Patient perspectives and priorities on NICE’s evaluation of highly specialised technologies

Patient Charter
Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 160 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine.

Genetic Alliance UK undertakes various projects and programmes that adds evidence and knowledge to improve health service provision, research and support for families. These initiatives include:

- Rare Disease UK, a stakeholder coalition brought together to work with Government to develop the UK Strategy for Rare Diseases.
  www.raredisease.org.uk

- SWAN UK (Syndromes Without A Name), a UK-wide network providing information and support to families of children without a diagnosis.
  www.undiagnosed.org.uk

Download a copy of this Patient Charter here:
www.geneticalliance.org.uk/hstcharter.htm

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Executive summary

This Patient Charter makes 29 recommendations for improving the evaluation of treatments for very rare conditions through the National Institute for Health and Care Excellence’s Highly Specialised Technology (HST) evaluation framework.

Premise

It is right that HST evaluation exists as a means of ensuring that the NHS can commission effective, highly priced medicines for small populations

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| 5 Mentoring and support for all patient groups should be available from a NICE-contracted third-party | NICE |
| 6 NICE should seek out existing and newly established patient groups for the duration of the HST evaluation process | NICE |

Scope and transparency: getting the right technologies into the HST evaluation process

| 7 Topic identification and selection processes, methods, mode of deliberation and outcomes should be fully transparent and publicly available | Department of Health, NICE, NIHR Horizon Scanning Centre |
| 8 Patient groups should be involved in the process of topic identification and selection | NICE, NIHR Horizon Scanning Centre |
| 9 Topic selection criteria need to be tightened to clarify their meaning as some are at risk of misinterpretation | Department of Health, NICE |
| 10 Repurposing of medicines should be encouraged by allowing treatments with multiple indications to qualify for multiple HST evaluations | NICE |
| 11 The definition of ‘clinically distinct’ requires updating so that it reflects a modern understanding of the genetic and molecular basis of disease and the frequent variation in clinical presentation common in rare diseases | NICE |
12 The number of HST evaluations carried out should be determined exclusively by the number that meets the revised selection criteria, which includes a consideration of appropriateness

13 The timeline of HST evaluation should permit ‘clock stops’ to allow flexibility and enable all patient groups to participate

Finding out where and how the patient voice is taken into account

14 The nature and format of the proposed patient group evidence submission needs clarification

15 An explanation of ‘impact beyond direct health benefits’ and its value in an HST evaluation is required

16 The Evaluation Committee should be able to accommodate sufficient ‘nominated experts’ so as to reliably reflect the diversity of opinion in the relevant patient community

17 Nominated patient experts should be permitted to make a brief, formal presentation to the Evaluation Committee

18 The patient evidence submission should be seen in its original form by the Review Group and Evaluation Committee

19 The patient evidence submission’s use and impact should be communicated back to patient groups

Updating the health economist’s tool box

20 All calculations made by health economists during an HST evaluation should be communicated back to patient groups

21 For HST evaluations, a measure of health outcomes more applicable to rare diseases should be developed and used in place of the EQ-5D

22 Expectations of clinical trial data must be pragmatically aligned to reflect the limitations of data derived from studies on small numbers of patients

23 NICE should work with medicine regulators in a coordinated way to provide advice to companies regarding clinical trial design and data collection; and guidelines for the manufacturer’s evidence submission

Generating additional evidence

24 To facilitate equitable access to new treatments, research recommendations should not be subject to restrictive eligibility criteria

25 Patients should be involved in outlining the nature and timeline of any post-evaluation research recommended by NICE

26 Use of NICE-commissioned HSTs in the NHS should be monitored as part of routine clinical care to ensure expected patient outcomes are met

27 Research that examines dosage and clinical trials evaluating
the impact of dosage should be encouraged, with the view to making HSTs more effective and more affordable

Risk versus effectiveness in a NICE evaluation

28 Re-examination of benefit/risk by NICE should be explicitly justified, involve patient consultation and refer to patient testimonies collected by the EMA

29 Patients should make the ultimate decision on whether the benefits of a new drug outweigh its risks, in partnership with their doctor

The diagram below illustrates the key stages of NICE’s HST evaluation process annotated with each of the 29 recommendations made in this Patient Charter:
Introduction

Having a rare disease should not act as a barrier to receiving high quality services and treatment. Consequently, a robust and patient-friendly process needs to be in place to improve patient access to treatment for rare, life-limiting conditions that require expensive therapies.

Existing appraisal systems have been designed without specific reference to the challenges of developing, trialling and approving the nationwide commissioning of treatments for rare and ultra-rare conditions. Very small target patient populations mean new treatments are difficult to test, with smaller clinical trials producing less data; and are difficult to recoup investment in research and development from. With affected individuals dispersed around the country, a ‘postcode lottery’ for treatment access is also a risk unless nationwide commissioning policies are in place. If the current appraisal systems are unable to account for these factors, many new and potentially life-altering treatments for rare diseases may be falling through the gaps and not reaching the patients who need them.

As we look to the future and begin to understand disease better, it is also becoming clear that what we used to think of as one disease is in fact a collection of molecularly and genetically distinct diseases. Consequently, the number of rare conditions - and drugs specific for those conditions - is set to increase; strengthening the need for a process that can robustly, effectively and transparently appraise high-cost treatments for small patient populations.

What is a highly specialised technology?

A technology includes all drugs, therapies (such as enzyme replacement), and surgical procedures that can be classed as a medical intervention. NICE has not chosen to define an HST by the number of patients that would be able to use it, but instead as one used by a population ‘so small that treatment will usually be concentrated in very few centres in the NHS’.

The determination of whether very rare disease treatments should be recommended for NHS-wide commissioning in England has, from May 2013, been the responsibility of the National Institute for Health and Care Excellence (NICE), through an interim Highly Specialised Technology (HST) Evaluation Programme. This process replaces assessment by the Advisory Group for National Specialised Services (AGNSS). The evaluation criteria set by AGNSS were generally considered fit for purpose but the system itself only appraised two drugs (and approved one) before it was replaced following the restructuring of the NHS in line with the passing of the Health and Social Care Act 2012. Alongside the HST evaluation system, there remains provision for NHS England to produce commissioning policies in the absence of NICE guidance.

Patients are an important stakeholder in any framework that looks to determine whether a new treatment should be made available; and last year NICE met with a number of stakeholders, including patients, to develop the interim HST framework. With a review of this framework taking place before the end of the year, the timing is right for patients to re-examine this process and ensure that it is fit for purpose before custom and practice prevent further improvements from being made.

There have been a number of other recent policy developments concerning improved access to treatments and services for those affected by rare diseases. In November 2013, the Department of Health published the UK Strategy for Rare Diseases and a subsequent debate in the House of
Commons on rare diseases highlighted access to medicines as a key issue\(^3\). The forthcoming review of NICE’s HST evaluation framework is also carried out in the wider context of **specialised services**, both the logistics of service provision and the implications of resource allocation.

In order to ensure that the **patient voice** is heard during the review of NICE’s interim HST evaluation programme, Genetic Alliance UK has produced the **Patient Charter** outlined in this document. It has been shaped through **collaborative discussion** across the patient group community, specifically including groups that might have to participate in a future HST evaluation. As a result, the Charter represents a strong, clear and consistent statement, outlining **key recommendations** to be communicated back to NICE, from the perspective of **patients and their families**.

The Charter is laid out to reflect the stages of the HST process; from its role in the **wider commissioning landscape** to its **scope** and capacity for **patient engagement**. It concludes with a broader consideration of **NICE’s role in the evaluation of benefit and risk**. Since only two treatments have been appraised through AGNSS, eculizumab (Alexion) and tafamidis (Pfizer), this Charter has referred to these case studies to help illustrate specific points within the Charter.

Any guidance produced by NICE comes with a **mandate** that it be followed by **NHS England**. In line with this mandate, the Patient Charter will consider HST evaluation in the context of England and not the devolved nations. However, reviews of the appraisal processes for orphan and ultra-orphan medicines have also recently taken place in both **Scotland** and **Wales**, with a view to improving access to effective rare disease treatments. Genetic Alliance UK has responded to both of these consultations in separate documents\(^4,5\).

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This Patient Charter is a collation of the issues raised and discussed by the patient group community during a workshop held by Genetic Alliance UK in November 2013; and the recommendations they made for change.

Genetic Alliance UK hope the Patient Charter will act as a useful reference point for the patient perspective on this issue and will be used to initiate a necessary dialogue on the interim HST evaluation process and how it could be improved.
This Patient Charter is premised by the recognition that there is public, patient and governmental support for the NHS-wide commissioning of highly priced medicines for small patient populations with serious, life-limiting conditions\(^3,6,7,8,9,10\). This consideration is afforded particularly to sick children, where society generally favours ‘the benefit of the doubt’ being given when deciding whether a new treatment should be made available\(^6,7\).

