatory processes by which drugs are often approved and be supported by adequate infrastructure to enable collection of real world evidence.

Address systemic issues to build a strong environment for access to orphan and ultra-orphan medicines:

Resolve systemic issues such as consistency in evaluations, balancing value for money and patient needs, and ensuring appropriate infrastructure is in place to maximise the value of these treatments.

Increase sustainability of funding for rare diseases: Increase sustainability in funding arrangements for orphan and ultra-orphan medicines by reinvesting savings made from appropriate use of biosimilars and generics, and agreements such as VPAS, into the orphan medicine ecosystem.

Recommendations for changes in the way orphan and ultra-orphan medicines are appraised

Update the evaluation framework to better account for the unique challenges of rare and ultra-rare diseases:

As an outcome of the NICE Methods Review, assessments should be adapted to determine the value of orphan and ultra-orphan medicines holistically, by capturing direct health benefits and indirect benefits. This can be achieved by amending the way that clinical and cost effectiveness are calculated and pragmatically used, and increasing the flexibility for incremental cost-effectiveness ratio (ICER) thresholds through modifiers, to ensure the process is fairer and more robust.

Evaluate orphan medicines and ultra-orphan medicines through a single rare disease process: Adopt a single process to ensure that all orphan and ultra-orphan medicines are assessed by a process that accounts for their unique challenges.

Assess empirically based ICER thresholds on a sliding scale: Create a sliding scale of thresholds for assessing orphan medicines supported by clear criteria on where an orphan medicine falls on the scale, to remove the need for arbitrary thresholds.

Continue to create a supportive atmosphere for patient groups: Strengthen NICE's existing approach to empower patient groups by identifying and addressing the concerns of smaller patient organisations, improving communication with stakeholders during the evaluation process and providing clarity on how evidence presented by patient groups translates into decisions.



Introduction and background

There is a high unmet need for rare disease patients

3.5 million people in the UK will be affected by a rare disease at some point in their lifetime and 75 per cent of rare diseases affect children². Approved medicines are available for only five per cent of rare diseases; so many patients live with debilitating symptoms or die prematurely³. This, of course, places a huge burden on caregivers, families and society.

Rapid strides in new technologies are leading to new treatment paradigms for conditions that previously had no treatments. In addition to benefitting patients with rare diseases, such technological progress can lead to broader indications, unveiling novel treatment opportunities for common diseases and economies of scale. For instance, RNAi therapies were first approved for rare genetic disease hereditary transthyretin (hATTR) amyloidosis. Now, more than ten phase III clinical trials of RNAi therapies are currently underway for more common liver-related diseases⁴.

The importance of accelerating new innovations for the treatment of rare and ultra-rare diseases is reflected in the EU Orphan Regulation, which has been in place since 1999 and provides 10 years of market exclusivity alongside protocol assistance, reduced fees for regulatory activity and additional incentives for small to medium enterprises. In addition to this framework, the European Medicines Agency (EMA) can grant accelerated assessment and conditional market authorisation, prior to availability of comprehensive data sets, on the basis of data collection. The UK has additional supporting mechanisms such as the Early Access to Medicines Scheme (EAMS), which allows patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need.

Yet whilst these incentives support further development of medicines for rare diseases and accelerated access to the market from a regulatory perspective, they are disconnected from country level reimbursement pathways and often the process of determining value undermines any regulatory efforts to accelerate patient access⁵. Health systems must create efficient and effective processes to value rare disease medicines (known as orphan medicines) and create appropriate incentives in order to foster this innovation and reduce delays to patient access.

² Genomics England, Rare disease genomics [online] Available at: <https://www.genomicsengland.co.uk/understanding-genomics/rare-disease-genomics/>

³ PhRMA (2015) A decade of innovation in rare diseases [online] Available at: <http://phrma-docs.phrma.org/files/dmfile/PhRMA-Decade-of-Innovation-Rare-Diseases4.pdf>

⁴ Nature (2019) Why rare genetic diseases are a logical focus for RNA therapies [online] Available at: <https://www.nature.com/articles/d41586-019-03075-5>

⁵ Office of Health Economics (2009) Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries [online] Available at: <https://www.ohe.org/publications/access-mechanisms-orphan-drugs-comparative-study-selected-european-countries#>

Unlike treatments for common diseases, treatments for rare diseases face unique challenges

By definition, orphan medicines are targeted towards smaller populations (prevalence of fewer than 5 cases per 10,000 population⁶) compared to common disease treatments. In addition, many orphan medicines are targeted towards conditions that are life-threatening or chronically debilitating. Finally, the rare nature of these diseases means they are often not well understood. A combination of these factors creates a unique set of considerations that need to be accounted for while evaluating the value of such treatments.

- Orphan medicines often face limitations in data and many treatments have limited natural history and epidemiology data.
- There is a high level of uncertainty from clinical trial data due to small sample sizes, shorter trials, and the necessity for single-arm trials.
- Many orphan diseases have no current treatment alternatives and first-in-class treatments with no suitable comparators are inherently disadvantaged due to the great difficulty in proving their clinical and cost effectiveness.
- There is a high degree of burden on caregivers, society and the economy due to the severe nature of rare diseases and the fact they often afflict children⁷.

