Bridging the gap: lessons from divergence in decision-taking on rare diseases across the UK

Introduction

The Specialised Healthcare Alliance (SHCA) represents patients with rare and complex conditions. For many of these conditions, there are few, if any, treatment options available. Patients therefore rely on the health service to make new treatments available to them whenever they can, to give them a chance of a better life.

However, for health systems, new treatments often create additional pressures on their finances and infrastructure. As the number of new treatments has grown, so too has the challenge for health systems in finding the resources to provide high quality services. This challenge is particularly acute for treatments for rare or complex conditions as the number of these treatments has grown exponentially in recent years.

Different countries have sought to address these pressures in different ways, and considerable effort has been spent in measuring how these different approaches impacts on patients' access to treatment. The evidence suggests the UK lags behind comparable countries in speed of decision-making, with decisions taking around 26.5 months on average, compared to an average of 19 months in France and Italy, and in the numbers of treatments made available to patients, which is lower than in France and Germany.[1,2]

Less attention has been paid to comparing the four nations within the UK. However, due to the similarities of the four individual health services and of the populations they serve, these intra-UK comparisons are potentially more relevant when considering how to deliver equity of access to treatments for rare diseases. Since political devolution in 1999, there have been growing differences in the approaches taken by the health systems of the four countries in the UK. Recently, changes in the way in which the Scottish, Welsh, English and Northern Irish systems review both orphan and ultra-orphan treatments have resulted in increasing divergence across the UK.

Shining a light on this divergence can help identify where policymakers could make changes to improve access for patients. For example, as the system in England looks to reform NICE's methods and processes, there are lessons that can be learnt from the approaches taken in the devolved nations.

This short report sets out:

1. An overview of decision-taking on rare disease medicines in each of the four nations
2. Our assessment of the impact of the divergence on patients in the UK
3. Our conclusions and recommendations

1. An overview of decision-taking on rare disease medicines in each of the four nations

As stated above, the UK's four health systems have many similarities: each has a tax-funded health service with universal coverage, based on similar values and operating principles.[3] However, since devolution, there has been an increasing divergence in health policy in each of the four countries.[4] For example, Scotland and Wales have both abolished prescription charges; Scotland offers free personal social care for over-65s; and in Northern Ireland, the health service is administratively integrated with social services.

Decision-making mechanisms for the assessment and approval of new medicines also differ across the four countries.[5] This is a result of the different approaches pursued by policymakers in each of these countries, in response to a shared challenge.

New medicines can transform lives of patients with rare conditions, but they often come at a significantly higher per-patient cost than medicines for more common illnesses.[6] In recent years, scientific breakthroughs have allowed the development of an increasing number of new treatments for conditions that were previously too difficult to treat. In recognition of the rarity of the conditions they treat and the lack of other options for patients, these treatments are referred to as 'orphan' and 'ultra-orphan' medicines.

Challenges in decision-taking on rare disease medicines

However, as the number of new treatments developed increases, so too does the challenge for health systems in ensuring that they are equipped with the right tools to determine which treatments should be made available to patients. This task is made complicated by the common characteristics of rare disease treatments, which make them difficult to assess through traditional appraisal processes:

- The **relative price of treatments** for rare conditions, due to the small patient populations involved

- The **relative lack of information** and/or clinical trials data on new treatments for rare conditions, which means more uncertainty about the effect that these new treatments will have

- The **relative difficulty in capturing wider value** of such treatments, and in involving patients' and carers' feedback in assessment processes

Policymakers have sought to mitigate these challenges in a range of different ways. These approaches can be broadly categorised into four themes:

- **Creating separate assessment pathways** for rare disease medicines – introducing modified appraisal processes and decision-making criteria that include flexibilities that reflect the higher cost and/or the more limited data associated with smaller patient populations

- **Permitting conditional access** to rare disease medicines – funding medicines at a lower cost for a time-limited interim period, while more evidence is gathered to address gaps in the evidence at the time of the initial appraisal

- **Formally involving patients** and carers in decision-taking on rare disease medicines – creating mechanisms to take into account the views of patients on the benefits of a treatment and making this a major component of decision-taking

- **Taking a flexible approach to determining access on a case by case basis** – creating mechanisms to make decisions on individual patient access to treatments that have not been recommended for routine use, with specific allowances for patients with rare diseases

Action taken across the UK to respond to challenges in assessment

In the UK, all of the different health systems have taken actions in these areas to improve access to rare disease medicines. However, there is considerable variation in the extent to which they have made changes. The differences in approaches are summarised in figure 1 and are explored in further detail below.

