Review of the appraisal of orphan and ultra-orphan medicines in Wales

Report for the Minister of Health and Social Care

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October 2013

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List of abbreviations

AWMSG	All Wales Medicines Strategy Group
AGNSS	Advisory Group for National Specialised Services
CPAG	Clinical Priority Advisory Group
HTA	Health Technology Assessment
HST	Highly Specialised Technology
IPFR	Individual Patient Funding Request
NMG	New Medicines Group
NICE	National Institute for Health and Care Excellence
OHE	Office of Health Economics
QALY	Quality-Adjusted Life Year
WHSSC	Welsh Health Specialised Services Committee

Executive Summary

In May 2013, the Minister for Health and Social Services made a commitment to establish a Group to review the appraisal process for orphan and ultra-orphan medicines in Wales.

Specifically the review was to:

- Examine the current All Wales Medicines Strategy Group (AWMSG) appraisal process for orphan and ultra-orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.
- Determine whether the Quality Adjusted Life Year (QALY) methodology represents an effective tool to calculate cost-effectiveness for orphan and ultra-orphan medicines.
- Advise on the best way to support the timely uptake of new, innovative orphan and ultra-orphan medicines in Wales.
- Explore the equity of access to orphan and ultra-orphan medicines across the UK.

In conducting the review the intention was to be transparent and inclusive in accessing the wide ranging views and perspectives of as many patient groups and stakeholders as possible. A review of the literature was undertaken and the Review Group received thirteen presentations given by individuals and groups; interviews were conducted with seven experts involved in the management of patients with rare diseases and with commissioning services for these patients; written submissions were received from twenty stakeholder organisations and a patient event was held where thirteen patients, carers or representatives of patient groups came together to share their experiences of living with a rare disease and discuss issues with accessing orphan or ultra-orphan medicines.

A series of key principles have been used to inform the review process and the recommendations emanating from the deliberations. These principles are scientific rigour, inclusiveness, transparency, independence, challenge and review, support for implementation, timeliness, consistency, connectivity and equity.

The conclusions of the Review Group relating to each of the issues to be explored are:

- The Review Group were of the opinion that there should not be a separate fund for orphan and ultra-orphan medicines and the appraisal of these medicines should remain within the framework of AWMSG. The current lack of connectivity in the processes surrounding therapeutic appraisal in Wales, urgently needs to be addressed. Although the Individual Patient Funding Request (IPFR) process was not explicitly within the remit of this review, it would be short-sighted not to offer proposals as to how greater coherence and connectivity could be achieved within the AWMSG framework.

- There are strong grounds for adjusting the conventional approach to determining QALYs using a series of weights to reflect broader societal perspectives. It is also necessary to recognise that a larger set of criteria are required to appraise orphan and ultra-orphan medicines over and above clinical effectiveness, cost-effectiveness and to a lesser extent, budget impact.

- In order to enhance the timeliness of appraisal decisions and their subsequent implementation there must be greater involvement of all relevant parties (specialists, commissioners, manufacturers, patients and patient representatives) in the appraisal process, from its inception through to implementation. This must include the adoption of a monitoring and evaluation system and encompass registries to log actual patient outcomes in relation to the expected benefits at the time of the appraisals.

- The need to locate the medicine within the relevant treatment pathway and identify any infrastructure developments that need to be actioned prior to the medicine actually being prescribed should also form part of the overall appraisal process. This would necessitate greater collaboration between AWMSG and the Welsh Health Specialised Services Committee (WHSSC).

- Similarly, the IPFR process, when dealing with orphan/ultra-orphan medicines, needs to be more closely aligned with the AWMSG framework so that medicines not appropriate for the AWMSG limited submission or full submission routes can be speedily and equitably dealt with by IPFR panels. This could be supported by AWMSG whereby multiple requests received by IPFR panels, which require a cohort review of licensed usage, are transferred to the AWMSG process.

- There cannot be a guarantee that all medicines approved for use in England will be approved for use in Wales. Different methods across UK may result in difference in recommendations. Of greater importance is that there is fairness and equity across Wales. Access routes for orphan and ultra-orphan medicines need to be simplified and streamlined.

The review has provided a series of recommendations relating to process, criteria and equity.

Recommendations relating to process:

- There should not be a separate orphan/ultra-orphan medicines fund in Wales. All medicines classed as orphan and ultra-orphan should be appraised within the AWMSG framework. To facilitate this AWMSG should reconsider the criteria by which it determines the number of full appraisals, limited appraisals and no appraisals.

- AWMSG needs to give greater attention to involvement with key stakeholders at all stages during the appraisal process. There needs to be greater specialist involvement, closer working relationships with WHSSC and Health Board liaison. This will help inform financial planning and contribute to a more informed specification and scope for the appraisal mechanism.

- An Orphan/ultra-orphan Medicine Group should be established in parallel with the New Medicines Group (NMG) with greater representation from patient representative bodies - to supplement the lay representation - and the inclusion of clinical expert(s) and WHSSC. The recommendations from this new Group would feed through to the main AWMSG committee meeting. Consideration should be given to having specialist and patient representative organisations co-opted on to the AWMSG committee for purposes of discussions relating to the particular orphan or ultra-orphan medicine.

- Serious consideration needs to be given to the role of IPFR panels and whether these should become part of the AWMSG framework in relation to orphan/ultra-orphan medicines. The result would be a holistic and coherent system for appraisal of orphan and ultra-orphan medicines across Wales.

- The role of WHSCC should be amended to enable closer involvement and integration with the appraisal process. This would enable the complete patient treatment pathway to be taken into account and considered within the appraisal process.

- A system for on-going monitoring and evaluation must be established. Whenever possible, stopping criteria for orphan or ultra-orphan medicines need to be agreed and rigorously enforced. The role of patient registries is important in this regard; also the greater involvement of clinicians and commissioners at early stages of the process will also enable development of procedures for monitoring any reduction in usage of replaced therapies.

Recommendations relating to criteria:

- A wider societal perspective should be encompassed in the criteria employed in the appraisal process for orphan and ultra-orphan medicines. The value frameworks offered by the Office of Health Economics (OHE) and Advisory Group for National Specialised Services (AGNSS) represent useful approaches that should be considered further by AWMSG and its stakeholders.

- The levels of uncertainty surrounding all criteria metrics should be explicitly stated within submissions.

- The cost per QALY of orphan and ultra-orphan medicines should be included as an indicator of relative cost-effectiveness whenever possible within the appraisal criteria for orphan and ultra-orphan medicines. QALYs should be weighted along the lines of AWMSG/ National Institute for Health and Care Excellence (NICE) end-of-life procedures to reflect societal perspectives.

- Value for money considerations should take into account the cost difference between orphan or ultra-orphan medicines and conventional medicines whilst reflecting on the clinical context and opportunity costs.

- Manufacturers should endeavour to include patient (and carers) generated utility values in their determination of QALYs. A case should be made for any alternative approaches.