Many countries have created special considerations in their evaluation processes to tackle some of the unique challenges of rare diseases

Health systems around the world have recognised that it is not pragmatic to apply precise evaluation processes on data that is highly uncertain and/or riddled with assumptions. Recognising these unique challenges, many countries have introduced flexible mechanisms to evaluate orphan medicines and provide faster access to medicines for patients. We note some examples below:

- **Germany:** Access is immediate followed by a post-launch evaluation process that allows for a higher degree of uncertainty in the evidence presented. Marketing authorisation and orphan designation are sufficient parameters to grant additional benefit, provided the budget impact is less than €50 million per year⁸.
- **France:** Additional benefit for an orphan medicine is assumed to have been proven if the budget impact is less than €30 million per year. Fast track procedures exist for innovative drugs (including non-orphan)⁹.

- **Sweden:** The Swedish system has the flexibility to consider a higher cost-effectiveness threshold for orphan medicines and adjust the approach based on the level of unmet need and uncertainty¹⁰.
- **Taiwan:** Almost every listed product is reimbursed through a separate budget dedicated to rare disease treatments. A comprehensive rare disease health and social support system provides special nutritional products for patients with rare diseases and a high degree of subsidies and assistance for patients and carers^{11 12}.
- **Scotland:** The Scottish Medicines Consortium's (SMC's) has a new pathway that provides conditional access to ultra-orphan medicines for three years while further information is gathered¹³. Furthermore, the SMC evaluation process for orphan medicines includes a Patient and Clinician Engagement (PACE) meeting, giving patients and clinicians a stronger voice¹⁴.



⁶ European Commission. (2020). Rare diseases. [online] Available at: https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en

⁷ Bonner N, Hall R, Tritton T, Grimes R, Trennery C, Spencer H, Bennett B (2017) Rare Diseases, Are Caregivers Just As Affected As Patients?

⁸ Kawalec P, Sagan A, Pilc A (2016) The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe, Orphan Journal of Rare Diseases, 11:122

⁹ RTI Health Solutions (2018) HTA and Reimbursement Considerations for Rare Diseases in European Markets: What Are the Implications for Manufacturers? [online] Available at: <https://www.rtihs.org/publications/hta-and-reimbursement-considerations-rare-diseases-european-markets-what-are>

¹⁰ Adkins EM, Nicholson L, Floyd D, Ratcliffe M, Chevrou-Severac H (2017) Oncology drugs for orphan indications: how are HTA processes evolving for this specific drug category?, Clinicoeconomics and Outcomes Research, 9:327–342

¹¹ Taiwan Ministry of Health and Welfare M. policies and events and The Rare Disease and Orphan Drug Act. 2015 [online]. Available at <https://www.hpa.gov.tw/EngPages/Detail.aspx?nodeid=1038&pid=10598>

¹² Dharssi, S., Wong-Rieger, D., Harold, M. et al (2017) Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet J Rare Dis 12, 63

¹³ Scottish Government (2018) Treatments for rare conditions [online] Available at: <https://news.gov.scot/news/treatments-for-rare-conditions>

¹⁴ Scottish Government (2018) Treatments for rare conditions [online] Available at: <https://www.scottishmedicines.org.uk/how-we-decide/pace/>

While England has taken steps to account for the challenges of orphan medicines, a few principal issues exist that can be improved upon

A report from the Office of Health Economics¹⁵ noted that fewer than half of orphan medicines are reimbursed in England, compared to over 80 per cent in Germany and France. For those that are reimbursed, the process is far slower on average, at roughly 28 months in England, compared to 20 months in France and immediate access in Germany.

This is not to suggest England has been ignoring the issue. The National Institute for Health and Care Excellence (NICE) replaced the Advisory Group for National Specialised Services (AGNSS), introduced its Highly Specialised Technologies (HST) process in 2013 and revised it in 2017 to create a new pathway for evaluating ultra-orphan medicines¹⁶. Whilst this was a positive step forward, and access times of ultra-orphan medicines in this process have decreased in the past year¹⁷, the move increased the emphasis on quality-adjusted life year (QALY)-based decisions, a challenge which we expand on further in this report.

Furthermore, only 12 medicines have been evaluated under the HST process in the seven years since it was created¹⁸, while the bulk of orphan medicines have historically ended up in a non-HST process, which is not typically suitable for evaluating orphan medicines¹⁹. More can be done to adapt the value assessment to orphan medicines, ensure fast access without undermining sustainability or value for money.

There are several reasons for England's modest level of access to orphan and ultra-orphan medicines, and numerous reports have explored the topic (including those from the Genetic Alliance²⁰, the Office for Health Economics²¹, and the 2019 All-Party Parliamentary Groups (APPG) Report on Access to Medicines and Medical Devices²²). The principal issues with the current evaluation system are:

- **Orphan medicines can fall through the cracks.** Orphan medicines often end up being assessed by processes that were designed for drugs with much larger target populations. Because the HST process (the only process designed for orphan medicines) has such narrow eligibility criteria, orphan medicines and even some ultra-orphan medicines fall into the Single Technology Appraisal (STA) process²³, which was designed for evaluating medicines for common diseases. This puts orphan medicines at a disadvantage.
- **The existing evaluation processes and frameworks do not accommodate for orphan medicine nuances.** This includes, for example, the limited ability to use disease specific tools for collecting Quality of Life (QoL) information. Such bespoke frameworks are important for rare diseases since they capture nuances not captured otherwise by generic instruments such as the EQ-5D. Furthermore, whilst the HST framework acknowledges the importance of indirect treatment benefits (e.g. impact on carers and society), in reality their role in the evaluation process is limited.