This premise is based on the reports of NICE's Citizen Council on the ‘rule of rescue’\(^8\) and inequalities in health\(^9\), as well as on parliamentary debates\(^3,10\). It is also a component of the NHS Constitution, which states that the NHS should provide a comprehensive service available to all and that it should promote equality by paying “particular attention to groups or sections of society where improvements in health and life expectancy are not keeping pace with the rest of the population”\(^11\).

This Patient Charter reasserts the right of patients affected by rare, life-limiting conditions to benefit from high cost treatments, which are free at the point of access. The Charter aims to ensure that NICE’s HST evaluation framework is fit for this purpose and, therefore, will not revisit the arguments that resulted in it coming into existence.

**Premise**

It is right that HST evaluation exists as a means of ensuring that the NHS can commission effective, highly priced medicines for small populations

Ensuring that HST evaluation is fit for purpose in the wider commissioning landscape

The HST evaluation process’ relationship with the wider commissioning landscape should be clarified

Action by: Genetic Alliance UK, NHS England, NICE

It was felt among patient representatives that the existing systems for accessing high cost medicines through the NHS were complex and unclear. An overview of all the potential routes was called for.

This should take account of NICE's HST evaluation and Health Technology Assessment (HTA) processes, appraisal by Clinical Reference Groups (CRG) at NHS England, Individual Funding Requests (IFRs), the Cancer Drugs Fund, patient access schemes, early access schemes and adaptive licensing. It should outline the differences between each route, how they interact with each other and how each can be accessed.

Clarity was also called for over how the suspension of the ‘Specialised Services Commissioning Innovation Fund’ and its apparent replacement with ‘Commissioning through Evaluation’\(^12\), and the introduction of value-based assessment may have an impact on the evaluation of HSTs at NICE.

The forthcoming revision of the interim HST evaluation process provides the opportunity to reexamine the relationships between these appraisal routes and funding mechanisms and identify where some new treatments may currently ‘fall through the gaps’. In particular, this should consider how patients can gain access to effective treatments through the NHS if the drug does not qualify for HST evaluation at NICE.
Genetic Alliance UK plans to consult on and develop another Patient Charter on this issue, with the aim of adding clarity and highlighting where gaps or inconsistencies may exist between HST evaluation and alternative routes; and address the impact of introducing new assessment criteria and funding options. By responding to a wider review of the commissioning landscape such as this, stakeholders should be able to ensure that all new treatments are captured by an appropriate appraisal system, sensitive to patient need and resource allocation.

Patient representatives welcomed the fact that the HST evaluation framework at NICE was being developed as an appraisal process tailored to rare disease treatments, noting that existing systems are not sufficient for access. However, they recognised that under some circumstances HST evaluation may not be a beneficial tool.

As a result of compassionate use programmes and clinical trials, as well as the potential for adaptive licensing to become a feature of rare disease treatments in the future, a significant proportion of people affected by a rare disease may already be using a new treatment before its evaluation at NICE has begun.

In these situations, patient representatives felt that an HST evaluation at NICE may be inappropriate. If the majority of patients are already on a new treatment, a positive recommendation from NICE would have a limited impact on improving patient access, while a negative outcome would effectively 'close the door' for patients not already on the treatment. There was concern that this would be a significant step backwards for patient access to medicines.

Patient representatives also raised the issue that such a situation would encourage clinicians to increase the number of patients taking a treatment before an evaluation begins, as even a negative outcome at NICE does not usually result in treatment withdrawal. Patient groups were keen to ensure that the criteria for HST evaluation would avoid introducing this kind of perverse incentive.

Budget implications for NHS England

Representatives of NHS England’s specialised services team should be non-voting experts at NICE’s Evaluation Committee meetings

Action by: NHS England’s specialised services team, NICE

NICE recommendations come with a mandate for NHS commissioning. Patient representatives therefore felt that having a member of the specialised services team from NHS England present at all Evaluation Committee meetings was important to ensure HSTs were considered in the broader context of specialised services. This would guarantee dialogue between NHS England and NICE on the implementation of guidance through associated service delivery. This was a feature of the AGNSS system that patient groups were keen to ensure was retained.
A second motivation was to enable joined-up thinking around the specialised services budget. No additional money has been assigned to cover HST procurement and future specialised services budgets will likely be subject to austerity measures. In this environment, patient representatives felt that the knock-on effects of a NICE mandate for a costly new treatment will likely be subject to austerity measures. In this environment, patient representatives felt that the knock-on effects of a NICE mandate for a costly new treatment should be carefully considered to ensure that it did not reduce access to currently available treatments.

‘Allocative efficiency’, i.e. the impact that a positive recommendation would have on the specialised services budget, is included in the HST evaluation criteria. Clarity over how this will be taken into account and the degree of impact it will have on the final decision was called for by patient groups.

At the first HST Evaluation Committee meeting, NHS England were represented through membership of the Review Group (Annex 3). It is encouraging that NICE’s awareness of this issue and their response to it was in line with the recommendation made by patient representatives here.

Enabling the patient voice

Following Genetic Alliance UK’s patient group workshop, the process of generating and using the patient evidence submission during HST evaluations was identified as the top priority for change. In particular, there was concern that for many rare diseases, patient groups are small, under resourced or may not exist at all. It was agreed that without effective, engaged patient groups, the critically important patient voice would be lost from the HST evaluation process.

Moreover, patient representatives felt that there was additional pressure on groups and individuals to provide high-quality patient evidence submissions due to the likely gaps in clinical trial data for rare disease treatments. With this in mind, over 60% of patient representatives that responded to the HST workshop feedback survey were either undecided or not confident that their patient group could produce a robust evidence submission. They were also concerned about the capability of groups smaller and less experienced than their own to produce an evidence submission.

Patient communities involved in an HST evaluation should be supported in the formation of patient groups if they do not already exist

Patient representatives felt that getting a valuable patient evidence submission was dependent on patient groups being encouraged to form and then being adequately supported throughout the HST evaluation process. Without this, there was concern that the patient voice would be absent from many evaluations. Patient representatives recognised that financial input, as well as coordination and support, was required in order to enable new patient groups to form.

“Clinicians are in a difficult position of ‘rationing’ drugs when these decisions [about prioritising funding] should be made by health economists”

“My concern is the capability of patient groups to produce the high level of patient statement required and the quality of patient expert needed”

Action by: Department of Health or NICE with Genetic Alliance UK
The Department of Health or NICE were discussed as potential sources of this funding, although patient representatives were hesitant about asking them to provide the practical support. Instead, it was suggested that this was an area where Genetic Alliance UK could be particularly constructive. As an organisation, Genetic Alliance UK has already received funding for a project that helped new patient groups to form in Scotland and would be interested in opportunities to continue this work nationally in the future.

One aspect of the AGNSS evaluation process that was valued by patient representatives was that funding was available to contract an independent third-party to support patient groups in the development of their evidence submission. This would involve interviewing patients to capture their experience and communicating their responses professionally, without losing the strength of a personal testimony. From the experience of aHUS patient groups during the assessment of eculizumab by AGNSS, it is clear that this support was valued particularly highly, being described as ‘indispensable’. aHUSUK were keen to stress their belief that the evidence they submitted to the HST Evaluation Committee at NICE was greatly improved due to the support provided by AGNSS.

Patient representatives agreed that the funding for such support should not detract from the independence of the patient evidence submission, so financial support from manufacturers was considered unsuitable. They therefore proposed that NICE be responsible for ensuring third-party support was available to all patient groups.

Unfortunately, it is suspected\(^1\) that NICE will have a more restricted budget than was available to AGNSS, and that this might reduce their capacity to provide patient group support. This was met with anxiety by patient representatives, who were concerned that this may produce an ‘unlevel playing field’, where only those diseases that have experienced, well-resourced groups are able to generate a sufficiently robust evidence submission. There was additional concern that, without targeted support from NICE, patient communities that have learning difficulties, may not speak English as a first language or are primarily children would be particularly hard hit.

Patient representatives felt that providing third-party support was indispensable in order to ensure an equitable process and, therefore, that its provision must be mandatory and funded by NICE.

At Genetic Alliance UK’s patient group workshop, Josie Godfrey revealed, on behalf of NICE, their plans to launch a project in the coming year to investigate how NICE can best support patient groups in order to enable them to generate an evidence submission. This was welcomed by Genetic Alliance UK and the patient representatives in attendance.
The appeals process

NICE should seek out existing and newly established patient groups for the duration of the HST evaluation process

Patient representatives were comfortable with the appeals process. They felt that the immediate priority for the patient community was to ensure that the framework for HST evaluation was right since having a robust appeals process is important but only for those that are dissatisfied with the process.

With this in mind, patient representatives noted that only those patient groups identified during the HST evaluation process are able to launch an appeal after guidance has been issued. Consequently, patient representatives were keen to ensure that NICE will seek out all patient groups during the scoping stage, support patient populations where no group currently exists and continue to look for new patient groups or smaller factions throughout the process.