Unlike the rest of the UK, in Northern Ireland, decision-taking on access to new medicines takes place through a relatively unstructured process of considering whether to endorse decisions taken by one or more of the other nations. It has therefore been excluded from the majority of our analysis of decision-taking processes.

Figure 1: differences in approaches towards the assessment of rare disease medicines across the UK

	Separate assessment pathway for rare disease medicines	Conditional access to rare disease medicines	Specific mechanism for formal patient involvement in decision-taking on rare disease medicines	Case by case access
England	Only for ultra-rare disease medicines	Only for rare cancer medicines	No	Very limited allowances for rare conditions
Scotland	Yes, for both rare and ultra-rare disease	Only for ultra-rare disease medicines	Yes	Yes
Wales	Yes, for both rare and ultra-rare disease	Only in very limited circumstances	Yes	Yes
Northern Ireland	n/a	n/a	n/a	New process due to be introduced

Separate assessment pathways for rare disease medicines

England, Scotland and Wales have all introduced separate assessment pathways for rare disease medicines. These pathways all provide additional flexibilities in decision-taking on patient access to rare disease treatments, reflecting the higher costs and more limited data associated with these medicines at the point of appraisal.

However, there are significant differences in the approaches taken by the different health systems, both in relation to which treatments qualify for additional flexibility and the level of flexibility that is applied.

In England, decisions about which medicines should be made available on the NHS are taken by NICE and NHS England. There are a number of different routes through which medicines can be assessed, but only one these, NICE's Highly Specialised Technologies (HST) programme, has been specifically designed for the assessment of rare disease treatments.

However, the HST programme is reserved for ultra-orphan treatments for very rare conditions, which must meet seven very narrow criteria in order to qualify for assessment. As a result, it only reviews a very small proportion of new rare disease medicines; only 10 HST appraisals have been carried out in full since the programme launched in 2013.[7]

In addition, the level of flexibility that NICE can take in assessing medicines through the HST programme was limited in 2017 when NICE introduced a 'cost-effectiveness threshold' to its decision taking process. This threshold sets a limit on the NHS's willingness to pay for a new ultra-rare disease medicine. The introduction of the threshold to the HST process was criticised at the time, as it had previously been widely accepted that such thresholds were inappropriate for ultra-rare disease treatments.[8] The impact of this change in practice is explored later in this paper.

The strict limits on entry to the HST programme mean that the majority of rare disease treatments do not qualify for HST appraisal and are therefore assessed through less flexible processes, including:

- NICE's standard Single Technology Appraisal (STA) process – this process is used for the majority of treatments appraised through NICE, including treatments for common and rare conditions. Some limited flexibilities are available for rare disease treatments through this process, but only if they are used at the end of patients' lives or if they are treatments for cancer
- NHS England's policy development process – this process considers a wide range of treatments not reviewed by NICE, including both rare and non-rare disease treatments. The process is ostensibly designed to incorporate additional flexibilities for rare disease treatments, but NHS England has never clarified how such flexibilities work or provided examples of how they have influenced decision-taking. From April 2020 the assessment of licensed

medicines through the policy development process will end, with these medicines instead due to be appraised by NICE

In Scotland, the Scottish Medicines Consortium (SMC) is responsible for providing advice to the NHS on which new medicines should be made available. Unlike NICE, the SMC effectively has separate assessment processes for both orphan treatments for rare diseases and ultra-orphan treatments for very rare diseases. The SMC has adopted international standard definitions of what constitute orphan and ultra-orphan medicines. This means that, unlike in England, it is clear when treatments qualify for additional flexibility and there is greater consistency in decision-taking on assessment routes.