- **Communication with patient groups can be improved.** As noted in the Genetic Alliance report and confirmed through our discussions with various patient groups, once a medicine enters the evaluation process, the progress is not often well communicated. Furthermore, smaller patient groups noted that given their limited experience with NICE and the limited resources they possess, they face challenges in effectively navigating the process (e.g., in determining the type of evidence that might be most meaningful in a NICE evaluation process). Whilst there are many good examples of NICE engaging with patient groups, we believe more can be done.
- **Other systemic issues exist.** As noted in the APPG report, there is lack of clarity on how and where rebates from schemes such as VPAS (the voluntary scheme for branded medicines pricing and access) is reinvested. It is also unclear whether or how the UK re-invests savings created from the increased use of generics and biosimilars when older medicines lose exclusivity. There are concerns about the variability of NICE's assessment outcomes by the Evidence Review Groups (ERGs) which should be addressed. Finally, in many cases the infrastructure required to enable treatments to be most effective is missing.

¹⁵ Office of Health Economics (2017) Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries [online] Available at: <https://www.ohe.org/publications/comparing-access-orphan-medicinal-products-omps-united-kingdom-and-other-european>

¹⁶ NICE (2017) Interim Process and Methods of the Highly Specialised Technologies Programme Updated to reflect 2017 changes [online] Available at: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf>

¹⁷ Genetic Alliance (2019) Action for Access [online] Available at: <https://actionforaccess.geneticalliance.org.uk/>

¹⁸ NICE Guidance and Advice List, Highly Specialised Technologies Guidance [online] Available at: <https://www.nice.org.uk/guidance/published?type=hst>

¹⁹ MAP BioPharma (2019) Access to Orphan Medicines: A Case for Change [online] Available at: <https://mapbiopharma.com/home/publications/access-to-orphan-medicines-a-case-for-change/>

²⁰ Genetic Alliance (2019) Action for Access [online] Available at: <https://actionforaccess.geneticalliance.org.uk/>

²¹ Office of Health Economics (2018) Appraising Ultra-Orphan Drugs: Is Cost-Per-QALY Appropriate? A Review of The Evidence

²² All-Party Parliamentary Group on Access to Medicines and Medical Devices (2019) NICE Methods Review [online] Available at: <https://mapbiopharma.com/wp-content/uploads/2019/09/NICE-Methods-Review-Report-APPG-on-Access-to-Medicines-and-Medical-Devices.pdf>

²³ MAP BioPharma (2019) Access to Orphan Medicines: A Case for Change [online] Available at: <https://mapbiopharma.com/home/publications/access-to-orphan-medicines-a-case-for-change/>

The events of COVID-19 have raised the important issue of social inequity. There are many parts of society whose health has been more severely impacted by COVID-19, and the situation has galvanised many stakeholders within the ecosystem to act urgently to address the disparity in health outcomes. This demonstrates that the NHS and the government, if willing, can make effective and efficient decisions at pace by cutting through regulatory, political and bureaucratic hurdles while keeping patients' interests and needs at the forefront. For patients with rare and ultra-rare diseases every day is an emergency and we need to act with the same level of urgency to address the issue of access to orphan and ultra-orphan medicines.

Finally, early access to patients and rapid reimbursement are fundamental to the way industry sets investment and launch priorities. If the situation continues the UK risks losing its status as an attractive early launch market, which will only increase the delays for patient access to these life saving medicines.



Case study 1

Nusinersen (Spinraza) for Spinal Muscular Atrophy (SMA)

SMA is a rare, genetically inherited neuromuscular condition causing progressive muscle weakness and muscle wasting in patients, with the most severe types affecting babies and young children. Spinraza, the first and only disease-modifying treatment for SMA, was approved by the European Medicines Agency (EMA) in June 2017²⁴.

NICE considered that the number of patients was likely to be too high for consideration under the dedicated ultra-orphan HST process²⁵. Spinraza

was therefore assessed under the STA process. Due to uncertainty about the treatment's long-term benefits and cost-effectiveness, it received a 'not recommended' decision in August 2018. However, NICE reconsidered the decision in July 2019, almost two years after the EMA approval was granted. The drug is now available, after Biogen, the manufacturer, entering into a Managed Access Agreement (MAA) with NHS England²⁶.

Spinraza's delay can be attributed to three key factors. One, lack of a clear

path for evaluating rare disease treatments (HST vs. STA). Two, lack of a well-defined conditional approval pathway for rare diseases when there is uncertainty. Three, evaluating a rare disease treatment under the inflexible STA process imposes unrealistic expectations about available evidence and ability to meet tight cost-effectiveness thresholds.

Delays and process deadlocks such as in this case can ultimately cause significant and irreversible damage to many patients.

²⁴ European Medicines Agency (2017) First medicine for spinal muscular atrophy [online] Available at: <https://www.ema.europa.eu/en/news/first-medicine-spinal-muscular-atrophy>

²⁵ NICE (2018) STA: Nusinersen for treating spinal muscular atrophy, Response to consultee and commentator comments on the draft remit and draft scope (pre-referral) [online] Available at: <https://www.nice.org.uk/guidance/ta588/documents/scope-consultation-comments-and-responses>

²⁶ NICE (2019) Spinraza Access Agreement Extended [online] Available at: <https://www.nice.org.uk/news/article/nice-recommends-first-ever-treatment-for-children-with-rare-muscle-wasting-condition>



Recommendations for a new process

To address the issues described above, we have several recommendations for a new framework for evaluating orphan and ultra-orphan medicines in England. To ensure this framework aligns with the values and principles of NICE and the NHS, and works well for all stakeholders, we have also established a set of guiding

principles which act as guardrails for our recommendations. These principles are aligned and complementary to those described in similar recommendations for valuing and funding medicines such as the ones published by the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL)²⁷.