- In submitting evidence of clinical effectiveness of orphan and ultra-orphan medicines, manufacturers should aim to include appropriate, objective outcome measures with a distinction between clinical improvement, stabilisation and reducing rate of deterioration. The proposed position of the medicine within clinical treatment pathway should also be included with the specific submission.

- AWMSG should consider how value based pricing could be incorporated within the appraisal process when this becomes more widely used.

Recommendations relating to equity:

- Access routes for orphan and ultra-orphan medicines need to be simplified and streamlined.

- The relationship between AWMSG, WHSSC and health board IPFR panels needs to be clarified and greater collaboration and connectivity established when dealing with orphan and ultra-orphan medicines. This could be supported by AWMSG whereby multiple requests received by IPFR panels, which require a cohort review of licensed usage, are transferred to the AWMSG process.

- Cohort funding needs to be addressed.

- Elements of the IPFR process needs to be reviewed in order to achieve greater alignment with the AWMSG process.

- An established system for monitoring and evaluation should provide regular reports and information to a range of stakeholders on the provision of orphan and ultra-orphan medicines.

The Review Group is of the opinion that a sustainable and improved process that will be produced by the speedy implementation of these recommendations will incorporate greater patient and expert clinical involvement in decision making process and will considerably enhance the outcomes and experiences of patients with rare diseases and their families in Wales.

1. Aims of the review

The Review Group (Appendix 1) was invited to:

- Examine the current All Wales Medicines Strategy Group appraisal process for ultra-orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.

- Determine whether the Quality Adjusted Life Year methodology represents an effective tool to calculate cost-effectiveness for orphan and ultra-orphan medicines.

- Advise on the best way to support the timely uptake of new, innovative orphan and ultra-orphan medicines in Wales.

- Explore the equity of access to orphan and ultra-orphan medicines across the UK.

2. Background and introduction

There is no single, widely accepted definition for rare diseases, a term that is used interchangeably with orphan diseases. Some definitions rely solely on the number of people living with a disease, while other definitions are based on different factors, such as the lack of adequate treatments or the severity of the disease. The European Commission has defined rare diseases as life-threatening or chronically debilitating diseases of relatively low prevalence - generally meaning fewer than 1 in 2,000 people, which would equate to some 1,500 patients in Wales. Ultra-orphan diseases, as defined by NICE, have a prevalence of 1 in 50,000 people – equivalent to 60 patients in Wales.

There are estimated to be between 5,000 and 7,000 rare diseases, but only a relatively small proportion of these have available treatments. The number of orphan medicines being licensed for use has increased in recent years and the trend is likely to continue with developments, such as stratified medicines, set to add to the number of conditions that are classified as orphan diseases. While regulations exist to support the research and development of medicines for rare diseases, including market exclusivity for 10 years, reduction of licensing fees, assistance with marketing applications and provision of specific research grants, the appraisal of medicines in orphan and ultra-orphan diseases has aroused considerable discussion and debate, which has intensified in recent times, as the number of medicines, and their share of overall drug budgets, has increased.

The nature of orphan and ultra-orphan medicines tend to place them at a 'disadvantage' when they are appraised using the widely accepted conventions of clinical effectiveness and cost-effectiveness (incorporating the cost per QALY metric) as employed within health technology assessment frameworks. The question as to whether medicines for rare diseases should be treated differently in relation to their appraisal for use in NHS Wales is hence a highly pertinent one, and led to the circumstances surrounding Kalydeco (ivacafator) and the commissioning of this review.

In Wales, the appraisal of all new licensed medicines, unless they meet the AWMSG exclusion criteria,[1] is undertaken by AWMSG, using internationally recognised criteria to assess their relative effectiveness and cost-effectiveness. AWMSG was established in 2002 to provide advice on all aspects of medicines management and prescribing to the Welsh Government's Minister for Health and Social Services in an effective, efficient and transparent manner.

The strategic aims of AWMSG are set out under three headings:

- Quality, safety and effectiveness
    - Medicines used in Wales are acceptably safe, clinically effective and cost effective
    - Systems are in place to support evidence-based prescribing
- Access and timeliness
    - The people of Wales have access to clinically effective and cost-effective medicines at the time they need them
- Optimal use (patient focus and efficiency)
    - Medicines are used in Wales in a way that will lead to good health outcomes
    - Wastage of medicines is minimised
    - NHS Wales adopts a whole system and integrated approach to medicines across all health and social care sectors, designed to meet the needs of patients

Between 2002 and June 2013, AWMSG conducted 166 medicine appraisals, of which 130 were for conventional medicines, 13 were for orphan medicines and 8 for ultra-orphan medicines. The positive recommendation rate for these medicines is 78%, 57% and 62% respectively.

AWMSG has recognised the need to employ differential criteria in relation to ultra-orphan medicines and published its *AWMSG Policy relating to ultra-orphan medicines* in July 2012.[2]

These criteria, in order of priority are:

- The degree of severity of the disease as presently managed, in terms of quality of life and survival;
- Whether the medicine can reverse, rather than stabilise the condition;
- Whether the medicine may bridge a gap to a 'definitive' therapy (e.g. gene therapy) and that this 'definitive' therapy is currently in development;
- The innovative nature of the medicine and whether:
    - It represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment); and
    - It can plausibly generate substantial health gains over existing treatment for the individual

In contrast to ultra-orphan medicines, there is no explicit AWMSG policy relating to medicines for orphan conditions. While there have been occasions when medicines have been approved (or received conditional approval) when their cost-effectiveness is uncertain or in excess of the accepted threshold, there has been difficulty in achieving consistency in

interpretation as to what constitutes an ultra-orphan or orphan medicine within the appraisal process.

This distinction between orphan and ultra-orphan medicines is one that NICE concluded was key in determining whether an alternative appraisal mechanism was required. It indicated that no particular scientific or technical problems had arisen, during its appraisal of 14 medicines for conditions that had been granted orphan medicine designation, and therefore did not consider that any changes were required in the appraisal of orphan medicines. In Scotland, on the other hand, a Rare Conditions Medicines Fund has been established in recognition of the difficulties posed by both orphan and ultra-orphan medicines for conventional health technology assessment processes.

The assessment of ultra-orphan medicines in England that formerly was under the jurisdiction of the AGNSS has now been taken over by the Highly Specialised Technologies (HST) Programme of NICE. Medicines for rare diseases also fall under the remit of the Clinical Priority Advisory Group (CPAG), a sub-committee of the NHS England Board. CPAG is advised by a specific Clinical Reference Group that has responsibility for technologies for rare diseases, whereby medicines that have received a negative recommendation from NICE would be considered for use in sub-groups of patients who would benefit from such treatments. CPAG also considers off-label use of treatments and develops policies and processes for patient cohorts identified through the individual patient funding route.