The SMC's orphan and ultra-orphan assessment processes allow it to accept more uncertainty in the economic case in appraisals and take other factors into account, such as whether the drug treats a life threatening disease; substantially increases life expectancy and/or quality of life; can reverse, rather than stabilise, the condition; or bridges a gap to a potentially curative therapy.[9]

In Wales, the All Wales Medicines Strategy Group (AWMSG) is responsible for adopting NICE guidance (where available) and appraising new medicines that NICE has not assessed or is not due to assess in the near future.[10] As in Scotland, clear definitions of orphan and ultra-orphan medicines are used and there are separate processes for the assessment of these treatments, allowing for additional flexibility in the consideration of cost and uncertainty.[11]

Conditional access to rare disease medicines

While England, Scotland and Wales have all created some form of bespoke assessment pathway for rare disease treatments, there is more variation in the adoption of 'conditional access' arrangements.

In England, conditional access is only formally available for medicines that treat cancer. Where a cancer medicine appears to be promising, but there is considerable uncertainty in the data, NICE can recommend that it receives funding for a time limited period through the Cancer Drugs Fund (CDF). During this period, additional data is collected, which is intended to be used by NICE to inform a final assessment as to whether the treatment should be made available on a permanent basis.[12]

In Scotland, changes were recently made to the appraisal pathway for ultra-orphan treatments to introduce the option of conditional access, involving a period of interim funding of up to three years to enable data collection. After this period the treatment is subject to a full appraisal to enable the SMC to make a decision on routine use in NHS Scotland. The criteria for entry to the ultra-orphan pathway are narrow but they are potentially less restrictive than those used by NICE for the HST programme in England.

In Wales, the 'One Wales Interim Commissioning Process' introduced in 2016 enables the NHS to make recommendations for conditional access to medicines for rare or common conditions where there is limited evidence.[13] However, the criteria

for approval through the process are strict and as a result only 13 treatments have been made available since its introduction.[14]

Specific mechanisms for formal patient involvement in decision-taking on rare disease medicines

All of the appraisal processes highlighted above include mechanisms to obtain patient input to inform the evaluation, whether through public consultations, requests for written evidence or invitations to provide oral evidence in person.

However, there is significant variation in the operation of these mechanisms, the extent to which they are designed for rare disease medicine assessment and in the weight applied to the evidence provided by patients in decision-taking.

In England, NICE invites patients and patient organisations to provide both written and verbal evidence to committees in the course of technology appraisals. In the case of the Highly Specialised Technologies programme, patient organisations have on occasion been more closely involved in the formation of NICE's recommendations, including through being signatories to the Managed Access Agreements setting out the terms on which patients will be able to receive medicines.[15] However, the extent to which patients and patient organisations are involved in the development of NICE's recommendations on rare disease treatments varies significantly and there is no standard process that gives formal weight to patient evidence or opinion.

By contrast, in Scotland, patient involvement is a central element of the assessments carried out through the orphan and ultra-orphan pathways. Where a medicine receives an initial draft negative recommendation, the submitting company can request that a Patient and Clinical Engagement (PACE) meeting is convened. The aim of the PACE meeting is to understand whether there are any benefits associated with the medicine that may not be fully captured within the conventional assessment process. Importantly, PACE involves patients, patient organisations and clinicians who understand what it is like to live with the condition in question and therefore are equipped to provide advice to the SMC based on lived experience and informed judgement. The output from the PACE meeting is a major factor in the SMC's decision-taking.[16]

In Wales, a similar process exists for rare disease medicine appraisals carried out by the AWMSG. In the case of an initial negative recommendation, a Clinical and Patient Involvement Group (CAPIG) can be convened. The aim of CAPIG meetings is to identify and consider in detail any additional benefits of the medicine from a clinical, societal and patient perspective. The CAPIG report is included in the AWMSG meeting papers and is a major component of the appraisal. [17]

Case by case access to rare disease medicines

All UK health systems have processes for determining case by case access to treatments not approved through their standard appraisal processes. As with the

appraisal processes themselves, the nature of decision-taking and the allowances given for rare diseases differ across the UK.

In England, clinicians can apply to NHS England for funding for a treatment that is not routinely available to patients through the Individual Funding Request (IFR) process. However, NHS England has put in place very strict criteria for the approval of such requests, including that patients need to be judged to be 'exceptional', in that they are different compared to other patients with the same condition and therefore they will derive an additional benefit from receiving the treatment. This criterion is very hard to meet, particularly for patients with rare diseases, as they are already part of a very small group of patients. In practice the criteria used by NHS England therefore presents significant barriers to access through this route to treatments for rare diseases.