Guiding Principles

Ensure all patients have **equity of access** to medicines

Provide patients with **access to medicines 'immediately'** after authorisation, without delays

Simplify the complex reimbursement landscape that exists today

Create **value** for all stakeholders, including patients, the NHS and industry

Be **accommodative** of the unique issues faced by orphan medicines

Ensure **transparency** to all the stakeholders involved

NICE is currently conducting a detailed health technology evaluation methods review²⁸. Given this context, we have separated our recommendations into two categories, those that we believe should be adopted immediately through the NICE Methods Review process, and those that may need a longer timeframe for adoption.

Whilst the NICE Methods Review offers a platform to anchor our recommendations, we believe that amending the methodology of the appraisal process does not go far enough and NHS England will need to drive fundamental 'system level' change to improve patient access to orphan and ultra-orphan medicines.

²⁷ Annemans, L., Aymé, S., Le Cam, Y. et al. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). *Orphanet J Rare Dis* 12, 50 (2017). <https://doi.org/10.1186/s13023-017-0601-9>

²⁸ NICE (2019) NICE announces details of health technology evaluation methods review [online] Available at: <https://www.nice.org.uk/news/article/nice-announces-details-of-health-technology-evaluation-methods-review>

Recommendations that will require system level change

1

Accelerate access by accounting for uncertainty through the use of a conditional access period

For medicines with unresolved areas of uncertainty in value, we recommend granting conditional access within three months of marketing authorisation through a managed access agreement (MAA). A three-month initial evaluation period would be followed by a more thorough re-evaluation after a period of time agreed on an individual medicine basis. The Conservative Government's proposal to expand the Cancer Drugs Fund (CDF)²⁹ to include other innovative medicines through the Innovative Medicines Fund (IMF)³⁰ is a positive step towards improving access to cutting-edge treatments, and would be the ideal vehicle to fund the MAA.

As noted earlier, other countries such as France and Germany provide temporary and conditional pathways to support rapid access to orphan medicines with reassessments post launch to establish a more complete picture of value. These pathways fulfil an important role and help to accelerate patient access to important treatments without undermining the sustainability of the health system. Conditional launch also increases the attractiveness of clinical research in England as sponsors benefit from continuity of access from clinical development to commercial launch.

Such an approach would not only accelerate average patient access to rare disease treatments in England by over two years, but would also provide NICE with a more informed evidence base as additional evidence is collected during the conditional access period.

Our recommendation envisages three stages for a MAA: initial evaluation, conditional access, and re-evaluation.

a) Initial evaluation

An initial evaluation process should be used to agree the terms by which the medicine will be later evaluated.

This three-month evaluation period would be similar to that of the pathway supported by the CDF. A simple 'yes', 'no', or 'recommended for conditional approval' decision would be reached, depending on the initial certainty of the data. As far as possible, EMA and Medicines and Healthcare products Regulatory Agency (MHRA) approval and NICE designation of plausible clinical benefit should be harmonised. Where this is not feasible, the manufacturer should provide additional information to determine the clinical benefit judged against the local standard of care.

The pricing in the interim period could be determined during this period in a similar approach used in by the French Autorisation Temporaire d'Utilisation (ATU) process. The ATU process facilitates accelerated conditional access by granting the manufacturer freedom to set the price, with provisions to clawback any difference between the set price and the final price determined after the final evaluation³¹. NHS England's budget impact test, which constitutes an annual ceiling of £20M in the first three years of treatment, is a healthy check to ensure the system is sustainable³².



²⁹ NHS England (2016) Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund), A new deal for patients, taxpayers and industry [online] Available at: <https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf>

³⁰ ABPI (2019) ABPI welcomes Innovative Medicines Fund pledge [online] Available at: <https://www.abpi.org.uk/media-centre/news/2019/november/abpi-welcomes-innovative-medicines-fund-pledge/>

³¹ Xcenda (2016) Rapid Access in the US, UK, and France [online] Available at: <https://www.xcenda.com/insights/htaq-fall-2016-rapid-access-in-the-us-uk-france>

³² NICE (2017) Budget impact test [online] Available at <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/budget-impact-test>

b) Conditional access

Medicines should be granted a period of conditional access whilst further evidence is collected and the details (and methodology) of a more thorough evaluation are agreed. The period for conditional access needs to be agreed on a medicine by medicine basis between the manufacturer and the NHS. We expect that novel treatments with higher areas of uncertainty may need longer time periods than those that are relatively well understood.

Specific areas of uncertainty, and the basis on which the medicine will be evaluated at the end of the conditional access period, need to be agreed upon. There should be a commitment to generate real world evidence (RWE) during the conditional access period and the appropriate infrastructure for data collection needs to be in place. Alignment will be needed to decide who collects the data, how it is collected and for how long.

Where possible these areas of uncertainty should be discussed during clinical development through NICE's Scientific Advice and Office for Market Access teams. This would allow for manufacturers to plan for effective and immediate collection of data in advance of launch. This will be particularly relevant in the case of new cell and gene therapies that are launching with prices in the range of £1 million per patient where immediate demonstration of effectiveness will be required.