An additional route of access for orphan and ultra-orphan medicines in Wales is available through the IPFR process, where access to innovative treatments may be approved by local IPFR panels when a case for exceptional clinical benefit for individual patients is made by clinicians. This involves individual practitioners referring cases directly to one of several local health board IPFR panels (or in some defined conditions to the WHSCC IPFR panel). The decisions are made on individual basis according to a national policy[3] with a panel constituted in a defined way and outcomes based on the concept of exceptionality.

The case for having different appraisal and assessment systems for ultra-orphan medicines has been well made, but it is less clear for orphan medicines and the results from surveys of populations seeking societal views on the funding and reimbursement of orphan medicines do not lend support to the view that premium prices should be paid for rarity. While people in general, would be keen to support issues relating to disease severity, unmet needs and the wider societal perspective, both a UK and Norwegian study confirmed that there was little evidence for a societal preference for rarity if treatment of patients with rare diseases was at the expense of treatment of those with common diseases.[4, 5]

The next section of the review outlines the approaches employed to address the questions posed by the Minister for Health and Social Services in relation to the appraisal of orphan and ultra-orphan medicines in Wales.

3. Methods

In conducting the review the intention was to be transparent and inclusive in accessing the wide ranging views and perspectives of as many patient groups and stakeholders as possible.

- The Review Group received 13 presentations given by individuals and groups (Appendix 2).

- Interviews were conducted with 7 experts involved in the management of patients with rare diseases and with commissioning services for these patients (Appendix 3).

- Written submissions were received from 20 stakeholder organisations (Appendix 4).

- A patient event was held where 13 patients, carers or representatives of patient groups came together to share their experiences of living with a rare disease and discuss access to orphan or ultra-orphan medicines. This was consistent with the theme of ensuring that the patient's voice was heard at every opportunity and contributed to every debate. The patient event was held at towards the end of the process in order to test emerging themes with a diverse panel. (Appendix 5)

A series of principles in conducting the review were established by the Co-Chairs during the initial stages of the review and these informed the processes and procedures for dealing with the body of evidence collected. The evidence presented to the Review Group and provided in the literature review was synthesised and classified into themes that related to the aims of the review. These themes formed the basis for the recommendations that have emerged following discussions with the Review Group.

The following section (4) provides an insight into the nature of the evidence provided to the Review Group and on which the recommendations are derived.

4. The issue of assessing orphan and ultra-orphan medicines

4.1. Findings from the literature review

The literature review was set up to address four issues of relevance to the review:

- What processes and procedures are in place to assess the effectiveness and cost-effectiveness of orphan and ultra-orphan medicines from perspective of healthcare systems?
- To what extent do orphan and ultra-orphan medicines sit comfortably within conventional Health Technology Assessment (HTA) frameworks?
- What criteria should be used to assess whether orphan and ultra-orphan medicines can be placed on formularies?
- How can societal considerations be factored into assessment of orphan and ultra-orphan medicines?

The literature has provided no indication what might constitute the most suitable assessment framework for orphan and ultra-orphan medicines. It is widely recognised that orphan and ultra-orphan medicines present a number of challenges in the assessment of their effectiveness and cost-effectiveness and in the development of appropriate funding mechanisms. These challenges are being grappled with across many healthcare systems with no clear consensus emerging as to what constitutes an acceptable vehicle for their assessment. In addition, differences in policies and requirements for submissions of orphan and ultra-orphan medicines are a major contributory factor in accounting for differences in reimbursement decisions between countries, and the resulting inequities that emerge.

It is also evident that conventional HTA frameworks fail to do justice to these medicines, unless the view is taken that the same criteria should be employed across all therapies. The costs of drug development that need to be recouped from a relatively small number of patients serve to adversely affect the price of such medicines, while the limited patient numbers make it extremely difficult to generate a sound portfolio of evidence on which to demonstrate effectiveness and cost-effectiveness as with conventional medicines. Other studies from within the literature have argued that manufacturers may take advantage of a degree of monopolistic power in the market for orphan and ultra-orphan medicines to artificially inflate the price of medicines. The net result, irrespective of the viewpoint adopted, is that orphan and ultra-orphan medicines have a significant price premium relative to conventional medicines and a commensurate evidence deficit that conspire to reduce the likelihood of orphan and ultra-orphan medicines being awarded positive appraisal decisions within conventional HTA frameworks.

The issue of which criteria should be employed is still equivocal, with many calls for a broader set of assessment criteria, but with limited insight provided as to the nature of the criteria and how they can be measured within an assessment framework. A report from the Office of Health Economics has highlighted the use of multi-criteria decision analysis as an approach to value orphan medicines.[6] The authors undertook a literature review and conducted three workshops with pharmaceutical industry Research and Development managers, clinical and health economics experts and rare diseases' patient groups. Participants refined and weighted the attributes to be used within a value framework and tested the sensitivity of the overall ratings to changes in weights and scores when applied to example orphan medicines. Eight non-monetary attributes were agreed:

- Disease Specific
    - Availability of effective treatment options
    - Survival prognosis
    - Morbidity-disability
    - Social impact of the disease on patients' and carers' daily lives
- Treatment specific
    - Treatment innovation
    - Evidence of clinical efficacy and patient clinical outcomes
    - Clinical safety
    - Social impact of the treatment on patients' and carers' daily lives

The authors concluded that an appropriate value framework can be developed to increase clarity ad transparency in assessing the relative value of orphan medicines.

The use of a decision-making framework was employed by AGNSS in assessing ultra-orphan medicines[7], with similar facets to that developed by the OHE, and which also provides a potential value framework for further consideration. There are 12 core criteria, organised into 4 groups:

Health gain	Societal value	Reasonable cost to public	Best clinical practice
severity and ability of patients to benefit	stimulating research and innovation	average cost per patient	best clinical practice in delivering the service
clinical safety and risk	needs of patients and society	overall cost impact and affordability (including opportunity cost)	economic efficiency of provision
clinical effectiveness and potential for improving health		value for money compared to alternatives	continuity of provision
			accessibility and balanced geographic distribution

Additional detail and specification is provided within the AGNSS document.[7] Both frameworks offer an insight as to how societal values can be embraced within the appraisal system, although it has to be recognised that the metrics on which the criteria can be measured are rather more subjective than the criteria within the other domains.

The use of equity weights alongside the cost per QALY has also been advocated, which is in line with AWMSG and NICE policies relating to end-of-life therapies - by a number of commentators, as a means by which the estimate of QALY (and by implication 'value') can be enhanced to reflect equity considerations and the characteristics of ultra-orphan medicines. This approach is currently being examined in the Netherlands and while the jury is still out it represents an interesting way of thinking and factoring equity into the conventional approaches employed in health technology assessment.

4.2 Evidence from oral presentations to Review Group

The list of stakeholders that provided an oral submission to the Review Group is included as Appendix 2.

The evidence presented was highly informative and served to illuminate the issues and considerations that had emerged from the literature review. There was a general consensus that the appraisal of orphan and ultra-orphan medicines warranted a step change in approach, although the degree of change was dependent on the particular stakeholder perspective, ranging from modest changes to the current processes, procedures and criteria to a completely separate and distinct appraisal process.