The challenges with exceptionality have been recognised by the other health systems in the UK, all of which have introduced reforms to their processes in recent years to move away from this criterion.

In Scotland, the Peer Approved Clinical System (PACS) process has been created to take decisions on access outside of SMC guidance. Unlike in England, PACS does not require patients to demonstrate exceptionality and cost is explicitly not part of the decision-taking criteria.[18]

In Wales, the requirement to demonstrate exceptionality was removed following an independent review that highlighted the challenges this created for patients with rare diseases.[19] Decisions are now made on the basis of clinical benefit for the individual patient concerned and the cost-effectiveness of the treatment in question.

In Northern Ireland, the Department of Health announced in October 2018 that its IFR process would be reformed following a lengthy process of evaluation. The Department of Health has not yet published full details of the process, but it has indicated that it is intended to improve access to medicines by increasing clinical input into decision-taking.[20]

2. Our assessment of the impact of the divergence

It is clear that there is substantial variation in decision-taking processes between the nations of the UK and in the extent to which they have been designed to address the challenges associated with the evaluation of rare disease medicines.

In theory, it should be relatively straightforward to assess the impact of this divergence, as the organisations involved in taking decisions are all committed to high levels of transparency. However, in practice there are a number of issues that create challenges in measuring the impact of these differences in approach:

- The **time taken for medicines to be appraised** – the different systems can take decisions at different speeds, making up-to-date comparisons challenging, while the lengthy nature of medicines appraisals means that it can take many years for the impact of changes to decision-taking to become apparent

- The **confidentiality of decision-taking processes** – due to the commercial negotiations involved, a significant element of decision-taking processes are confidential and it can therefore be challenging to identify the precise reason for a positive or negative decision from the publicly available documentation

- The **variation in transparency of access decisions** – while the outcome of decisions taken by NICE, SMC and AWMSG are relatively clear, decisions made through other routes, such as the case-by-case systems, are often not transparent, not published or not centrally collated, meaning that access to a treatment that has not been recommended nationally may appear poorer that it is in practice for patients on the ground if it has been made available to a high proportion of individual applicants

It is therefore difficult to draw definitive conclusions on patient access to treatments across the UK. However, there are a number of different issues that can be analysed to build an indicative assessment of the likely impact of the differences in approaches in several areas:

- The trends over time in the approval of new rare disease medicines
- The speed at which medicines are approved by different systems
- The views of patients towards the different systems

Our assessment in each of these areas is set out below.

The approval of new medicines

As set out above, it is challenging to conduct a direct comparison of decisions on individual rare disease medicines across the UK. However, it is possible to identify changes in trends in decision-taking within countries following the introduction of updated processes for rare disease treatments.

In 2016 the Scottish Government published an independent review of the impact of the introduction of changes to the assessment of rare disease treatments. The Montgomery Review found that the approval rate for orphan medicines had improved from 63% to 85% following the creation of the orphan medicine pathway and the introduction of PACE meetings.[21] It also found that access to treatments through case-by-case arrangements had increased over the same period.

More contemporary evidence suggests that the positive impact of the changes has continued in recent years, with our analysis of the SMC's decisions in 2018 finding that it approved 86% of the treatments considered through its orphan process.[22]

However, the Montgomery Review also found that the approval rate for ultra-orphan medicines for very rare conditions was only 14% in the period following the introduction of the changes. This led to the review recommending changes to ultra-orphan assessment, which were eventually implemented as the conditional access ultra-orphan pathway, highlighted in the previous section.

The new ultra-orphan pathway was only created in October 2018 and has yet to make any recommendations, so it is not yet possible to identify what impact it will have on access. However, the introduction of the pathway was welcomed by patient organisations and it is anticipated that it will enable more ultra-orphan treatments to be made available to patients in Scotland in time.

In Wales, the AWMSG published a review in 2018 of the impact of the 2015 changes to the assessment of rare disease medicines. The review found that the approval rates for orphan medicines was much higher following the introduction of the changes, with 100% of the treatments approved compared to 52% in the period from 2002 to 2014.[23] The review also found that the approval rate for ultra-orphan medicines was slightly higher, at 80% compared to 73%, than for the previous period.