Importantly, RWE is not in itself a panacea to the issue of uncertainty. Many rare diseases are barely understood and some treatments are applicable to only a handful of patients in the UK. In such cases, RWE may not materially resolve all the areas of uncertainty and the re-evaluation process will still need flexible mechanisms to evaluate rare disease treatments (discussed in the next recommendation).

c) Re-evaluation

A thorough re-evaluation will be needed to determine the final access decision and price. This second in-depth evaluation would mean the drug undergoes a full assessment based on a renewed Health Technology Assessment (HTA) submission by the manufacturer that incorporates the analysis from the data collected during the conditional access period. This process would need to take several factors into consideration, such as the nature of the condition, clinical effectiveness, cost effectiveness, and the wider non-clinical benefits³³. Whilst the current HST process does factor in these areas, there are certain elements that can be better addressed (these are discussed in the next section).

This recommendation raises some additional considerations for NICE, the NHS and manufacturers

Firstly, the proposed NHS England's Commercial Framework for Medicines³⁴ can provide the guidance in determining the type of commercial arrangement and the engagement required at various stages between the manufacturer and NICE/NHS England. We see the proposed Commercial Framework as a welcome step in improving communication and clarity between various parties and hope that the framework will continue to evolve with execution experience and keep pace with new technological advancements.

Secondly, RWE should form the backbone of MAAs, and collecting and analysing the necessary data requires thought and investment. Industry should continue to play a key role in supporting and funding the collection of data. The Systemic Anti-Cancer Therapy (SACT) dataset³⁵, which supports RWE collection for cancer therapies is a positive example of the collaboration between industry and the NHS.

Thirdly, in some cases, the conditional access period will not be enough to overcome the uncertainties that surround the value of orphan and ultra-orphan medicines. Due to the small number of patients there are cases where there will never be enough data to satisfy the robust nature of the evaluation process and a pragmatic approach is required in these cases.

³³ Source Health Economics (2019) The NICE HST Process (2/3) – Differences in Assessment of Cost-Effectiveness between the HST and STA [online] Available at: <https://www.source-he.com/post/2019/10/22/the-nice-hst-process-23-differences-in-assessment-of-cost-effectiveness-between-the-hst>

³⁴ NHS (2020) NHS Commercial Framework for Medicines [online] Available at: <https://www.engage.england.nhs.uk/consultation/nhs-commercial-framework-for-medicines/>

³⁵ SACT Systemic Anti-Cancer Therapy Chemotherapy Dataset [online] Available at: <http://www.chemodataset.nhs.uk/home>

2

Address systemic issues to build a strong environment for access to orphan and ultra-orphan medicines

We recommend three actions to resolve a number of systemic issues with orphan and ultra-orphan medicines:

a) Adapt the culture to balance value for money for the NHS with patient needs.

Patient groups and industry sponsors have noted a reluctance from NICE to move away from the traditional, highly evidence-based quantitative system. Indeed, NICE may be at risk of sacrificing its principles on equity of access and providing a high standard of care in order to maintain its reputation as a stringent evidence-based regulator^{36 37}. In the case of rare diseases, we believe NICE must be more flexible about which guidelines, thresholds, and metrics have greatest importance. We also believe NICE should adopt an approach of structured pragmatism, using case-by-case assessments where it makes sense to do so.

b) Reduce variability among Evidence Review Groups (ERGs).

Industry insiders have noted variability in the outcomes of assessments depending on which ERG handles the case³⁸. An analysis of outputs across ERGs can validate or reject this claim. Appropriate steps can be taken to improve the consistency of outcomes (such as creating an independent audit committee that could be sponsored by industry, implementing new training for ERGs and allowing ERGs to access the scarce experts in rare diseases who could also be consulting manufacturers). As NICE has committed to assessing all new medicines within VPAS, the volume of assessments will increase, and the issue of consistency may be further exacerbated. It is therefore essential that the right checks are in place to reduce variability.

c) Place a greater emphasis on the deployment of the infrastructure required to make an efficacious treatment more effective.

NICE has a role in promoting the availability of fundamental resources such as diagnostics to enable early detection, follow up support and counselling, symptom relief and social care to ensure patients with rare diseases are fully supported.

3

Increase sustainability of funding for rare diseases

NHS England should work towards increasing sustainability in funding arrangements for orphan and ultra-orphan medicines. We believe NHS England could do more to reinvest savings made from appropriate use of biosimilars and generics, and agreements like VPAS, into the orphan medicine ecosystem. This would be a significant step in making the UK an attractive location for research and development for cutting-edge treatments in line with the Life Sciences Industrial Strategy.



³⁶ Hashem F, Calnan MW, Brown PR (2018) Decision making in NICE single technological appraisals: How does NICE incorporate patient perspectives? *Health Expect*, 21(1):128-137

³⁷ Timmins N, Rawlins M, Appleby J (2016) A terrible beauty: A short history of NICE [online] Available at: http://www.idshealth.org/wp-content/uploads/2016/02/A-TER-RIBLE-BEAUTY_resize.pdf

³⁸ RTI Health Solutions (2018) Review of Possible Causes of Variation in National Institute for Health and Care Excellence (NICE) Technology Appraisals [online] Available at: <https://www.rtihs.org/publications/review-possible-causes-variation-national-institute-health-and-care-excellence-nice>

Recommendations for changes in the way orphan and ultra-orphan medicines are appraised

4

Update the evaluation framework to make it more appropriate for orphan and ultra-orphan medicines

We recommend an updated evaluation framework that better accounts for the unique challenges associated with rare and ultra-rare diseases to ensure fairer and more robust decisions. Specifically, we propose introducing elements to increase flexibility when evaluating orphan medicines and ultra-orphan medicines.