It was widely felt that NICE’s existing methodology for identifying and contacting patient groups worked well. However, patient representatives wanted to ensure, despite many HSTs being for rare diseases, that NICE recognised the number and diversity of patient groups would be comparable to other conditions. Furthermore, as demonstrated by the aHUS patient community, the appraisal of a new treatment can catalyse the formation of patient groups, so that new groups appear and become more formally established during the course of an evaluation process.

An appreciation of this and its accommodation into the HST process is needed to make certain that the patient voice captured is truly reflective of the proposed patient population.

Scope and transparency: getting the right technologies into the HST evaluation process

The determination of which medicines are chosen for HST evaluation occurs in two stages: identification and selection. The National Institute for Health Research (NIHR) Horizon Scanning Centre is responsible for identifying candidate new medicines. They summarise and send to NICE all the information available on each new medicine, including why it is novel and the medical need it addresses. This occurs before a market authorisation application. NICE first discount all those technologies that fall outside of remit (e.g. vaccination, population screening or HIV treatments). NICE then decide which technologies from this list progress to HST evaluation and which are selected for other appraisal routes within NICE. Technologies selected for HST evaluation must meet all of the set filtration criteria. The importance of each of the short-listed technologies is then considered against the prioritisation criteria, all of which have to be met. This is done by the Secretary of State and ultimately determines which technologies are referred to NICE for HST evaluation.

Unless all the filtration and prioritisation criteria are met, then the treatment will not be evaluated by NICE’s HST process and an alternative appraisal or commissioning route would need to be sought.
Given that the topic selection stage governs which technologies enter into HST evaluation at NICE, it is critical that the process and methodology is fit for purpose and accessible to patient groups. From Genetic Alliance UK’s patient group HST workshop, it was apparent that the entry requirements new treatments would need to meet in order to be appraised through HST at NICE was one of the areas that patient representatives were most dissatisfied with.

### Improving transparency

**7 Topic identification and selection processes, methods, mode of deliberation and outcomes should be fully transparent and publicly available**

**Action by:** Department of Health, NICE, NIHR Horizon Scanning Centre

Patient representatives were concerned with the extent to which decision making during topic selection occurred ‘out of sight’. Clarity was called for over the topic selection process and the key stakeholders and decision makers at each stage. This included the role of the NIHR Horizon Scanning Centre: how they identify technologies for HST and how regularly information is relayed to NICE. Patient representatives added that all reports on potential HST candidates from the Horizon Scanning Centre to NICE should be available and easily accessible for patient groups and the wider public.

Similarly, NICE should openly publish the reasons why each technology may or may not have successfully passed the filtration or prioritisation stages of topic selection. Ideally, this would involve an online portal on the NICE website that would track the progress of individual technologies through each decision point in the topic selection process, and could be searchable by either the medicine name or disease indication.

This would ensure that the transparency that characterises the remainder of the HST evaluation process is maintained consistently throughout. Since March 2012 the European Medicines Agency (EMA) has published all medicines that are under evaluation for a market authorisation, and all orphan designations are published as they are decided. There should therefore be no reason why the names of medicines under consideration for HST topic selection could not be made similarly available.

**8 Patient groups should be involved in the process of topic identification and selection**

**Action by:** NICE, NIHR Horizon Scanning Centre

Patient representatives were dissatisfied with the apparent lack of patient involvement in topic identification and selection. They felt that the contribution they could make to the process had either not been recognised or was poorly promoted.

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**The filtration criteria:**

1. The new formulation or technology is at, or likely to be at a significantly different price.
2. There is appropriate evidence, such as would enable evaluation, either available or anticipated to be available in the near future.
3. The timing is right - NICE is committed to publishing timely guidance within six months of the marketing authorization.
4. The relevant clinical question(s) can be addressed by the application of the highly specialised technologies evaluation methodology. This would exclude topics on which guidance to NHS England would be of inadequate value in the absence of broader guidelines on the clinical pathway within which the technology should be contextualised.
The NIHR Horizon Scanning Centre website has a publicly accessible ‘suggest a topic’ facility. Clarification was called for over how valued this route is in the topic selection process and whether patient groups could use it. Moreover, patient representatives were keen to establish whether there was information that patient groups could be called upon to provide to the NIHR Horizon Scanning Centre during topic identification that would be valuable if this then fed into NICE’s deliberations on topic filtration and selection for HST evaluation.

This is particularly important given that part of the NIHR Horizon Scanning Centre’s remit is to summarise the evidence relating to whether a technology has the potential to have a positive impact on patients, and that currently further information is sought exclusively from clinicians.

Patient representatives believed that effective mechanisms for incorporating the views of patients, carers and families should be a critical part of topic selection, and requested such provision be made if not already available.

The prioritisation criteria:

1. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS.
2. The target patient group is distinct for clinical reasons.
3. The condition is chronic and severely disabling.
4. The technology is expected to be used exclusively in the context of a highly specialised service.
5. The technology has the potential for lifelong use.
6. The need for national commissioning of the technology is significant.

Case study: Eculizumab for the treatment of aHUS

Atypical haemolytic uraemic syndrome (aHUS) is a blood disorder that is often inherited, and affects 140 people in the UK (2012); many of whom are children. Other than eculizumab, no treatment is available to prevent the death or organ damage associated with aHUS, with plasma exchange and dialysis forming the basis of existing care.

The evaluation of eculizumab at NICE is not a useful case study from which to extrapolate the effectiveness of the HST evaluation framework for a number of reasons. Firstly, eculizumab has already been rigorously appraised by AGNSS. As part of the AGNSS system, the aHUS patient community received “indispensable” third-party support during the development of their evidence submission, which is not expected to be available as part of NICE’s HST process.

Moreover, after the first AGNSS appraisal, all parties, including patient groups and manufacturers, had the opportunity to revisit and improve their evidence submissions with feedback from the AGNSS committee, vastly strengthening the case presented to NICE’s Evaluation Committee.

It has also been asserted that, under the current topic selection criteria, eculizumab would not qualify for HST on the grounds that is has already been made available through the NHS for the treatment of paroxysmal nocturnal haemoglobinuria (PNH).

Finally, for NICE to deliver a negative recommendation for eculizumab would be a highly controversial decision, given that it had been recommended by AGNSS. For all of these reasons, we cannot look to eculizumab to provide guidance on whether the topic selection and interim process and methods put forward for HST evaluation at NICE is, in itself, fit for purpose.
When discussing whether the criteria used at the topic selection stage was fit for purpose, patient representatives highlighted a number of issues.

There was some concern that by using the number of NHS centres required to deliver a technology as a measure of disease rarity (prioritisation criterion 1), NICE would be adding another level of complexity on top of previous definitions of a rare disease based on population size\(^21,22\). It would also risk allowing an artifact of a health system to affect decisions that should be made entirely on the merit of medical need. Overall, however, the fact that no distinct cut-off had been proposed was welcomed.

Clarification of some of the criteria was also a priority for patient representatives. Prioritisation criterion 4, for example, could be interpreted to imply that the technology would need to be for use in only one specialised service. This should be modified to ensure that technologies used in a small number of specialised services are not at a disadvantage. Similarly, prioritisation criterion 5 implies that one-off curative treatments can be dealt with adequately through other commissioning routes. Given that this may not be the case, this criterion should be reconsidered so as to ensure that it will not create a barrier to patient access in England.

Patient representatives agreed that the repurposing of existing drugs has the potential to address significant unmet medical need within the rare disease community and should, therefore, be actively encouraged in health care policy. As a result, patient representatives were concerned by assertions that, despite eculizumab being the first medicine to undergo HST evaluation at NICE, it would not normally have qualified for HST evaluation. It has been proposed that this is due to eculizumab previously having been made available through the NHS for patients with PNH. Although the ineligibility of eculizumab on these grounds has been asserted by NICE\(^14\), it is unclear exactly which topic selection criteria this relates to.

Patient representatives considered eculizumab to be a suitable candidate for HST evaluation and were keen to ensure other technologies would not be similarly excluded from this process in the future at either the topic identification or selection stages.
Through discussion with NICE, it is apparent that the current interpretation of the term 'clinically distinct' does not recognise either genotypically defined or biomarker-positive subgroups as 'distinct'.

Stratification of patient populations dependent on the clinical presentation of symptoms or disease severity and progression will also not occur at topic selection under this criterion. Instead, disease nomenclature will be the primary method used to demarcate 'clinically distinct' patient subgroups.

As a result, determination of whether a condition is rare enough to be considered for HST evaluation is not based on the size of these subgroup populations but on the number of people affected by the overarching condition. An example would be the number of people affected by breast cancer compared to a subgroup of breast cancer patients positive for a specific biomarker who may not respond to some treatments or for whom a new treatment has been purposefully developed.

Patient representatives considered this definition of 'clinically distinct' to be impractical and outdated for three reasons:

1. Increasing knowledge of the genetic and molecular basis of disease has revealed that what used to be considered a single disease is in fact a collection of related but fundamentally distinct conditions. Moreover, this improved understanding has led to greater recognition of the fact that different subgroups within a condition may respond differently to medical interventions. This makes identifying these subgroups and differentiating between them in a clinical setting of critical importance.