In England, it is more challenging to assess trends in access to orphan medicines over time as the system has not undergone the same level of reform in recent years as Scotland and Wales. It is therefore challenging to set a benchmark against which to measure progress. However, it is worth noting that it appears that where NICE has introduced greater flexibility, in the form of the CDF, access to treatment has improved. Prior to the introduction of the CDF, NICE approved 59% of the cancer treatments that it assessed. Following the relaunch of the CDF, this approval rate has increased to 76%.[24]

In relation to access to ultra-orphan medicines in England, the low total number of HST appraisals makes robust evaluation difficult. However, the introduction of a cost-effectiveness threshold to the process in 2017 does appear to have led to an increase in the proportion of negative recommendations. Prior to the announcement of the threshold, NICE had not issued final negative guidance on any treatments. However, in the following period it has published negative recommendations for four treatments, meaning that they have not been made routinely available to patients. These appraisals now seem to be effectively paused, as they are now marked with an expected publication date of 'TBC' on NICE's website.[25]

The speed at which medicines are approved

While the outcome of medicines appraisals is vital to patients, the speed of decision-taking is also hugely important. Rare diseases can be progressive, with limited windows within which treatment can be effective, meaning that delays in assessment can be the difference between life and death.

The need for prompt appraisal is recognised by assessment agencies across the UK, each of which has set targets for the length of appraisal processes:

- NICE – Up to 49 weeks for an STA and 27 weeks for an HST
- SMC – Up to 18 weeks for the standard process, with PACE meetings requiring an additional 12 weeks
- AWMSG – Approximately 20 weeks for the standard process, with CAPIG meetings requiring an additional 12 weeks

These targets suggest that the SMC and AWMSG's processes are quicker than NICE's, with the exception of the HST programme. However, in practice, appraisals can often take significantly longer than anticipated. For example, the typical length of an HST in practice is over a year, with some having taken several years to complete.

The SHCA therefore sought to identify differences in the speed of approval for rare disease treatments between England and Scotland, using the date of final guidance publication as a proxy. Our analysis, based on those treatments approved for use through the SMCs orphan medicines pathway in 2018, found that the date of publication of guidance was broadly similar for many medicines, however there were some important differences:

- **One cancer medicine was approved two years earlier in England** than Scotland. This medicine had previously been made available through the CDF in England and this was recognised by NICE to be a factor in its approval as the company was able to use additional data gathered through the CDF to support its application[26]
- Three rare disease treatments were **approved by the SMC over six months earlier** than NICE
- Two rare disease treatments approved by the SMC **have still not been assessed in England**

While the sample size is limited, this analysis appears to indicate that the SMC's processes may be better equipped to approve rare disease treatments more quickly than NICE's, except potentially in the case of cancer treatments, where the additional flexibility in the CDF may support earlier access in some cases.

The views of patients on the different systems

In addition to quantitative analysis of appraisal outcomes and the timeliness of processes, the views of patients and patient organisations are important to consider in assessing the relative merits of different decision-taking processes.

To understand more about the perceptions of the different systems, the SHCA both reviewed publicly available information and carried out a survey of our members and corporate supporters.

In England, publicly available information on patient groups' views on the suitability of the NICE process for the assessment of rare disease medicines indicates that there is a high level of dissatisfaction with the current system. For example, responses to NICE's consultation on the introduction of the cost effectiveness threshold to the HST programme in 2017 highlighted significant concerns from patient organisations about the implications for access to rare disease treatments, as well as a lack of support for NHS England's commissioning policy prioritisation process.[27] In addition, submissions from charities to a recent Health Select Committee inquiry into access to a rare disease treatment highlight support for reforms to current assessment processes to provide greater flexibility for rare disease medicines.[28]

These findings are supported by feedback to our survey, with over half of respondents reporting that they were not confident in the suitability of NICE's standard process for rare disease treatments and 89% of respondents calling for more flexibility in NHS assessment processes in England to reflect the small population sizes of rare diseases.[29]

Publicly available evidence also indicates that there is strong support from the patient group community for the reforms that have been implemented in Scotland. Feedback provided to the Montgomery Review in 2016 by patient organisations highlighted a number of areas in which the reforms had delivered improvements that were valued, with particularly strong support for PACE meetings. Respondents to the review commented that PACE meetings had allowed patient organisations to share views based on real patient experiences and has increased the perception that patient groups are 'listened to'.[30]

Again, these findings are supported by feedback to our survey, with 60% of respondents reporting that the changes introduced in Scotland had improved access to treatment. The constructive nature of engagement, and the willingness to engage with patient organisations were identified as key characteristics of the Scottish system. Similarly, the willingness to engage with patient organisations, clinicians and manufacturers, as well as the flexibility of the process, were highlighted by respondents as key characteristics of the Welsh system.