The proposed changes to the evaluation include:

a) Allow for the adoption of a tailored health measurement framework and a set of clinical endpoints through early discussions between manufacturers and NICE.

Standard instruments such as EQ-5D may not always be appropriate to capture disease specific nuances for rare diseases³⁹ (e.g. standard tools do not often adequately capture health improvements in many paediatric conditions and progressive diseases). Hence, we recommend increasing the openness to adopt bespoke frameworks as part of NICE's evaluation. This requires manufacturers to engage with NICE's Scientific Advice and Office for Market Access teams during clinical trials to ensure smoother downstream evaluation. We recognise however, that these teams would need increased investment to support the scale that comes with the vast number of new treatments that require their own bespoke measurement frameworks. NICE will need to work with the EMA and MHRA to encourage companies to engage with the Scientific Advice framework during their regulatory discussions.

b) Increase the flexibility of ICER thresholds.

Given the unique challenges faced by orphan and ultra-orphan medicines, flexibility will be needed in using ICER thresholds to determine the cost-effectiveness of a medicine. We recommend having modifiers for unmet need, severity and therapeutic innovation to ensure such treatments are given the appropriate incentives to be made available in England. We note that NICE's current value judgement framework 6.3.3 provides discretion for the Appraisal Committees to use modifiers, but in practice they are barely exercised.

Regardless of the ICER threshold, we believe that the reliance on a cost-per-QALY measure when evaluating orphan medicines needs to be reduced. NICE could identify cases where the QALY is inappropriate (for example, where a medicine slows the progression of the severity of a paediatric disease), and instead uses additional elements to capture the real value provided by the medicine similar to the elements in the HST process.

c) Include consideration of wider holistic and societal benefits to patients, caregivers and families.

For patients and their families, the ability to manage their condition and go to school, university or work makes a huge difference on both a personal and socio-economic level. Whilst the HST process recognises the wider benefits in the framework, the importance given to such benefits is not clear. Furthermore, the STA process, which evaluates the

bulk of orphan medicines, does not recognise the wider benefits as part of the evaluation criteria and hence needs to be broadened.

We recommend that the framework clearly outlines the weighting given to the wider societal benefit for a treatment (e.g., caregiver benefits, societal benefits, long-term benefits to the NHS through research and innovation) and define the type of data that manufacturers will need to collect to support claims regarding these wider societal benefits.

d) Adopt appropriate discount rates of 1.5 per cent for evaluating benefits.

This should be aligned with the Treasury Department. The existing application of a 3.5 per cent rate significantly underestimates the benefits for treatments in the long term⁴⁰. The discounting approach values outcomes accrued today more than outcomes accrued in the future. This penalises medicines which can be taken from an early age with the aim of slowing disease progression and delivering extended survival benefits far into the future. The current system, therefore, is not well designed to value the benefits to people with chronic conditions that require treatment over a lifetime.

e) Exclude direct medical costs during the 'period of extended life' from cost-effectiveness analyses, as these can penalise potentially life-saving medicines. Dynamic pricing assumptions should also be incorporated into long-term modelling.

³⁹ Office of Health Economics (2019) How Should We Measure Quality of Life Impact in Rare Disease? Recent Learnings in Spinal Muscular Atrophy [online] Available at https://www.ohe.org/system/files/private/publications/OHE%20Briefing%20-%20How%20Should%20We%20Measure%20Quality%20of%20Life%20Impact%20in%20Rare%20Disease_finalv2.pdf?download=1

⁴⁰ Charlton, V (2019) NICE and Fair? Health Technology Assessment Policy Under the UK's National Institute for Health and Care Excellence, 1999–2018, Health Care Analysis

5

Evaluate orphan medicines and ultra-orphan medicines through a single rare disease process

We recommend creating one process for orphan medicines and ultra-orphan medicines, separate from the STA process for non-orphan medicines. Having a single process for all such medicines will negate the need for the controversial criteria that create arbitrary divisions between orphan and ultra-orphan medicines. Not only will this ensure that these medicines are assessed by a process tailored to their specific characteristics, it will also reduce the time spent deciding on which process a medicine will be evaluated.



Case study 2

Cerliponase alfa (Brineura) for neuronal ceroid lipofuscinosis type 2 (Batten disease)

Brineura (cerliponase alfa) is an enzyme replacement therapy for treating a type of Batten disease (neuronal ceroid lipofuscinosis type 2). Batten disease is a rare, fatal, inherited disorder of the nervous system that typically begins in childhood. It causes vision loss, seizures, psychosis, progressive loss of movement and speech, and eventually death.

Brineura has been shown to slow disease progression, preserving a patient's ability to walk and see for longer. The treatment was licensed in 2017 but was refused funding by the

HST process in February 2019. This was because BioMarin, the manufacturer, was unable to address concerns about long-term effectiveness⁴¹. An MAA was eventually reached in September 2019⁴².

In the two years taken to reach this decision, the symptoms of children with Batten disease will have irreversibly progressed. In contrast, our recommended process of conditional approval would have given patients near-instant access to this life-changing treatment.