2. The current definition of 'clinically distinct' is at odds with government policy, which aims to augment the development and use of 'stratified medicines', tailored to the genetic or molecular basis of an individual's condition. At a time when the government has committed to sequencing the genomes of 100,000 cancer and rare disease patients in order to better understand the causes of disease and develop better treatments, it is impractical to have a definition of 'clinically distinct' that does not recognise such advances in medical understanding.

3. Variation between individuals in the severity and progression of a disease, and incomplete penetrance of all the features associated with a condition, is common in the rare disease field. Often this is determined by the age of disease onset, for example in Pompe disease. Here, infantile onset is associated with cardiac or respiratory complications, while the primary symptom of adult onset is muscle weakness. In cases such as these, where patients have clinically distinct needs, they may benefit from different types of medical intervention. For any framework to be effective in evaluating drugs for rare diseases, it is essential that the criteria used reflect the realities of rare diseases as they present in the clinic.

The HST evaluation framework at NICE appears to be an ideal mechanism through which 'stratified medicines' for small populations, defined by genetics, biomarkers or clinical presentation, could be...
appraised. However, without modifying NICE's interpretation of ‘clinically distinct’ this will not be possible. With NICE planning a review of the interim HST framework in 2014, there is an ideal opportunity to update this definition so that it is fit for purpose now and in the future. This could be undertaken as part of NICE’s existing engagement with the Technology Strategy Board’s ‘Stratified Medicine Innovation Platform’²⁴.

Any change to the interpretation of ‘clinically distinct’ or other topic selection criteria would need to be clearly communicated back to the NIHR Horizon Scanning Centre to ensure they were able to gather and relay the required information back to NICE to inform topic selection discussions.

Case study: T351i positive chronic myeloid leukaemia²⁵

Chronic myeloid leukaemia (CML) is characterised by the excessive production of white blood cell precursors in the bone marrow. This is caused by a genetic change that means two genes on two different chromosomes fuse together producing an oncogene called BCR-ABL1. White blood cells that contain this oncogene divide and reproduce in an uncontrolled way. CML has three phases the last of which, ‘blast crisis’, results in a fatal acute leukaemia which is very hard to treat. The disease is very rare, with an incidence of 1-2 people in 100,000.

In most cases, CML is treated with a type of drug called a tyrosine kinase inhibitor (TKI), which helps to stop the signalling pathways that make the white blood cells divide uncontrollably. However, in some patients their cells contain a second DNA mutation, called T315i, which makes their disease resistant to all the currently available TKIs. The T315i mutation is very rare – anticipated to be only present in around 15 CML patients in the UK per year – but it is easily identified through genetic testing.

Ponatinib is a new TKI that has been developed specifically to target T315i but has also proven to be very effective against a number of other TKI resistant mutations. For patients with the T315i mutation, this drug is potentially life-saving. The EMA marketing authorisation covers the T315i mutation as well as CML patient populations with other specific TKI resistant mutations.

Under the existing HST criteria, it is not clear whether the genetically identifiable T315i positive population of CML patients would qualify as ‘clinically distinct’, thus enabling ponatinib to qualify for this HST criteria. If this biomarker-defined population is not recognised as being clinically distinct, CML itself is unlikely to be considered sufficiently rare to qualify for HST. This would leave unaddressed a significant unmet medical need in patients with the T315i mutation, despite an effective drug being available.

Increasing capacity

The number of HST evaluations carried out should be determined exclusively by the number that meets the revised selection criteria, which includes a consideration of appropriateness

Action by: Department of Health, NICE

NICE has stated that it will only be able to carry out three HST evaluations each year¹⁴. This figure was informed by an analysis of the drug development pipeline and decided upon through discussion between NICE, the Department of Health and NHS England.
During the workshop, patient representatives questioned the suitability of a retrospective analysis for determining the future demand for HST evaluations, given the dynamic nature and rapid growth in this area of drug development as well as government strategies aimed at increasing the number of stratified medicines\textsuperscript{26}, some of the most obvious candidates for HST evaluation. Indeed, the number of new treatments that have been designated orphan products, aimed at treating small populations, has grown almost every year with over 100 products granted orphan status in 2013 by the EMA\textsuperscript{27}.

Patient representatives were also uncomfortable with the overall concept of having a cap on HST evaluation capacity. In particular, they took issue with the potential impact it may have on equity of access, given that there are over 6000 recognised rare diseases\textsuperscript{28}. Consequently, patient representatives felt that not having an annual restriction on the number of HST evaluations was critical to the success of the framework. They instead suggested that NICE carry out HST evaluations out on as many technologies as meet the criteria.

**Modifying the timeline**

The timeline of HST evaluation should permit ‘clock stops’ to allow flexibility and enable all patient groups to participate

Overall, patient representatives felt that the timeline proposed for the NICE HST evaluation was reasonable, and were keen to ensure that a good quality decision was promoted above a rushed one. However, they did feel that some increased flexibility should be allowed for in the framework, in particular, to ensure that patient groups had time to respond during the consultation stages, especially smaller or newly formed groups. To this end, the introduction of ‘clock stops’ was proposed.

Another issue raised with regard to timeliness was that of patient groups being made aware of their role in informing NICE of any new medicines currently being considered for market authorisation. It is critical to NICE’s processes that they learn in advance of new treatments coming through the technology pipeline. A formalised route through which patient groups can engage at this stage, alongside manufacturers, would be beneficial.

**Finding out where and how the patient voice is taken into account**

Clarity on how input from patients and patient groups will be used, who will read it and how much weight it will be given in the HST evaluation process, was a high priority for patient representatives. This was driven in part by a sense of responsibility to the patient community, having produced the submission or acted as a nominated expert, to see what impact it had; and by an appreciation for the uniquely important role patient testimony has to play in HST evaluation when there may be questions left incompletely answered by clinical trial data.
The value of direct communication from patients to all those involved in HST evaluation and decision making was demonstrated in a recent study illustrating what the patient community already knew – that the values and concerns of patients are not fully mirrored by clinical and health economic ‘experts’. In particular, it highlighted that patients give greater weight to improvements in the quality of their daily life than ‘experts’.

This stresses the need for patients’ voices to be heard in their own words. This means ensuring that the patient evidence submission is not filtered before it reaches NICE’s Review Group and Evaluation Committee.

What information does NICE want?

### Patient evidence submission questions (in full in Annex 5):

1. How does the condition have an impact on patients, their families or carers?
2. What do patients, their families or carers consider to be the advantages and disadvantages of the technology?
3. Are there differences in opinion between patients about the usefulness or otherwise of this technology?
4. Are there any groups of patients who might benefit more or less from the technology than others?
5. What are the advantages and disadvantages of the new technology compared to current standard practice in the UK?
6. Does data from clinical trials reflect the patient experience of using the technology as part of their care/ any adverse effects experienced?
7. What would be the impact for patients, their families or carers of making this technology available or not making it available?
8. Equality: do you think that this evaluation could exclude any people protected by the equality legislation/ result in recommendations that impact differently on people protected by the equality legislation/ people with disabilities?

Patient representatives were keen for NICE to provide additional guidance on what information should be included in the patient evidence submission, and how this information should be presented. They asked for this to include how patients groups could best demonstrate a spectrum of disease severity in their patient community and similarly, variation between patients in their experience of a new treatment.

The importance of adequately dealing with these aspects of the patient experience was raised at the first Evaluation Committee meeting (December 2013), which looked at the treatment of aHUS with eculizumab.

At the meeting, Dr Mark Sheehan, Oxford NIHR Biomedical Research Centre Ethics Fellow; Research Fellow at the Uehiro Centre for Practical Ethics, University of Oxford; and ‘lay lead’ on the Evaluation Committee, aired reservations over whether the testimonies provided were reflective of patient experience. He suggested that additional case studies be included in the patient group evidence submission to make certain that any negative experiences of a new treatment were also covered; and as a result, ensure that the Evaluation Committee felt confident that they had been given an accurate and unbiased account.

While this suggestion has merit, it is important to recognise that the case studies provided by aHUSUK already represented 10% of all patients, a larger proportion than would normally be engaged for more common conditions. Moreover, all rare disease patient communities involved in an HST evaluation at NICE will likely have already contributed substantially to the marketing authorisation process at the EMA by providing patient testimonials and information.
Patient representatives were keen to have clarified what information NICE would be interested in above and beyond that already made available to the EMA and/or to what extent these could be made use of by NICE.

An explanation of ‘impact beyond direct health benefits’ and its value in an HST evaluation is required

The precise nature of the ‘impact beyond direct health benefits’ criterion NICE will use in an HST evaluation has yet to be fully described. There was concern among the patient group community that this referred primarily to enabling patients to return to work, although the opportunity provided by this criterion to potentially consider wider societal benefits was welcomed.

Consequently, patient representatives called for clarity over what types of ‘impact’ would be included and whether this would apply exclusively to the patient or also to carers and families. They also wanted to ensure that rare disease treatments were not discriminated against if they did not allow a return to employment, given that many rare diseases are severely debilitating and progressive.