Stakeholders (other than those representing AWMSG) were united in their regard for the AWMSG process and its work since its inception. A number of suggestions relating to changing processes and procedures were offered advocating a significantly more focussed and targeted process to benefit the people, professionals, patients and NHS in general in Wales.

There was general agreement that the level of involvement with the AWMSG process, by specialists and patients and their representatives, needed to be increased in order to realise an improvement in the timeliness of the decision-making process and to enable greater levels of consensus and consistency. Ensuring that the medicine was viewed within its clinical, treatment and commissioning context was also considered to be a vital factor in improving the speed of the process, which therefore required greater levels of involvement from specialists, to provide the clinical and treatment context, and commissioners (in particular WHSSC in relation to orphan and ultra-orphan medicines) to offer the wider commissioning perspective. Greater involvement from the clinical community would also afford an ownership of the recommendation post-hoc, plus opportunities to contribute appropriate outcomes measures along with a commitment to actively participate in the

monitoring and evaluation of the effectiveness of the medicines in the real world of every day clinical practice.

There was a view that the patient perspective within the appraisal process often did not appear sufficiently reflective of the precise nature and clinical impact of the conditions. While the lay members at NMG and AWMSG were keen to make informed contributions, they were constrained by, in many appraisals, by the lack of engagement by the relevant patient representative organisations. The patient representative organisations that contributed to the process expressed the view that there was confusion surrounding the AWMSG process and that completion of the pro-forma, as provided, did not appear to be an effective vehicle for securing meaningful engagement. An actual presence at the appraisal meetings by patients and their representatives was advocated as providing greater insight into the patients' perspectives which would align with some of the wider criteria proposed for the appraisal of orphan and ultra-orphan medicines. The difficulty in securing engagement and involvement with patient representative organisations was addressed during these presentations, which was attributed to confusion over process and procedures and communication deficits.

The role of WHSSC in the implementation of AWMSG recommendations featured during presentations. Further, representatives from WHSSC were also keen to inform the Review Group that their engagement and involvement with the appraisal process from its inception, as opposed to the current situation where they participate post-recommendation, is likely to deliver a speedier process from submission to AWMSG through recommendation to actual implementation and the availability of medicines for patients. In this way, they would also be able to contribute to more informed intelligence relating to patient numbers, inclusion and exclusion criteria and pertinent evidence to inform the appraisal process. As part of the overall commissioning framework, the financial aspects should also be factored into the process, whereby earlier intelligence as to which medicines were in the appraisal pipeline, the likelihood of a positive recommendation and a more informed estimate of the budget impact would all lead to a speedier process towards implementation of AWMSG recommendations.

The view was also consistently expressed that greater alignment and co-ordination of the IPFR process in relation to orphan/ultra-orphan medicines with the AWMSG framework was imperative to alleviate the lack of consistency and indeed equity across Wales. While the IPFR process was not encompassed within the terms of reference for this review, the perceived variation of the IPFR process and different approaches by the respective panels across Wales had contributed to the levels of confusion around the transparency and understanding of the process by clinicians, patients and manufacturers. The benefits from greater integration and collaboration would extend to locating the medicine within evidence-based clinical treatment pathways and the on-going monitoring and evaluation of medicines approved under the IPFR scheme, so as to ensure that the benefits perceived at

point of 'assessment' translate into real and quantifiable patient benefits in real-world settings.

The criteria used for assessing orphan and ultra-orphan medicines were the subject of considerable frustration as voiced by the patient representative organisations, especially the use of the cost per QALY and the threshold of £20,000 per QALY gained. Other stakeholders vouched for its usefulness as an indicator of relative cost-effectiveness in conventional medicines, yet acknowledged the issues and difficulties surrounding its use in relation to these medicines. The prevailing view was that relative cost-effectiveness should feature in the criteria used for appraisal of orphan and ultra-orphan medicines, but that a wider perspective embracing societal benefits should be used, with necessary adjustments made to the cost per QALY threshold to reflect these.

Presentations from colleagues in NICE and NHS England were highly informative and confirmed the notion that there were no readily available solutions to the orphan and ultra-orphan drug appraisal dilemma. The use of principles to underpin the process of appraisal by the NICE HST programme was decisive in guiding the thinking of the Review Group while grappling with the multi-faceted and complex issues surrounding the appraisal of these medicines. The involvement of NICE colleagues as part of the Review Group also provided a sounding board as themes and possible recommendations emerged.

4.3 Interviews with other key stakeholders

It was not possible to arrange for all key stakeholders to provide oral presentations. It was therefore arranged that the Co-Chairs would visit and interview key individuals with experience of dealing with patients with rare disease on a national basis and who in their respective fields had influenced policy developments in this area, along with organisations that could not attend any of the meetings of the Review Group. The interviewees are listed at Appendix 3.

The Co-Chairs were deliberately selective in requesting interviews with key individuals and stakeholders but the information gleaned from these was instrumental in validating some of the assertions made in the oral presentations and exposing the perceptions and interpretations of the Co-Chairs to more detailed scrutiny.

Positive comments regarding the work of AWMSG were forthcoming and the need to maintain the level of rigour in their processes and procedures was emphasised. The transparency of the AWMSG process was also affirmed by the interviewees and the attempts to secure clinical and patient involvement were valued, although the need for greater involvement of these groups at all stages during the appraisal process was a consistent theme. It was evident that the lay members of the appraisal committees are keen to act as patient advocates during the process but felt hamstrung by the lack of

information provided by the patient organisations' submissions. The view of the 'average' person was also brought into consideration in this regard to have some notion of societal perspective. It was felt that a greater lay presence with actual patient representatives being present would lead to a more informed and balanced assessment of the evidence. It was strongly argued by a number of interviewees that AWMSG should make more effort to interact and engage with patient bodies and ensure that advantage was taken of all opportunities as presented.

The solutions offered were based around involvement of all relevant groups, working in conjunction with AWMSG. Greater collaboration with WHSSC, for example, would reduce the risks inherent within the current system that delays in implementation arise due to the lack of contextualisation of the recommendation. The establishment of 'stopping rules' where there was no demonstrable evidence of effect should also be factored into the recommendation, with key inputs from patients, specialists WHSSC and AWMSG.

In this regard, the establishment of patient registries was viewed as essential following approval for use of orphan and ultra-orphan medicines in NHS Wales. This might well have to be in conjunction with other UK and indeed European jurisdictions but data and information relating to patient benefit must be logged so as to inform the monitoring and evaluation processes relating to use of orphan and ultra-orphan medicines.