The issues surrounding long-term effectiveness could then have been addressed as part of the data collection agreement.

Brineura clearly illustrates the impact of inflexibility in the evaluation criteria. NICE acknowledged that the treatment had QALY gains of over 30. But it was still subject to the maximum ICER threshold of £300,000⁴³. This demonstrates the inflexibility in the current process that often result in delays or rejections.

⁴¹ NICE (2019) NICE says drug to treat Batten disease cannot be recommended for NHS use because company is unable to address concerns about long-term effectiveness [online] Available at: <https://www.nice.org.uk/news/article/nice-says-drug-to-treat-batten-disease-cannot-be-recommended-for-nhs-use-because-company-is-unable-to-address-concerns-about-long-term-effectiveness>

⁴² NICE (2019) Children with rare inherited condition to benefit from drug through managed access agreement [online] Available at: <https://www.nice.org.uk/news/article/children-with-rare-inherited-condition-to-benefit-from-drug-through-managed-access-agreement>

⁴³ NICE (2019) Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 [online] Available at: <https://www.nice.org.uk/guidance/hst12/chapter/4-Consideration-of-the-evidence>

6

Assess empirically based ICER thresholds on a sliding scale

This would ensure there are no cliff-edges between thresholds⁴⁴, such as that between the £20k to £30k STA threshold and the £100k HST threshold. Indeed, the £100k to £300k HST threshold appears to be arbitrary, having no empirical justification⁴⁵. A sliding scale of thresholds could be determined by analysing factors such as social preferences for treating rare conditions, direct health benefits and wider benefits, and ensuring an equitable return on investments for manufacturers of orphan medicines. Clear criteria would be needed to determine where an orphan medicine falls on such a scale based on the value delivered. The Swedish system, which makes special considerations for orphan medicines with much higher thresholds, is an example to emulate.



7

Continue to create a supportive atmosphere for patient groups

NICE has undertaken many initiatives to connect with patient groups. NICE's Public Involvement Programme team⁴⁶ offers support and advice on patient group involvement across NICE's work areas including HTAs. NICE has also organised several forums to connect with patient groups and hear their concerns. Furthermore, EURORDIS acts as a pan European alliance connecting patients, families and patient groups, as well as by bringing together all stakeholders and mobilising the rare disease communities. Such initiatives are welcome and laudable. However, despite these efforts smaller patient organisations, who lack the resources and skills to understand and navigate the evaluation landscape, still feel disadvantaged.

a) Increase support to smaller patient organisations and conduct tailored workshops to address their concerns.

Smaller organisations, in many cases, are run by parents who must find time in busy working lives while also caring for a child affected by a rare disease.

Organisations with no prior exposure to the evaluation process can feel daunted by the process and unclear about what is expected of them. Furthermore, organisations may not always have full clarity on what type of evidence is

acceptable to NICE. In one example shared during our interviews, a particular patient group brought in several video testimonials during the evaluation process which were deemed to be not so helpful.

Organising a set of customised workshops for such organisations can help alleviate some of these concerns. Effort is needed to better outline the evidence patient groups need to bring to the table and how it will be evaluated.

b) Communicate effectively with stakeholders at all stages of an evaluation.

Opportunities to improve the patient voice across all stages of the process need to be enhanced. For example, the participation of patient groups in managed access agreement discussions.

⁴⁴ Gortana S, Rare disease policy in the UK: The future for patients and industry [online] Available at: <http://lexcomm.co.uk/rare-disease-policy-in-the-uk-the-future-for-patients-and-industry>

⁴⁵ Office of Health Economics (2018) Appraising Ultra-Orphan Drugs: Is Cost-Per-QALY Appropriate? A Review of The Evidence

⁴⁶ NICE Public Involvement [online] Available at: <https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement>



A new way forward

Our recommendations represent a new way forward for evaluating orphan and ultra-orphan medicines in England

Together, these recommendations will enable all stakeholders with an interest in providing or obtaining access to treatments for rare and ultra-rare diseases – NICE, the NHS, manufacturers, and patients – to come to a new and more pragmatic understanding of the true value of what are often life-changing and life-extending treatments. This is an opportunity to rethink the evaluation process that all stakeholders agree needs to be enhanced to give patients faster access to new medicines.

To make this happen, all stakeholders involved will need to work together. The NHS will need a clear strategy on how the health system will fund the changes. As discussed earlier, countries such as Taiwan have already made major commitments and created a comprehensive and effective health and social system to help rare disease patients. If the NHS wants to achieve world-class pharmaceutical and biotech innovation and leadership in areas such as gene therapies, it needs to commit funding.

NICE will need to review and agree on the proposed framework and the corresponding details as part of its Methods Review. Additional analysis will be necessary in some cases to finalise the details. For example, increasing the flexibility of ICER thresholds and adopting modifiers for severity, unmet need and therapeutic innovation will require an assessment of the impact on the system.

Early engagement will smooth the evaluation process, ensuring the data collected is acceptable to NICE and consequently informs a better clinical trial design and analysis of data. It will also mean the NHS can signal to manufacturers what type of commercial arrangements might make sense for a treatment, given the level of uncertainty expected in the evidence. This, in turn, means that after licensing, manufacturers can bring proposals to NICE that are more likely to be accepted.