Patient representatives noted that disease itself is not cost neutral for the individual and that the beneficial impacts of a treatment beyond direct health benefits should be recognised at an individual as well as a societal level.

In order to provide information that can usefully answer to the ‘impact beyond direct health benefits’ criterion, patient groups felt it essential that not only was the definition of the criterion clarified, but that details of how this data should be generated should be outlined. This may involve the provision of specific support, given that not all patient groups would be capable of producing this type of information. For example, a Cancer Research UK funded study revealed the ‘cost’ of cancer in Europe due to work missed through sickness or dying young, or because of families providing care. It is unlikely that the majority of patient groups would be in a position to produce similarly persuasive data for two reasons – lack of resources and scarcity of patients – potentially causing inequity.

Nominating experts

The Evaluation Committee should be able to accommodate sufficient ‘nominated experts’ so as to reliably reflect the diversity of opinion in the relevant patient community

Patient representatives were supportive of ‘nominated experts’ primarily because it gives patients the opportunity to speak directly to the Evaluation Committee as well as the ability to nominate clinicians to speak on their behalf. However, there were concerns that the number of patient experts able to attend was limited to only two.

“It is an improvement on AGNSS because of the greater emphasis on patient evidence and consideration of societal impacts, that is, non-NHS costs in calculating cost benefits and savings”

“The testimony of patients [during an HST evaluation] is what has to ‘compete’ against the cost of the drug”
Patient representatives felt that this put a lot of pressure on any nominated patient expert, and were sensitive to the fact that differences in the ability of individuals to be effective in this role may impact significantly on the meeting’s outcome.

In addition, more than two patient groups may wish to be directly represented at the Committee meeting. As with more common conditions, multiple patient groups can exist for a rare disease that may differ in their approach, priorities or “desired goals”, and provision should be made to accommodate this.

To address these issues, patient representatives called for the cap on the number of ‘nominated experts’ to be lifted in order to allow more patients to participate, and that this provision should also be extended to the number of patient group-nominated clinicians.

Action by: NICE

In the first HST Evaluation Committee meeting\(^1\), a summary of the ‘patient perspective’ was given by Dr Mark Sheehan, the ‘lay lead’ on the Evaluation Committee.

While the presentation reflected the salient points covered in the patient evidence submission, it was notable that the original phrasing used by patients was rarely referenced. In addition, it was clear that a degree of personal interpretation had been applied to the submission, giving it a somewhat detached, objective and critiqued feel. Given that it has been shown in a recent study that ‘experts’ and patients often weigh aspects of disease severity and treatment benefits differently\(^2\), this is concerning.

In addition, a recent report from the EMA\(^3\), produced as part of their work to improve the patient voice in medicine evaluations, revealed that patient input was considered ‘particularly valuable’ when given ‘in person’ rather than as ‘advice in writing’.

With this in mind, patient representatives felt it was reasonable that the nominated patient experts be permitted to present the patient evidence submission summary to the Evaluation Committee. For consistency, this summary could be agreed on in advance by the NICE secretariat and the patient community being represented.

In the HST workshop feedback survey, respondents were generally satisfied with the level and type of patient engagement during HST evaluation at NICE. However, the role of the nominated expert, and particularly their inability to address the Committee unless invited to do so, was raised as an area of concern.

Provision for nominated patient experts to provide a summary, in person, directly to the Evaluation Committee would adequately address this concern.
What happens to the patient evidence submission?

18 The patient evidence submission should be seen in its original form by the Review Group and Evaluation Committee

Patient representatives were uncomfortable with the idea that after having produced the evidence submission, it would get filtered and summarised during the evaluation process. They were concerned that this could result in the priorities and opinions put forward by a patient group being altered without their knowledge. Patient representatives therefore recommended that patient evidence submissions be made available to all those involved in the HST evaluation process in their original form, and that they should not be subject to reinterpretation at any stage.

Action by: NICE

19 The patient evidence submission’s use and impact should be communicated back to patient groups

There was uncertainty among patient representatives over how the patient evidence would be received and viewed by individuals involved in HST evaluation. They would like to see the Evaluation Committee take a universal approach to HST appraisal and urged the Committee to give equal weighting to the patient's and manufacturer's evidence submission.

In order to see whether these calls are acted upon during an HST evaluation and to better understand how input from patient groups is actually used, patient representatives proposed that NICE provide feedback, outlining at what point information from patient submissions or nominated experts was used to make a decision and what impact it had. They felt that this would add clarity and transparency to the process, as well as enable patient groups to learn from each other and share best practice.

Action by: NICE

“NICE aren’t used to personal testimonies; more attention and consideration needs to be given to case studies”

Updating the health economist’s tool box

The majority of a health economist's calculations are premised by attributing the highest value to interventions that give the greatest gain to the largest population at the lowest cost.

According to a recent study of historical decisions at NICE, the best predictor of whether a treatment will receive a positive recommendation is the cost per Quality Adjusted Life Year (QALY) that is calculated. If a treatment has a cost per QALY of up to £30,000, there is a good chance of it having received a positive recommendation from NICE. With rare and ultra-rare diseases, however,
treatments are often expensive, with costs per QALY regularly exceeding £30,000. Target populations are also small and often the degree of benefit a treatment offers can appear comparatively limited. It is clear that under the existing health economics framework, it would be difficult for an HST to be recommended for NHS commissioning.

Despite this, provision of high cost drugs for small populations with severely debilitating diseases is supported by the general public and government\textsuperscript{3,6-10}. As health economists consider the justification of NHS-wide commissioning of rare disease treatments, it is clear that their tool box needs updating so that it reflects public and government opinion; and sufficiently addresses a significant area of unmet medical need and growth in drug discovery.

***Action by: NICE***

Given how important the calculations made by health economists are in NICE’s decision making\textsuperscript{32}, patient representatives were concerned that they currently had an incomplete understanding of how these calculations are made. They were keen that any calculations carried out were explained in lay language and formed part of the feedback that they have called for NICE to provide to all patient groups engaged with an HST evaluation.

In particular, they were keen to determine whether any data from the patient submission had informed the calculations and what impact this had; or whether the type of information that patient groups are able to provide would, in general, not be considered sufficiently robust to be included. They felt that providing this information was essential to making the process transparent and accessible to all patient groups and the general public.

***Action by: Department of Health, Genetic Alliance UK, NICE (NICE International)***

For HST evaluations, a measure of health outcomes more applicable to rare diseases should be developed and used in place of the EQ-5D.

In order to measure disease burden and the benefit of a new treatment, health economists often use a type of survey called an EQ-5D\textsuperscript{33}. They ask patients to complete this survey before and after starting a treatment and use the difference between their responses to quantify the value of a treatment. This measure of ‘health related quality of life’ encompasses five areas of wellbeing (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), with three or five degrees of measurement e.g. no difficulties, some difficulties or extreme difficulties. It is valued by health economists because it is easy and quick, ensuring that as many patients as possible provide feedback.

Patient representatives felt that the crude nature of the EQ-5D made it inappropriate for capturing the particular type and range of symptoms, emotions and disadvantages experienced by patients affected by rare conditions. They felt that an in-depth measurement of disease burden and treatment benefit was of greater value in a rare disease context than a quick and easy method. Consequently, they called for a more sensitive system to be introduced, tailored to rare disease indications.
Importantly, patient representatives noted that while improvements to the existing quantitative method for capturing health outcomes (the EQ-5D and its equivalents) was necessary, it should in no way be seen as a way of undermining or replacing qualitative data and the value of information that can only be truly captured through personal testimony.

Another aspect of the EQ-5D that concerned patient representatives was that the general public, and not the patient community, determined the ‘value scores’ attributed to each wellbeing state. This is based on the rationale that since the general public finance the NHS, they should determine what the health service values most\textsuperscript{6}.

Patient representatives were concerned that the quality of life impact of apparently minor improvements may be undervalued by the general public due to a comparatively limited awareness of rare diseases and how they affect patients and their families. They therefore asked for those members of the public who participate in the process to be better informed before they determine value measurements.

NICE is already engaged with addressing some of these issues through participation of NICE International with a research project called ADVANCE-HTA. This project aims to identify ways of improving the value measurements for rare diseases in health technology assessments and to better understand how value measures may differ between patients and the general public\textsuperscript{34}. Genetic Alliance UK welcomes the opportunity to work with ADVANCE-HTA and NICE International in order to explore these issues through our patient group membership, and feed this into the development of new tools for measuring the health related quality of life for patients affected by rare diseases.

Case study: ADVANCE-HTA: Rethinking the future of Health Technology Assessment

ADVANCE-HTA is a research project funded by the European Commission's Research Framework Programme (FP7). The aim of the project is to investigate and improve the process and implementation of health technology assessments (HTA), and in particular, the tools used to measure and quantify the ‘value’ of a treatment. It is a partnership of 13 Consortium members and is led by the London School of Economics (LSE Health). There are a number of aspects of the project’s research remit that are particularly relevant to rare disease patients.