Proposals for the systemisation and simplification of the appraisal processes within Wales were also a feature of the interviews. The ability for manufacturers to have a number of possible assessment and entry routes was viewed as confusing, inefficient and the cause of many problems relating to inequity of provision across Wales. The calls for greater clarity and a joined up approach for medicines evaluation within Wales resonated with the views presented to the Review Group, with greater integration between AWMSG and the IPFR processes across Wales being requested by clinicians and other stakeholders alike.

The whole spectrum of views was evident with regard to the notion of a separate fund for orphan and ultra-orphan medicines:

- Maintaining the current AWMSG process with some slight modification to reflect societal views within the appraisal of ultra-orphan medicines;
- Greater modifications of the current system including the establishment of a separate committee, to run in parallel with the current New Medicines Group, making recommendations to the AWMSG committee; and to
- The establishment of a separate fund similar to the Rare Conditions Medicines Fund in Scotland and or the Cancer Drugs Fund in England.

The consensus was that the AWMSG process was highly regarded and that its processes and procedures should be adapted to accommodate the differences required enabling a more equitable approach viz-a-viz orphan and ultra-orphan medicines. It was also acknowledged

that more work is needed to clarify the position regarding the definition attached to orphan and ultra-orphan medicines relative to patient numbers. There are, within the Welsh context, many examples of appraisal that could be construed as being orphan or ultra-orphan in terms of patient numbers, but which would never be specifically defined as such by the relevant agencies.

The need for a metric for assessing cost-effectiveness was generally recognised, along with the need for consistency, although no clear view as to how the notion of utility and what it should embrace in the context of orphan and ultra-orphan medicines was evident. Adjustments along the lines of the end-of-life criteria as employed by AWMSG and NICE, to enable a weighted QALY approach to be utilised were advocated, but the issue as to what would constitute an appropriate cost per QALY threshold remain unresolved. The need for greater clarity surrounding the definition and assessment of cost-effectiveness and the budget impact in their clinical context of ultra-orphan medicines was advocated. This may be a reflection of previous inconsistencies. The importance of objective outcome measures captured in patient registries was emphasised as a key feature in the appraisal process, by a number of interviewees. Data on outcome measures would inform 'stopping criteria' in monitoring and evaluating the extent of patient benefit as a result of their adoption.

The issue of equity was also subject to wide variation in interpretation, but there was a general consensus that equity within Wales was more relevant and valuable than comparisons with other jurisdictions. In this regard the current IPFR process was seen as in need of attention, with the interpretation afforded to exceptionality viewed as imprecise on occasions. Further, there was general consensus that timeliness was a key factor and improvements would go a long way to generating greater confidence among clinicians and patient representative groups. Coupled with timeliness was the engagement factor whereby greater involvement at all stages of the process would significantly enhance the degree of ownership of recommendations and decisions relating to the approval of orphan and ultra-orphan medicines.

4.4 Written submissions

The Co-Chairs received written submissions from a number of individuals and organisations as presented in Appendix 4. A number of the submissions made direct reference to the decision made by the Minister relating to Kalydeco (ivacafator). Such submissions were keen to use this opportunity as the vehicle for instigating change.

It was evident, and the focus of most attention in the submissions that the current 'divide' between the AWMSG and the IPFR processes was the cause of significant concern within the current system of therapeutic appraisal of orphan and ultra-orphan medicines in Wales. The variation in IPFR processes employed, in interpretation of evidence and criteria used for assessment, in timeliness, in interpretation of rarity and exceptionality were common themes presented and were, it was suggested, a major factor in the perceived lack of equity that existed for some treatments within Wales.

The precise role of WHSSC within the appraisal process and following recommendations also featured in the submissions. Greater co-ordination and integration of the various system components was consistently advocated, along with more engagement with manufacturers to provide intelligence and information to inform the scope of the appraisal. It was also suggested that greater engagement with manufacturers would enable an enhanced role for the limited submissions appraisal route and for more flexibility of wording used on the AWMSG website following a non-submission from a manufacturer.

Further, the delays in implementation and uptake of orphan and ultra-orphan medicines approved by AWMSG were an obvious source of frustration among manufacturers. This was also emphasised in relation to situations where negative recommendations by AWMSG had led to IPFR applications. This that further delayed specialists being able to use medicines they regarded as significant in the treatment of their particular patients.

The definitions of orphan and ultra-orphan medicines and their interpretation in a Welsh context would appear to warrant clarification, as a degree of confusion was evident as to the conditions when the application of the AWMSG ultra-orphan policy would be used. This fostered a perception that such medicines may have an 'advantage' relative to orphan medicines.

The problems surrounding the 'limitations' of conventional appraisal criteria in the assessment of orphan and ultra-orphan medicines were highlighted by some submissions, with requests made for the adoption of broader approaches that reflected societal perspectives, encompassing carer perspectives and employment potential, for example. However, while specification of some of the broader issues were provided, the actual the relevant metrics to reflect such perspectives were less forthcoming.

4.5 Patient event

This event provided the opportunity to test the emerging themes with patients with rare disease and key patient groups. The overwhelming view was that there was a need to improve the current system of appraisal for orphan and ultra-orphan medicines and that there was a desire to ensure a more joined up approach between decisions made by AWMSG and IPFR panels across Wales.

> *'there is a disjoint between IPFR and AWMSG'*

> *'there is not a level playing field if the same process is used to appraise orphan and ultra-orphan medicines as regular medicines'*

Better engagement and involvement of both patients and specialists was identified as a key area for improvement.

> *'rather than a lay member summarising evidence about a condition of which they have no specific knowledge, could patients be involved more? '*

> *'getting the patient voice heard is important'*

> *'centres of excellence do want to be involved ...so important in understanding and managing the condition'*

It was generally agreed that the QALY was an acceptable measure to use providing the application of this metric to orphan and ultra-orphan medicines could be adjusted in terms of weighting, flexible with regard to threshold values given and was not used exclusively. Quality of life measures and broader societal benefits would need to be considered jointly with the QALY measures and these may differ for different rare diseases or conditions.

> '*QALY doesn't really reflect quality enough or patient individuality'*

> *'must be adjusted – treatments for rare diseases will always be more expensive because of the low patients numbers, cannot be related the same as conventional medicines'*

> *'every condition is different so why can't the QALY threshold be different'*

Participants at the patient event acknowledged that as a devolved administration, the NHS in Wales could and should take its own decisions whenever appropriate regarding orphan and ultra-orphan medicines approval, but the rationale for such decision making should be transparent and have resulted from a process that engaged and involved key patient groups and appropriate specialists at the right time.

> *'we may not like the decision but we need to understand how it was made and how differences in decisions made over the border has reached a different outcome'*

5. Drawing conclusions from evidence submitted and received

5.1 The principles used in considering the evidence

As with the processes employed by the NICE HST Programme, a series of key principles have been used to inform the Review process and the recommendations emanating from the deliberations. These principles are:

- **Scientific rigour:** every effort has been made to ensure that arguments, presentations and submissions are evidence-based and not based on assertion and supposition. Obviously, there are differences in interpretation of evidence but the Review Group has endeavoured to consider a balance of views from a wide range of stakeholders, on which to base the recommendations.