3. Conclusions and recommendations

Given the divergence between the UK health systems noted above, and our assessment of the impact this has on patients, we make a series of conclusions and recommendations in this section.

Conclusions

Our conclusions are:

- The degree to which healthcare systems involve patients in assessment decisions is mixed. In Scotland and Wales, new processes have been introduced in recent years which enable patients to provide evidence which is taken into account by decision-takers. This compares favourably to England, where patient involvement is much more limited

- The introduction of additional flexibilities for the assessment of rare disease medicines in Scotland and Wales has resulted in an increase in the proportion of positive recommendations made, whereas in England there is no such system for rare disease treatments, potentially delaying access to treatments, while there are also warning signs in relation to access to ultra-orphan treatment since the introduction of the cost-effectiveness threshold to the HST programme

- It is too soon to assess the impact of the introduction of conditional approval arrangements for ultra-rare disease medicines in Scotland, but evidence from the Cancer Drugs Fund in England indicates that it is likely to lead to an increase in approvals and may provide a more viable route for rapid access than the HST system in England

As the Government, NICE and NHS England consider the future of medicines appraisal in England, they must consider how best to implement changes to ensure that decisions about which treatments are made available on the NHS are taken collaboratively, fairly and equitably. Lessons from approaches taken in the devolved nations should be explored as part of this process.

Recommendations for reform

We therefore recommend that the following steps are considered:

- First, **formally involving patients in the decision-taking process through a specific mechanism**, learning lessons from Scotland's PACE and Wales' CAPIG processes, as well as other examples of international best practice. This means both establishing an additional formal mechanism to gather patients' views on rare disease medicines and including the outputs as a major factor in decisions

- **Second, applying more flexibility for rare disease assessment,** through taking additional factors outside of cost-effectiveness into account in appraisals, reviewing the eligibility criteria for HST assessment, introducing

modifiers that reflect the challenges in evidence generation for rare disease treatments and reviewing the existence of the cost-effectiveness threshold for ultra-orphan medicines.

- **Third, using 'conditional approval' to address uncertainties in the appraisal of rare disease medicines where possible,** learning from the conditional access provided through the SMC's ultra-orphan pathway and the CDF in England

- **Fourth, introducing a rapid resubmission process following the introduction of any reforms to enable treatments that were appraised under the old system to be re-evaluated,** learning from the approach taken in Scotland following the introduction of reforms to its processes

All health systems are grappling with similar challenges in relation to costs, complexity of medicines and uncertainty. In the UK, national systems are taking different, and constantly evolving, approaches to tackling these challenges.

This divergence has led to a highly complex and varied landscape across the UK. For patients, this divergence is both confusing and potentially life-altering, as it can lead to inequalities in access to treatment determined by borders, for patients who potentially only live a few miles apart.

In light of this mixed picture we can't say definitively that any one country in the UK has the 'right' system. However, Scotland and Wales have made a series of changes in recent years aimed at improving the patient voice in decision making and ultimately improving access to rare disease treatments. It may be too early to definitively state that these are having the desired impact, particularly in relation to ultra-orphan treatments.

However, these changes are aligned with reforms that have been introduced in France and Germany, which have resulted in higher levels of access to treatment for rare diseases. The early signs in Scotland and Wales are encouraging, and we hope that approval rates will continue to increase, in order to continue to allow patients to access these life-changing treatments. In contrast, there are signs that the situation in England is becoming increasingly challenging, particularly since the changes to HST were brought in in 2017.

The SHCA looks forward to working with the Government, NHS England and NICE as they consider the future of medicines assessment in England, in order to ensure the patients, the SHCA represents receive fair and equitable treatment regardless of the nature of their condition or their postcode.

November 2019

Appendix – about the Specialised healthcare Alliance

The Specialised Healthcare Alliance is a coalition over 120 patient-related groups and 8 corporate supporters, which campaigns on behalf of people with rare and complex conditions.

The secretariat to the Specialised Healthcare Alliance is currently provided by Incisive Health.

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