With reference to how the patient perspective of treatment benefit and disease burden is captured (where the EQ-5D is used as a generic tool), these research aims include:
1. Exploring how disease severity, burden of disease, innovation and the quality of the available evidence can be incorporated into an HTA process in a quantifiable way;
2. Exploring new tools (analytical frameworks) for measuring value;
3. Using specific disease cases studies to investigate how alternative tools may impact on value measures.

With reference to how health states are assigned a ‘value’ as part of the EQ-5D, or an equivalent, some research will also:
4. Investigate the potential differences between the general population and defined patient groups when assigning ‘value’ to health related quality of life states;
5. Establish the causes of any differences;
6. Define the advantages and disadvantages of the value sets drawn by the general population and patient groups;
7. Consider the potential implications of using patient-defined value measures.

“There are issues with the public prioritising certain things over others, even though they may have no knowledge of it themselves, for example, what it’s like to be in a wheelchair”
While patient representatives welcomed the fact that the HST process recognised that evaluation of treatments for ultra-rare diseases was distinct from more common ones, they were concerned that this was a significant development only if this recognition was carried throughout the process.

With this in mind, patient representatives were in agreement that HST clinical trial data could not and must not be held to the same standard as other treatments assessed by NICE. The fact that clinical trials may not include a placebo control or that the ‘best available’ comparator could be limited to palliative care, was seen as an unavoidable weakness when working with rare diseases. However, patient representatives felt that this could be offset, in part, by a balanced consideration of the experiences of patients and clinicians.

There are understandable limitations to the data that can be gathered from clinical trials with small participant numbers and/or no control groups. Therefore, it is critical that the data that is collected is as robust and relevant as possible. When discussing how health economists use and consider trial data, patient representatives were keen to establish what information these types of clinical trial could produce that would be valued by health economists. Patient representatives agreed that HST trials should have greater emphasis on patient reported outcome measures (PROMs), to capture a more complete and sensitive picture of the impact of an intervention from the patient perspective.

A joined-up approach to research and development, clinical trials and regulation of new treatments is essential to ensure that the data required and the data collected are in line with each other. To achieve this, there needs to be constant dialogue between patients, manufacturers, regulatory bodies and clinical researchers. Patient representatives felt that it was important, once the HST evaluation process has been in place for some time, that a review of the strengths and weaknesses of received manufacturer submissions be carried out. This information should be made available to interested stakeholders in order to provide guidance on clinical trial design and inform future HST evaluations.

In November 2013, the EMA announced its plan to work with the European network for Health Technology Assessment (EUnetHTA) in order to provide guidelines on clinical trial design so that data relevant to the assessment of both benefit and risk at the EMA and relative effectiveness assessments at HTA bodies, can be generated. 

Expectations of clinical trial data must be pragmatically aligned to reflect the limitations of data derived from studies on small numbers of patients

Action by: NICE (Evaluation Committee)

“There will inevitably be questions about significance of research results with low participant numbers. Will NICE treat these results with caution, accept them without question, or somewhere in between?”

NICE should work with medicine regulators in a coordinated way to provide advice to companies regarding clinical trial design and data collection; and guidelines for the manufacturer’s evidence submission

Action by: NICE, EUnetHTA, EMA, pharmaceutical companies
Generating additional evidence

The impact that ‘gaps’ in the evidence provided by the manufacturer, including clinical trial data, have on the outcome of an HST evaluation was the second greatest concern of patient representatives.

Sometimes these ‘gaps’ are unavoidable, either because the target patient population is very small or because the nature of the condition makes it difficult to reliably measure treatment benefit. However, some ‘evidence gaps’ could be addressed with further research.

When NICE issues its guidance on an HST, it can choose to make the treatment available only in the context of further research. A Citizen’s Council report from NICE on the use of this type of recommendation concluded that ‘treatments for life-threatening conditions where there is no other remedy available’ should be given the ‘benefit of the doubt’ with an ‘only in research recommendation’ rather than a ‘no’.

Patient representatives agreed with this statement and proposed that in the context of rare diseases research recommendations be made more frequently to enable additional data to be gathered in support of future NHS-wide commissioning while making the treatment available.

However, patients have experienced exclusion from clinical trials for a number of reasons including their age, disease state or living too far away from the trial centre. Therefore, in order to facilitate equitable access while allowing additional evidence to be gathered, patient representatives were keen for NICE to ensure that studies carried out as part of research recommendations take a broader, more inclusive approach to eligibility than standard trials.

Given that NICE does not consider who would carry out any research¹, or provide any mandate or incentive, patient representatives also thought it essential that NICE clarify for patients and the public what happens if the requested research is not carried out.

Patients should be involved in outlining the nature and timeline of any post-evaluation research recommended by NICE

Patient representatives stated that the research recommended by NICE should be clearly defined and outline measurable outcomes that can be obtained over a feasible timeframe. The evidence gathered should also have the potential to significantly increase the likelihood of a restriction-free recommendation being made in the future.

Action by: NICE

“Patients should be given the right to try if evidence is not available”

“Safety is paramount – but there is some willingness to accept a greater degree of risk when it is under clinical guidance management”

Action by: NICE
In the designing of research that meets these stipulations, patient representatives felt that the patient voice had a central role to play. The patient perspective on research type and methodology, as well as on the practicalities of recruitment, was considered to be an invaluable aspect of feasibility. Consequently, it was recommended that patients be directly involved in designing further research, perhaps through a formal consultation stage prior to the final Evaluation Committee meeting.

Involving the NHS in further research

**Use of NICE-commissioned HSTs in the NHS should be monitored as part of routine clinical care to ensure expected patient outcomes are met**


Continual assessment of treatment efficacy and long-term follow-up was considered by patient representatives to be a research priority. They felt knowledge of real-world outcomes over a longer time period was particularly important with HSTs, where recommendation decisions may have been based on limited clinical trial data. Patient representatives agreed that the collection of this type of data should be built-in to routine care, regardless of whether NICE guidance was positive or if the treatment was recommended only in research; and that the data should form a key part of the information NICE uses to review its guidance (Annex 3).

Indeed, patient representatives were keen to see this type of follow-up research made an integral part of the service NHS England provides to patients affected by both rare and more common conditions. It was suggested that digitisation of health records, which could be accessed and contributed to by patients as well as their clinicians, could be a way of capturing this data and making it available. A move towards creating and managing patient data registries in order to improve the quality of health care provision has received recent support in government.

Patient representatives identified NHS England as the organisation best placed to promote uptake of nationally commissioned services that incorporate the collection of data that can be made available for analysis. This could involve NHS England building on the work of the General Practice Research Database, the Clinical Practice Research Datalink and the rare disease community through close collaboration.

**Research that examines dosage and clinical trials evaluating the impact of dosage should be encouraged, with the view to making HSTs more effective and more affordable**

Action by: NHS England

For many rare disease treatments, clinical trials to examine treatment efficacy over a range of doses has not been carried out. Often too, doses specific to children have been determined through calculations based on body weight rather than through clinical trial. For severely disabling, rare conditions that affect primarily children it is clear why this is the case, since recruitment to a trial where there is a chance that an effective dose of the treatment may not be given would be difficult to justify. Consequently, data to validate the recommended dose is often limited. In these circumstances,
there may be scope to consider reducing the dose, under clinical supervision, as a smaller dose per person would have a significant impact on reducing treatment cost and may also reduce the number and/or severity of adverse outcomes.

Patient representatives felt that dosing was an area that could be explored by patients, in consultation with their clinicians, in the framework of NHS England. Trialling different doses on a patient-by-patient basis, with communication of findings between clinicians, would be a low-cost way of looking to make HSTs more affordable while still making the treatment available to everyone.

Risk versus effectiveness in a NICE evaluation

During an HST evaluation at NICE, the Evaluation Committee examines the potential benefits and adverse outcomes of a treatment when considering ‘clinical effectiveness’.

NICE will only recommend a treatment if the magnitude of benefit justifies the cost of the intervention. Insufficient benefit to justify cost was the reason why many of the orphan drugs not approved by NICE failed to gain a positive recommendation through its standard HTA appraisal system.

There is clearly a need for NICE to take into account benefit and risk in order to assess the overall cost-effectiveness of a treatment. However, in order to be evaluated by NICE, all medicines must have already have obtained a marketing authorisation from the EMA. If this authorisation is granted, then the treatment has already been judged to be effective, with the EMA determining that the benefits of the intervention outweigh the risks. This decision is made following consultation with patients from across Europe, with direct patient input at the pre-submission, evaluation and post-authorisation stages of a marketing authorisation application, and personal participation of patient representatives in advisory groups.

Is it appropriate that national HTA bodies such as NICE are able to effectively overturn a decision already made at the EMA by blocking patient access on the basis of perceived unacceptable risk?

A negative recommendation from NICE should only be on the basis of unreasonable expense for the degree of benefit, rather than on the basis of unacceptable risk. However, patient representatives were concerned that this was a ‘grey area’ and called for clarity over the roles of NICE and the EMA in legislating on ‘acceptable risk’ for a new treatment.