- **Inclusiveness:** in establishing the Review Group, the intention was to try and secure adequate representation across stakeholder groups. Further, the Review Group has made every effort to ensure that all relevant stakeholders have had their views presented or represented. When it was not possible to enable professionals and organisation to attend the meetings, the Co-Chairs arranged to conduct a series of interviews to include as many key opinions and cases as possible in the evidence to be assimilated and utilised in the development of recommendations.

- **Transparency:** the minutes of the meetings of the Review Group have been made available upon request to all interested parties, while the themes emerging from the evidence were first presented at the Patient Event.

- **Independence:** the Review Group has endeavoured at all times during the process to maintain an independent stance and not to be unduly influenced by any specific party or stakeholder group.

- **Challenge and review**: each of the presentations made to the Review Group and each of the interviewees were subject to challenge and questioning, while each written submission has been scrutinised to ensure that all issues raised and problems identified, suggestions for recommendations and potential solutions have been given due consideration. While the conclusions and recommendations of the review might not be in agreement with the stakeholder views, the Review Group can state with certainty that no presentation, no submission, no information provided within the interviews has been disregarded during the course of the review. The intention has been throughout the process to ensure that the conclusions and recommendations are cogent, deliberative, informed and representative of the views provided to the Review Group over the past few months.

- **Support for implementation**: the conclusions and recommendations will require a series of changes in the processes and procedures involved in the appraisal of orphan and ultra-orphan medicines in Wales. It is advocated that members of the Review Group work alongside the relevant parties to ensure a relatively smooth transition so that delays in the appraisal process can be minimised and that the benefits to patients with rare diseases in Wales, which the changes are designed to engender, can be implemented with a degree of speed and with minimum disruption.

- **Timeliness:** one of the key drivers of this review was the lack of timeliness between orphan and ultra-orphan medicines being made available through the licensing process and the decision as to whether they are approved for use by NHS Wales. The Review Group therefore make a plea that the findings, conclusions and recommendations emerging from this review are given due attention and consideration within a reasonable timescale and that changes to the current process within Wales are implemented as a matter of urgency.

- **Consistency:** one of the key components within any notion of equity is that of consistency. The Review Group has not been persuaded of the need for a separate fund for orphan and ultra-orphan medicines, in that it neither represents societal views (as evidenced from two population surveys) as to the treatment of rare diseases nor captures the essence of consistency of approach, and by implication equity, across all therapeutic assessments in Wales.

- **Connectivity:** it has been evident that patients and their representatives, practitioners, managers, manufacturers lack clarity with the current system surrounding therapeutic appraisals in Wales. The complexities and access routes only serve to compound confusion and delay speedy implementation. The Review Group has therefore sought to create a coherent appraisal system with the current variation in processes and access routes eliminated as far as possible.

- **Equity:** this is a multi-faceted concept that arouses much discussion and debate as to its meaning and how it can be reflected in public policy. The Review Group has taken equity to reflect notions of consistency, justice and fairness. Wales is a relatively small country but has a healthcare system configured to facilitate integration, and a population size sufficiently small to ensure that vulnerable and minority groups are not disregarded and disenfranchised. The case made by virtually all stakeholders that rare diseases are different and that treatments for them should therefore be treated differently from conventional therapeutic appraisals has resonated with the Review Group in relation to both justice and fairness, and the conclusions and recommendations have been crafted to try and reflect such a notion of equity.

5.2 Conclusions of the Review Group

The Minister for Health and Social Services invited the Review Group to:

- Examine the current AWMSG appraisal process for ultra-orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.
- Determine whether the Quality Adjusted Life Year methodology represents an effective tool to calculate cost-effectiveness for orphan and ultra-orphan medicines.
- Advise on the best way to support the timely uptake of new, innovative orphan and ultra-orphan medicines in Wales.
- Explore the equity of access to orphan and ultra-orphan medicines across the UK.

The conclusions of the Review Group relating to each of these in turn are:

5.2.1 Examine the current AWMSG appraisal process for ultra-orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.

The AWMSG framework for the appraisal of all new medicines not being assessed by NICE is generally well regarded.

The current system for the appraisal of ultra-orphan medicines seeks to make a differentiation between ultra-orphan medicines and conventional medicines. There is scope for enhancing the process of appraisal of ultra-orphan medicines through greater involvement of specialists, commissioners, manufacturers and patients/patient representative groups at all stages of the process.

The distinction should also be made between orphan and conventional medicines to identify orphan medicines that should also be appraised with greater direct involvement of patient groups as part of the lay representatives in the appraisal meetings.

The Review Group were of the opinion that there should not be a separate fund for orphan and ultra-orphan medicines. The appraisal of these medicines should remain within the framework of AWMSG. Where there was a case presented for a separate fund for orphan and ultra-orphan medicines, this was largely based on the English Cancer Drugs Fund. The case was unconvincing and there were countervailing opinions strongly expressing the need for transparency, consistency and connectivity in the overall process.

The current lack of connectivity in the processes surrounding therapeutic appraisal in Wales, urgently needs to be addressed. Although the IPFR process was not explicitly within the remit of this review, it would be short-sighted not to offer proposals as to how greater coherence and connectivity could be achieved within the AWMSG framework.

5.2.2 Determine whether the Quality Adjusted Life Year methodology represents an effective tool to calculate cost-effectiveness for orphan and ultra-orphan medicines.

The QALY methodology is far from ideal in assessing conventional medicines and its inadequacies are even more evident in relation to orphan and ultra-orphan medicines. However, the notion of the QALY as a common currency to gauge the relative cost-effectiveness of medicines in securing patient benefit across therapeutic areas, should also apply to the appraisal of orphan and ultra-orphan medicines.

There are strong grounds for adjusting the conventional approach to determining QALYs using a series of weights to reflect broader societal perspectives. It is also necessary to recognise that a larger set of criteria are required to appraise orphan and ultra-orphan medicines over and above clinical effectiveness, cost-effectiveness and to a lesser extent, budget impact.

5.2.3 Advise on the best way to support the timely uptake of new, innovative orphan and ultra-orphan medicines in Wales.

In order to enhance the timeliness of appraisal decisions and their subsequent implementation there must be greater involvement of all relevant parties (specialists, commissioners, manufacturers, patients and patient representatives) in the appraisal process, from its inception through to implementation. This must include the adoption of a monitoring and evaluation system and encompass registries to log actual patient outcomes in relation to the expected benefits at the time of the appraisals. The current system is beset by lack of involvement of relevant parties during the early phases of the appraisal process. While the difficulties of securing detailed and informative patient bodies' reports for the NMG has tended to negate the contribution of the more than willing and well intentioned lay members, greater involvement by all relevant parties would improve intelligence and evidence on which to undertake the appraisal and add significant value.