The pharmaceutical and life sciences industry will need to work with NICE and the NHS to come to pragmatic decisions about interim pricing, remembering that the central goal is providing patients with rare diseases fast access to life-changing medicines. The industry will need to support the NHS in building an appropriate infrastructure during the data collection period of conditional access.

England has an opportunity to improve access to orphan medicines

We believe the benefits of our package of recommendations will be widespread, offering new hope to patients, while providing a fairer, faster and more fitting evaluation process for the NHS, for industry, and more broadly for society.

Patients will benefit from innovative treatments that close the unmet need in rare diseases. And the burden on families, carers and patient organisations would be lessened.

The NHS will benefit from a more efficient and equitable allocation of resources. Fewer resources would be lost to a lengthy evaluation process that attempts to make assessments using uncertain data. It would also avoid the reputational risk that comes from being seen internationally as having a difficult, restrictive and slow process. Indeed, it would fortify the UK's global position as an early launch market, a leading research partner and gold-standard health system.

The pharmaceutical and life sciences industry would benefit from renewed support that comes with accelerated access to the market post marketing authorisation. This is essential if it is to continue to prioritise the UK as an early launch market. Concerns about Brexit have already negatively affected commercial decisions.

Many countries are optimising the way orphan and ultra-orphan medicines are evaluated to minimise the delay in access to patients and there is much we can learn from these systems. We welcome the consideration this is being given in ongoing policy debates, as well as the discourse from organisations like Genetic Alliance and the Office of Health Economics. Our recommendations are intended to enable a faster, rational and more pragmatic process. Rare and ultra-rare diseases place a heavy burden on patients, caregivers, families, society, and the NHS. We believe our package of recommendations will go some way to easing that burden.

Methodology

To inform our recommendations, we conducted a targeted literature review, digging deep into the issues with the current framework and taking into account a variety of voices. This included leading academic papers and thought leadership pieces, opinions and blogs, and documents from NICE and NHS organisations. We then developed a set of hypotheses that could help address the issues identified.

We benchmarked the practices of other countries to understand what best practice in access to orphan medicines might look like for England. This comparative analysis was mainly focused on leading healthcare systems in Europe, including Germany and France, but also explored other comparable countries such as the Netherlands, Sweden and Taiwan. We refined our hypotheses based on what we found in these systems.

We then conducted 25 stakeholder interviews to further explore the key issues with the current NICE process. This also ensured we could align on the guiding principles behind our recommendations and validate our hypotheses. We spoke to a variety of organisations, including industry leaders, patient groups, clinicians, and NHS England officials, and rare disease experts to build a balanced point of view.

We are grateful for the contributions of representatives from the following organisations:

Pharmaceutical and biotech companies

- Akcea Therapeutics
- Alexion
- Alnylam Pharmaceuticals
- Amicus Therapeutics
- Biogen
- BioMarin
- Ipsen
- Pfizer
- PTC Therapeutics
- Sanofi
- Sarepta Therapeutics
- Takeda
- Vertex Pharmaceuticals

Patient organisations

- Alex – The Leukodystrophy Charity
- Cancer Research UK
- CATS Foundation (The Cure & Action for Tay-Sachs)

- Charity Medicines Access Coalition
- Cystic Fibrosis Trust
- Duchenne UK
- Gaucher's Association UK
- Genetic Alliance
- Metabolic Support UK
- Tuberous Sclerosis Association

Representatives from official bodies

- NHS England
- Rare Diseases Advisory Group

Clinical group

- Royal College of Physicians

PwC Strategy&

- Global and UK rare disease policy subject matter experts
- Global and UK market access subject matter experts

Glossary

Rare disease

A disease affecting fewer than 1 in 2000 people within the general population (EMA)

Ultra-rare disease

There is no legal definition for an ultra-rare disease, but 1 in 50,000 people is a generally accepted prevalence in Scotland and <1 in 50,000 in England and Wales

Orphan medicine

A treatment for a rare disease which is life-threatening or chronically debilitating, or it is unlikely that the medicine would generate sufficient returns to justify the investment needed for its development (EMA)

Ultra-orphan medicine

A treatment for an ultra-rare disease which is life-threatening or chronically debilitating, or it is unlikely that the medicine would generate sufficient returns to justify the investment needed for its development

AGNSS

Advisory Group for National Specialised Services

CDF

Cancer Drugs Fund, a source of funding for cancer drugs in England. Access is via MAA while further evidence is collected to address clinical uncertainty

EMA

European Medicines Agency

HST

The NICE Highly Specialised Technologies programme, which evaluates some ultra-orphan medicines

HTA

Health Technology Assessment, the decision as to whether a treatment represents value for money to the NHS

ICER

Incremental cost-effectiveness ratio, 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

MAA

Managed Access Agreement, a conditional reimbursement scheme that enable new medicines to become available for a limited time period at a discounted price

MHRA

Medicines and Healthcare products Regulatory Agency, regulates medicines, medical devices and blood components for transfusion in the UK

NICE

National Institute for Health and Care Excellence

QALY

Quality Adjusted Life Year, a measure of cost-effectiveness that is 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). One QALY is equal to 1 year of life in perfect health

SMC

Scottish Medicines Consortium

STA

The NICE Single Technology Appraisal programme, which evaluates non-orphan, orphan and some ultra-orphan medicines

VPAS

Voluntary Pricing and Access Scheme for Branded Medicines, caps growth of the total medicines bill for each year of the agreement at 2%, with any NHS spending over this limit being repaid by the industry



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