The willingness to accept risk or adverse outcomes with a new treatment varies considerably both between and within patient communities. Whether it is what risk of adverse drug reactions can be tolerated or what improvements matter most, different patients have different perspectives and these may change over time as an individual ages or their disease progresses. This issue raises questions that are best addressed on a personal basis by patients and their families. Genetic Alliance UK explored how patients and families affected by genetic conditions perceive these issues in our ‘Risks and Benefits’ project (2012), which we are now expanding with a project that seeks to capture the perspective of patients from across Europe. For NICE and other regulatory bodies seeking to take
decisions in an open and transparent manner, reflecting the complex, variable and personal nature of the patient perspective of benefit/risk when issuing generic guidelines is a key challenge.

The EMA has the Europe-wide responsibility for carrying out a standardised benefit/risk analysis for all new medicines with an orphan designation, in the context of specific patient communities. Given that this is a primary role of the EMA, patient representatives felt that any assessment of benefit/risk at NICE should be subordinate to decisions made at the EMA. They questioned the value added by NICE repeating the process, particularly as a larger body of patient experience can be captured at a European level than at a national one.

Therefore, they felt it necessary that NICE be asked to justify and give specific reasons for any reassessment of benefit/risk that it carries out during an HST in order to clarify and add transparency to the process. This should include a clear statement of what additional dimensions they wish to consider that the EMA did not adequately address previously.

Moreover, patient representatives were concerned that if benefit/risk was to be reexamined, that NICE be required to consult and consider the patient voice, as at the EMA. This included ensuring that all the information that patient representatives provided to the EMA as part of their benefit/risk assessment was also made available, in its original form, to NICE.

In collaboration with EUnetHTA, the EMA has begun to work on improving the communication of benefit/risk and clinical effectiveness data between the EMA and national HTA bodies, such as NICE. They are also looking to improve the post-market authorisation collection of data in order to help further support decision making at the national level.

During the topic selection phase of HST evaluation, the potential benefits and risks of a treatment are also considered. Patient representatives were particularly concerned by this as it occurs prior to a market authorisation being granted and therefore, before the EMA has gathered patient testimonies on benefit and risk. At the NIHR Horizon Scanning Centre, further information about patient benefit/risk is currently sought exclusively from clinicians. Consequently, patient representatives thought it was essential that the NIHR Horizon Scanning Centre establish a formalised route to directly capture the patient perspective of benefit/risk during topic selection.

More generally, patient representatives suggested that the patient voice on acceptable risk should be embedded into treatment research and development, from drug design through to clinical trials and future regulatory decision making. They felt that this was particularly important in the field of rare diseases where it was felt that as a community, rare disease patients were more willing to accept risk.

The criteria by which the Evaluation Committee will judge clinical effectiveness:

1. The nature and quality of the evidence derived from manufacturers, academics and consultees. This includes the views expressed by clinicians with direct experience of the technology in clinical practice and of patient experts and carers on the condition and their experience of the technology.
2. Uncertainty generated by the evidence and differences between the evidence submitted for licensing and that observed in clinical practice.
3. The impact of benefits/adverse outcomes from a patient’s perspective.
4. The possible differential benefits/adverse outcomes for different groups of patients (e.g. different age, disease severity or indications).
5. How the technology fits with existing care and what the alternative care pathways are.

“Vulnerable patients with very rare conditions [should not be] denied treatments on the grounds of cost following an inappropriate cost benefit analysis”

Access to high-cost drugs for rare diseases report (APPG for Muscular Dystrophy)
A second aspect of risk at NICE is less about ‘acceptable risk’ in relation to a drug and more about the potential ‘risk’ of NICE making an incorrect judgment due to insufficient data. This is a particular issue for very rare diseases where a paucity of clinical trial data is well recognised.

Patient representatives agreed that for very rare diseases with unmet medical need, NICE should be encouraged to give new treatments the ‘benefit of the doubt’, and provide as much data as possible to enable patients to make informed decisions with their clinicians. It was felt that this provided the correct balance in rare diseases between patient-driven healthcare and the public expectation that if a medicine is made available, it must be ‘safe’. They felt this would ensure that NICE could not be accused of being more likely to overlook a potentially beneficial new treatment than to positively recommend a treatment that is later withdrawn.

Patient representatives called for NICE to ensure that it was making financially prudent rather than risk-averse decisions when evaluating HSTs for national commissioning and that it was not stepping outside of its remit by effectively overturning decisions made at the EMA on whether the benefit of a treatment outweighs its risks.

Ultimately, after a decision at the EMA, risk should not be a factor in determining patient access to new treatments: NICE should only consider the cost-effectiveness of treatment benefit, while the question of accepting or tolerating risk is for patients individually to consider, with the advice of their health professional.

“Patients are probably more willing to accept risk than NICE or the NHS”
Annexes

Table of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AGNSS</td>
<td>Advisory Group for National Specialised Services</td>
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<tr>
<td>aHUS</td>
<td>Atypical haemolytic uraemic syndrome</td>
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<tr>
<td>CRG</td>
<td>Clinical Reference Group</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EUnetHTA</td>
<td>European network for Health Technology Assessment</td>
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<tr>
<td>HST</td>
<td>Highly Specialised Technology</td>
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<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
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<tr>
<td>IFR</td>
<td>Individual Funding Request</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
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<tr>
<td>PNH</td>
<td>Paroxysmal nocturnal haemoglobinuria</td>
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<tr>
<td>PROM</td>
<td>Patient Reported Outcome Measure</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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Annex 1: Methods overview

Representatives of selected patient groups were invited to attend an interactive workshop on HSTs in London on the 28th November 2013. Patient groups were selected on the basis of their likely involvement in future HST evaluations and their degree of engagement with the issues surrounding access to medicines for rare disease patients. 16 patient groups were represented at the workshop.

Prior to the workshop, all attendees were provided with a briefing pack that summarised NICE's interim methods and processes for HST evaluation and highlighted some topics for discussion at the workshop. On the day, patient representatives had the opportunity to ask our invited speakers questions before breaking away into four work groups that each addressed specific aspects of the HST evaluation process. Each work group was assigned a member of the Genetic Alliance UK team to act as a scribe and capture the opinions and priorities voiced by the patient representatives. The workshop was carried out under Chatham House rules. Individuals were also invited to give their own views as part of a feedback survey made available to all attendees after the workshop had ended.

The outcome of all discussions on the day and from the feedback survey was collated and drawn up into the Patient Charter. This was then made available to the patient representatives that acted as facilitators of workgroup discussions for editorial comment. The Charter was subsequently circulated to the membership of Genetic Alliance UK for endorsement.
Annex 2: Workshop attendees

### Externally invited speakers

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation</th>
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<tbody>
<tr>
<td>Josie Godfrey</td>
<td>NICE</td>
</tr>
<tr>
<td>Dr Robin Lachmann</td>
<td>National Hospital for Neurology and Neurosurgery</td>
</tr>
<tr>
<td>Jon Sussex</td>
<td>Office of Health Economics</td>
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### Facilitators of work group discussions at HST workshop

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation</th>
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<tbody>
<tr>
<td>Dave Ryner</td>
<td>Chronic Myeloid Leukaemia Support Group</td>
</tr>
<tr>
<td>Robert Meadowcroft</td>
<td>Muscular Dystrophy Campaign</td>
</tr>
<tr>
<td>Dr Will Evans</td>
<td>Niemann-Pick Disease Group (UK)</td>
</tr>
<tr>
<td>Jayne Spink</td>
<td>Tuberous Sclerosis Association</td>
</tr>
</tbody>
</table>

### Additional workshop participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Organisation</th>
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<tbody>
<tr>
<td>Andy Soar</td>
<td>Action Duchenne</td>
</tr>
<tr>
<td>Ian Mackersie</td>
<td>aHUSUK</td>
</tr>
<tr>
<td>Sara Hunt</td>
<td>ALD Life</td>
</tr>
<tr>
<td>Nick Sireau</td>
<td>Alkaptonuria Society</td>
</tr>
<tr>
<td>William Davis</td>
<td>A-T Society</td>
</tr>
<tr>
<td>Emma Lake</td>
<td>Cystic Fibrosis Trust</td>
</tr>
<tr>
<td>Liz Ryburn</td>
<td>Jennifer Trust for Spinal Muscular Atrophy</td>
</tr>
<tr>
<td>Sophie Thomas</td>
<td>MPS Society</td>
</tr>
<tr>
<td>Lizzie Perdeaux</td>
<td>Myrotylitis Trust</td>
</tr>
<tr>
<td>Christiane Kellner</td>
<td>PNH Alliance</td>
</tr>
<tr>
<td>Martine Walmsley</td>
<td>PSC Support</td>
</tr>
<tr>
<td>Stephen Ffoulkes</td>
<td>UKPIPS (UK Primary Immunodeficiency Patient Support)</td>
</tr>
</tbody>
</table>
Annex 3: A summary of NICE’s interim process for HST evaluation

HST evaluation process

Topic selection
NIHR Horizon Scanning Centre & Department of Health

Consultees identified

Scoping
Ministerial referral

Evidence Review Group
Evaluation report

Evaluation Committee
Evaluation Consultation Document

Recommendations:
Recommended;
Recommended for some patients;
Recommended only in research;
Not recommended.