The need to locate the medicine within the relevant treatment pathway and identify any infrastructure developments that need to be actioned prior to the medicine actually being prescribed should also form part of the overall appraisal process. This would necessitate greater collaboration between AWMSG and WHSSC.

Similarly the IPFR process should be more closely linked with the AWMSG framework so that medicines not appropriate for the AWMSG limited submission or full submission routes can be speedily and equitably dealt with by IPFR panels with support from AWMSG by multiple requests received by IPFR panels which require a cohort review of licensed usage being readily transferred to the AWMSG process.

5.2.4 Explore the equity of access to orphan and ultra-orphan medicines across the UK.

There cannot be a guarantee that all medicines approved for use in England will be approved for use in Wales. Different methods across UK may result in difference in recommendations. Of greater importance is that there is fairness and equity across Wales. Access routes for orphan and ultra-orphan medicines need to be simplified and streamlined. The Review Group is confident that the recommendations of this review will ensure that the Welsh appraisal system will yield recommendations for orphan and ultra-orphan medicines within similar timescales to those in England and Scotland. There should be regular and on-going dialogue with colleagues in England and Scotland to help inform the appraisal process in Wales.

6 Recommendations

6.1 Recommendations relating to process

6.1.1 There should not be a separate orphan/ultra-orphan medicines fund in Wales. All medicines classed as orphan and ultra-orphan should be appraised within the AWMSG framework. To facilitate this, AWMSG should reconsider the criteria by which it determines full appraisals, limited appraisals and no appraisals.

6.1.2 AWMSG needs to give greater attention to involvement with key stakeholders at all stages during the appraisal process. There must be greater specialist involvement and closer working relationships with WHSSC and Health Board liaison. This will help inform financial planning and contribute to a more informed specification and scope for the appraisal mechanism.

6.1.3 An Orphan/ultra-orphan Medicine Group should be established in parallel with the New Medicines Group (NMG) with greater representation from patient representative bodies - to supplement the lay representation - and the inclusion of clinical expert(s) and WHSSC. The recommendations from this new Group would feed through to the main AWMSG committee meeting. Consideration should be given to having specialist and patient representative organisations co-opted on to the AWMSG committee for purposes of discussions relating to the particular orphan or ultra-orphan medicine.

6.1.4 The role of WHSCC should be amended to enable closer involvement and integration with the appraisal process. This would enable the complete patient treatment pathway to be taken into account and considered within the appraisal process.

6.1.5 Serious consideration needs to be given to the role of IPFR panels in relation to orphan and ultra-orphan medicines and whether these could become part of the AWMSG framework. The result would be a holistic and coherent system for appraisal of orphan and ultra-orphan medicines across Wales.

6.1.6 A system for on-going monitoring and evaluation must be established. Whenever possible, stopping criteria for orphan or ultra-orphan medicines need to be agreed and rigorously enforced. The role of patient registries is important. Greater involvement of clinicians and commissioners at early stages of the process will enable development of procedures for monitoring any reduction in usage of replaced therapies.

6.1.7 Information on how all new medicines become approved for use by NHS in Wales and how to access such medicines should be made available for the public, patients and healthcare professionals.

6.2 Recommendations relating to criteria

6.2.1 A wider societal perspective should be encompassed in the criteria employed in the appraisal process for orphan and ultra-orphan medicines. The value frameworks offered by the OHE and AGNSS represent useful approaches that should be considered further by AWMSG and its stakeholders.

6.2.2 The levels of uncertainty surrounding all criteria metrics should be explicitly stated within submissions.

6.2.3 The cost per QALY of orphan and ultra-orphan medicines should be included as an indicator of relative cost-effectiveness whenever possible within the appraisal criteria for orphan and ultra-orphan medicines. QALYs should be weighted along the lines of AWMSG/NICE end-of-life procedures to reflect societal perspectives.

6.2.4 Value for money considerations should take into account the cost difference between orphan or ultra-orphan medicines and conventional medicines whilst reflecting on the clinical context and opportunity costs.

6.2.5 Manufacturers should endeavour to include patient (and carers) generated utility values in their determination of QALYs. A sound case should be made for any alternative approaches.

6.2.6 In submitting evidence of clinical effectiveness of orphan and ultra-orphan medicines, manufacturers should aim to include appropriate, objective outcome measures with a distinction between clinical improvement, stabilisation and reducing rate of deterioration. The proposed position of the medicine within clinical treatment pathway should also be included with the specific submission.

6.2.7 AWMSG should consider how value based pricing could be incorporated within the appraisal process when this becomes more widely used.

6.3 Recommendations relating to equity

6.3.1 Access routes for orphan and ultra-orphan medicines need to be simplified and streamlined.

6.3.2 The relationship between AWMSG, WHSSC and Health Board IPFR panels needs to be clarified and greater collaboration and connectivity established.

6.3.3 Elements of the IPFR process needs to be reviewed in order to achieve alignment with the AWMSG process.

6.3.4 An established system for monitoring and evaluation (see recommendation 6.1.6) should provide regular reports and information to a range of stakeholders on the provision of orphan and ultra-orphan medicines.

The Review Group is of the opinion that a sustainable and improved process that will be produced by the speedy implementation of these recommendations will incorporate greater patient and expert clinical involvement in decision making process and will considerably enhance the outcomes and experiences of patients with rare diseases and their families in Wales.

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Acknowledgements

Information and support to the Review provided by:

- **Jenna Byers**
  Co-ordinator – Public Involvement Programme, National Institute for Health and Care Excellence
- **Claire Davis**
  Patient Liaison, All Wales Therapeutics & Toxicology Centre
- **Ceri Foley**
  Project Support Officer, Pharmaceutical Public Health, Public Health Wales
- **Julie Gilbourne**
  Technical Consultant – Groupware, Public Health Wales Microbiology Carmarthenshire
- **Josie Godfrey**
  Associate Director and Lead for HST Programme, National Institute for Health and Care Excellence
- **Tracey Goode**
  Senior Equality Manager, NHS Centre For Equality And Human Rights, Public Health Wales
- **Emma Hughes**
  Development Officer for Wales, Genetic Alliance UK / Rare Disease UK
- **Ray Henry**
  Head of Informatics, Public Health Wales
- **Heidi Livingstone**
  Advisor – Public Involvement Programme, National Institute for Health and Care Excellence
- **Lynne MacIntyre**
  NHS Centre For Equality And Human Rights, Public Health Wales
- **Andrea Matthews**
  Consultation & Liaison Officer, Community Health Councils in Wales
- **Isabel Puscas**
  Librarian, Library and Knowledge Management Service, Public Health Wales
- **Claire Sullivan**
  Communications and Engagement Coordinator, NHS Centre For Equality And Human Rights, Public Health Wales
- **Matthew Tester**
  Pharmacy & Prescribing, Department for Health and Social Services, Welsh Government

Appendix 1

Review of the appraisal of

orphan and ultra-orphan medicines in Wales

Task and Finish Group

TERMS OF REFERENCE

PURPOSE

To review the appraisal of orphan and ultra-orphan medicines in Wales.

ROLE

The purpose of this Group is to review the appraisal of orphan and ultra-orphan medicines in Wales and prepare a report which will provide recommendations to the Minister for Health and Social Services.

The Task and Finish Group may establish sub-groups to explore specific work- streams and report findings to the Task and Finish Group.

SCOPE

The duties of the Group are to:

- Examine the current All Wales Medicines Strategy Group (AWMSG) appraisal process for orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.

- Examine the current AWMSG appraisal process for ultra-orphan medicines and advise on the appropriateness of the process, and any alternative approach which may be adopted in Wales.

- Determine whether the Quality Adjusted Life Year (QALY) methodology represents an effective tool to calculate cost-effectiveness for orphan and ultra-orphan medicines.

- Advise on the best way to support the timely uptake of new, innovative orphan and ultra-orphan medicines in Wales.

- Explore the equity of access to orphan and ultra-orphan medicines across the UK.

Review of the appraisal of

orphan and ultra-orphan medicines in Wales

Task and Finish Group

MEMBERSHIP

The Task & Finish Group will be comprised of the following members:

- Paul Buss, Assistant Medical Director/Consultant, Aneurin Bevan Health Board
- Ceri Phillips, Professor of Health Economics, Swansea Centre for Health Economics, Swansea University
- Phillip Web, Head of Epidemiology and Evidence Support Team, Welsh Health Specialist Services Committee
- Louise Hendry, HTA Development Manager, Pfizer
- Peter Collins, Consultant Haematologist, University Hospital of Wales
- Hugo van Woerden, Director of Innovation and Development, Public Health Wales
- Sian Evans, Acting Consultant in Pharmaceutical Public Health, Public Health Wales

Co-chairs – Paul Buss and Ceri Phillips

The Group will reserve the right to co-opt others as necessary to support the achievement of the agreed work plan.

Professional secretariat will be provided by Sian Evans, Public Health Wales and administrative support by Matthew Tester, Welsh Government.

The Chief Pharmaceutical Officer, Welsh Government will be in attendance at the meetings.

REPORTING

The Minutes and progress of the Group will be presented to the Executive Group.

TIMESCALE

The Group should run for a period of 3 months. The final report will be presented to the Minister before the autumn half term recess.

FREQUENCY OF MEETINGS

Meetings will be held monthly in the first instance. Interim or virtual meetings may be required to move the work of the Group forward within the short timescale. Ongoing need will be reassessed as appropriate.

Presentations made to the Review Group Appendix 2

- **Carl Boswell, Programme Manager**
  Patient Access Schemes Liaison Unit, National Institute for Health and Care Excellence
- **Geoffrey Carroll**
  Medical Director, Welsh Health Specialist Services Committee
- **Tanya Collin-Histed**
  Chief Executive, Gauchers Association
- **Tom Crosby**
  Consultant Oncologist, Velindre Cancer Centre
- **Stuart John Evans**
  Clinical Effectiveness Pharmacist, Abertawe Bro Morgannwg University Health Board
- **Rob Holcolme**
  Deputy Director of Finance, Aneurin Bevan Health Board
- **Prof. Dyfrig Hughes**
  Co-Director, Centre for Health Economics & Medicines Evaluation Academic Lead, Betsi Cadwaladr University Health Board
- **Emma Hughes**
  Development Officer for Wales, Genetic Alliance UK /Rare Disease UK
- **Judith Maunder**
  On behalf of Cystic Fibrosis Trust
- **John Mills**
  Vasculitis UK
- **Mark Minchin, Technical Adviser**
  Patient Access Schemes Liaison Unit, National Institute for Health and Care Excellence
- **Kayleigh Old**
  Public Affairs Officer – Wales, Cystic Fibrosis Trust
- **Malcolm Qualie**
  Pharmacy Lead, Specialised Services, NHS England
- **Prof. Philip Routledge**
  Chairman, All Wales Medicines Strategy Group
- **Karen Samuels**
  Head of HTA & Medicines Management, All Wales Therapeutics & Toxicology Centre
- **Bethan Tranter**
  Chief Pharmacist, Velindre Cancer Centre
- **Judith Vincent**
  Chief Pharmacist, Abertawe Bro Morgannwg University Health Board
- **Phillip Webb**
  Head of Epidemiology and Evidence Support Team, Welsh Health Specialist Services Committee

Individuals agreeing to interview

Appendix 3

- **Peter Barrett- Lee**
  Consultant Oncologist & Medical Director Academic Breast Unit Velindre Cancer Centre
- **Geoffrey Carroll**
  Medical Director, Welsh Health Specialist Services Committee
- **Rick Greville**
  Director, ABPI Cymru Wales
- **John Guy**
  Patient representative, New Medicines Group
- **Sharon Hopkins**
  Director of Public Heath, Cardiff and Vale University Health Board
- **Graham Shortland**
  Medical Director, Cardiff and Vale University Health Board
- **Prof. John Wagstaff**
  South West Wales Cancer Institute & Swansea College of Medicine

Written submissions received

Appendix 4

- Association of the British Pharmaceutical Industry (ABPI) Cymru
- All Wales Therapeutics and Toxicology Centre
- Baxter Healthcare Ltd.
- Cystic Fibrosis Trust
- Ethical Medicines Industry Group (EMIG)
- Genetic Alliance UK
- Genzyme Therapeutics Ltd.
- Rick Greville, Director ABPI (Wales and International Affairs)
- Professor Dyfrig Hughes, Bangor University
- Hywel Dda Health Board
- Janssen-Cilag Ltd.
- Bethan Jenkins AM
- Myeloma UK
- Napp Pharmaceuticals
- Novartis Pharmaceuticals (UK) Limited
- Sanofi UK
- Shire
- Vertex Pharmaceuticals (UK) Ltd.
- Phillip Webb, Welsh Health Specialist Services Committee
- Hugo van Woerden, Public Health Wales

Patient event

Appendix 5

A half day event was held where patients or carers of patients with rare disease and patient representative groups participated in a series of workshops. The workshops were based on the three key themes of process, criteria and equity. The event was supported and facilitated by the NHS Centre for Equality and Human Rights and Public Health Wales. Patient liaison leads from the Public Involvement Programme (NICE) were invited attendees. The event was advertised through a series of networks including invites cascaded to patients by the Community Health Councils. There were 13 participants attending the event representing the following rare conditions:

- Atypical Haemolytic Uraemic Syndrome
- Alkaptonuria
- Ataxia
- Cystic Fibrosis
- Haemophilia
- Gaucher's Disease
- Pituitary tumors and disorders
- Spinal Muscular Atrophy

There was representation at the event from the following organisations:

- aHUSUK
- AKU Society
- Cystic Fibrosis Trust
- Genetic Alliance
- Pituitary Network Association
- UK Lysosomal Storage Disorders (LSD) Patient Collaborative Group