Final Committee meeting

Final Evaluation Determination

Guidance issued

Review date

Manufacturer
Pipeline information

Evidence Submission
Manufacturer / NHS England etc

Patient groups

Evidence Submission
Nominate experts

Patient engagement:
1. Written consultation
2. Scoping workshop

Consultation:
1. Formal (stakeholder)
2. Public (one week later)

Appeal
Open to all consultees in evaluation process

Update guidance?
Annex 4: Evaluation criteria

Below are the evaluation criteria copied from NICE's Interim Process and Methods of the Highly Specialised Technologies Programme. These are the criteria the Evaluation Committee will take account of in order to form guidance:

1. Nature of the condition
   - Disease morbidity and patient clinical disability with current standard of care
   - Impact of the disease on carers’ quality of life
   - Extent and nature of current treatment options

2. Impact of the new technology
   - Clinical effectiveness of the technology (further details on the criterion can be found on page 33)
   - Overall magnitude of health benefits to patients and, when relevant, carers
   - Heterogeneity of health benefits within the population
   - Robustness of the current evidence and the contribution the guidance might make to strengthen it
   - Treatment continuation rules

3. Cost to the NHS and Personal Social Services
   - Budget impact in the NHS and PSS
   - Robustness of costing and budget impact information
   - Patient access agreements

4. Value for money
   - Technical efficiency (the incremental benefit of the new technology compared to current treatment)
   - Productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used)
   - Allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)

4. Impact of the technology beyond direct health benefits
   - Whether there are significant benefits other than health
   - Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services;
   - The potential for long-term benefits to the NHS of research and innovation;

5. The impact of the technology on the delivery of the specialised service
   - Staffing and infrastructure requirements, including training and planning for expertise

The Committee will consider each of the criteria listed above and, after reviewing the evidence and commentary, reach a consensus on whether the highly specialised technology can be recommended for national commissioning.

Annex 5: Alternative routes for HST commissioning

Having an HST appraised through NICE is not the only way that new treatments could be commissioned for individuals with rare diseases. Currently there are a number of routes, both within and external to NICE, which have the potential to get rare disease treatments to patients with varying degrees of use and success. Genetic Alliance UK plans to review these in a forthcoming Patient Charter.
Despite being within the scope of the HST process, rare disease treatments may be appraised through NICE's standard HTA system. This is the process that is applied to all other medicines and as such, may be less sensitive to issues that are particularly applicable to rare diseases, such as:

- The vulnerability of very small patient groups with limited treatment options;
- The nature and extent of the evidence available;
- The challenge to manufacturers in making a reasonable return on their research and development investment due to the small patient populations treated.

Therefore, it is likely that only a minority of treatments for rare conditions would meet the HTA appraisal criteria needed in order for NICE to make a positive recommendation.

### NHS England's Clinical Commissioning Policies for Specialised Services

Treatments for rare diseases may be made available to NHS patients following appraisal by NHS England via the relevant Clinical Reference Group (CRG). There are over 70 CRGs, each representing different disease areas, which have their own defined services and commissioning policies, through which they may commission medicines. For example there are CRGs for Medical Genetics and Inherited Metabolic Disorders.

Potential topics for a CRG-based appraisal, and the generation of a Commissioning Policy, are identified via four 'routes':

1. CRG scoping;
2. Horizon scanning;
3. Through partnership with NICE;
4. Via Individual Funding requests (IFRs).

Under the IFR system, an individual can make an appeal, through their clinician, for access to a particular medicine (or specialised service), which is then forwarded on to the relevant CRG.

Topics can include new treatments or requests for a review of existing commissioning policy. Appraisals are managed through two systems; one that runs quarterly and a 'fast-track' route. For the quarterly appraisal, topics are proposed at least 6 weeks before each quarter and the appraisal completed within 3 months. A ‘fast-track’ appraisal aims to be completed within 6 weeks. This is often the route through which IFRs will be appraised.

When determining whether a rare disease treatment should be recommended or not, the CRGs consider four questions:

- **Does it work?**
  - Clinical effectiveness and potential for improving health; Clinical safety and risk; Severity and ability of patients to benefit.

- **Does it add value to society?**
  - Needs of patients and society; Stimulating research and innovation.

- **Is it a reasonable cost to the public?**
  - Average cost per patient; Overall cost impact and affordability (including opportunity cost); Value for money compared to alternative.

- **Is it the best way of delivering the service?**
  - Best clinical practice in delivering the service; Economic efficiency of provision; Continuity of provision; Accessibility and balanced geographic distribution.

With advice from the Clinical Priorities Advisory Group, who are in turn advised by the Rare Disease Advisory Group, CRG commissioning decisions are made on a case-by-case basis.
Clinical Commissioning Groups (CCGs)

CCGs are responsible for delivering local health services in England. They do this by commissioning health and care services. CCGs are made up of GPs from the local area and at least one registered nurse and one secondary care specialist doctor. They work closely with patients as well as local hospitals, authorities and community groups to ensure services meet local needs.

In NICE’s ‘Interim Process and Methods’ for HST evaluation, it states that if “NICE is unable to recommend the use in the NHS of a technology” because insufficient evidence was provided by the manufacturer, resulting in a termination of the appraisal, that NICE will provide an explanatory report “to help the NHS make local decisions on making the technology available”. This process is through CCGs. Given the likely high cost of rare disease treatments, it is unlikely that CCGs will designate resources for these if they receive a negative appraisal from NICE.

Annex 6: Proposed template for the HST patient evidence submission

The questions included in NICE’s patient evidence submission template are reproduced in full below:

The questions are there as prompts to guide you. You do not have to answer every question. Where appropriate, please provide case studies of individual patients, their families or carers. Please do not exceed 30 pages.

1. How does the condition impact on patients, their families or carers?

   - Please describe whether patients experience difficulties or delays in receiving: a diagnosis/appropriate treatment/helpful information about the condition, and the impact these difficulties have on patients and their families or carers.
   - Please describe how patients and their families or carers have to adapt their lives as a result of the condition, and the impact the condition has on the following aspects: physical health/emotional wellbeing/everyday life (including if applicable: ability to work, schooling, relationships, social functioning)/other impacts not listed above.

2. What do patients, their families or carers consider to be the advantages and disadvantages of the technology for the condition?

   - Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make for patients, their families or carers.
   - Please list any short-term and long-term benefits that patients, their families or carers expect to gain from using the technology. These might include the effect of the technology on: the course and outcome of the condition/physical symptoms/pain/level of disability/mental health/quality of life (lifestyle, work, social functioning etc.)/other quality of life issues not listed above/other people (for example friends and employers)/other issues not listed above.
   - Disadvantages: please list any problems with or concerns you have about the technology. Disadvantages might include: aspects of the condition that the technology cannot help with or might make worse/difficulties in taking or using the technology/side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)/impact on others (for example family, friends, employers)/financial impact on the patient or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

4. Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?
5. Comparing the technology with alternative available treatments or technologies. NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

- Please list current standard practice (alternatives if any) used in the UK.
- If you think that the new technology has any advantages for patients over other current standard practice, please describe them. Advantages might include: improvement of the condition overall/ improvement in certain aspects of the condition/ ease of use (for example tablets rather than injection)/ where the technology has to be used (for example at home rather than in hospital)/ side effects (please describe nature and number of problems, frequency, duration, severity etc).
- If you think that the new technology has any disadvantages for patients compared with current standard practice, please describe them. Disadvantages might include: worsening of the condition overall/ worsening of specific aspects of the condition/ difficulty in use (for example injection rather than tablets)/ where the technology has to be used (for example in hospital rather than at home)/ side effects (for example nature or number of problems, how often, for how long, how severe).

6. Research evidence on patient, family or carer views of the technology.

- If you are familiar with the evidence base for the technology, please comment on whether patients’ experience of using the technology as part of their care reflects that observed under clinical trial conditions.
- Are there any adverse effects that were not apparent in the clinical trials but have come to light since the treatment has become available?
- Are you aware of any research carried out on patient, family or carer views of the condition or existing treatments that is relevant to an evaluation of this technology? If yes, please provide references to the relevant studies.

7. Availability of this technology to patients.

- What key differences, if any, would it make to patients, their families or carers if this technology was made available?
- What implications would it have for patients, their families or carers if the technology was not made available?
- Are there groups of patients that have difficulties using the technology?

8. Equality: NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.
- Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.
References


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Homepage for the National Institute for Health and Care Excellence: www.nice.org.uk


More details about the project ‘Risks and Benefits II’: www.geneticalliance.org.uk/projects/eurorisksandbenefits.htm
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